Project No. TREN-05-FP6TR-S07.61320-518404-DRUID

DRUID
Driving under the Influence of Drugs, Alcohol and Medicines

Integrated Project
1.6. Sustainable Development, Global Change and Ecosystem
1.6.2: Sustainable Surface Transport

6th Framework Programme
Deliverable 1.1.2b

Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving

Due date of deliverable: (15.03.2010)
Actual submission date: (18.10.2011)

Start date of project: 15.10.2006
Duration: 48 months
Organisation name of lead contractor for this deliverable: UWURZ
Revision 2.0

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

6th Framework Programme

Deliverable D 1.1.2b

Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving

Status: Public

Authors: G. Berghaus[1,2], G. Sticht[2], W. Grellner[3]
by cowork of D. Lenz[1,2] , Th. Naumann[1] and S. Wiesenmüller[1,2]

[1] Center for Traffic Sciences at the University of Würzburg
[2] Institute of Legal Medicine, University Hospital of Cologne
[3] Institute of Legal Medicine, Georg-August-University Göttingen

Workpagage Leader: Anja Knoche, BASt, Germany
Project Co-ordinator: Horst Schulze, BASt, Germany

Date: 15th December 2010

Project Funded by the European Comission under the Transport RTD Programme
of the 6th Framework Programme

Acknowledgment

We would like to thank the student research assistants Michael Bruderek, Anna Kocjan, Matthias Krämer and Peter Singler for their intensive help in searching and supplying experimental studies and in managing the literature citations.

We thank Diploma Psychologist Eva Schnabel cordially for the voluminous job of formatting completely and optimally our manuscript.

Finally we would like to thank the Diploma Psychologists Dr. Volker Hargutt, Dr. Anja Knoche and Eva Schnabel for many profound suggestions to our work and for valuable discussions of different topics.

TABLE OF CONTENTS

1 OBJECTIVES

In essence two different scientific approaches exist to evaluate the effects of psychoactive substances on driving behaviour: epidemiology and experimental studies. The subtask "Meta-Analysis" of Task 1.1 of DRUID (Driving under the influence of Drugs, Alcohol and Medicines) defines the target to evaluate the relevant literature on experimental studies on the effects of psychoactive substances on human performance and driving behaviour for their impact on traffic safety. The evaluation should include

- "Medicines regarding to the frequency of driving under medicine influence or the insufficiency of documentation
- Drugs regarding to the frequency of driving under drug influence or their novelty with a suspected hazard to driving
- Prominent combination of drugs, medicines and alcohol
- Alcohol research data will serve as a reference data base" (Description of work)

The report at hand picks medicines, drugs (amphetamine, cocain, cannabis) and prominent combinations out as a central theme whereas the remaining aspects (alcohol, other illegal drugs) will be presented in other deliverables. For medicines and illegal drugs for that exist sufficient relevant literature about their effects on human performance, a meta-analysis is conducted to quantify the results of the experimental studies.

The report of the results of the meta-analysis is based on the publication of Berghaus (1997) who reviewed the literature on medicines some years ago. But two completely new approaches were introduced for this evaluation.

On the one hand the empirical data on the time-dependent performance impairment of a medicine p.a. was smoothed by an appropriate curve fitting to establish

- dose- and time-dependent impairment curves.

On the other hand – since one objective of the DRUID project is to determine concentration-dependent effects with emphasis on establishing concentration thresholds – a new research approach had to be established: In a time-consuming evaluation, kinetics (time-dependent course of concentrations of a medicine in blood) of many medicinal agents had to be calculated on the basis of appropriate kinetic studies. With the help of these kinetics we were in the position to establish

- concentration-dependent impairment curves.

The results will be a quantitative estimation of the effects of the various substances on driving related skills. As requested the knowledge on alcohol will serve as reference base because for alcohol an extensive body of results has been accumulated over the last years and especially the effects of different legal thresholds on driving safety are well understood.

Disclaimer: Although the information presented below has been gathered and evaluated with great care, we will not accept any liability after use of information by patients taking the medicines described.

2 MATERIAL AND METHODS

One essential aspect of the meta-analysis of the experimental studies dealing with the effects of drugs on human performance related to driving behaviour (Task 1.1 of DRUID) should be the comparison of effects under influence of alcohol with the effects under influence of medicines and illegal drugs. To fulfill this demand it was necessary to use the same technique of literature selection and processing of the relevant literature for medicines and illegal drugs than for alcohol. Since the deliverable on alcohol constitutes and explains in detail all the aspects of the method and the material we will concentrate in the following on those aspects that are different from the meta-analysis on alcohol. For those aspects that are the same as for alcohol we only will refer to the appropriate chapters of the deliverable on alcohol.

2.1 Literature selection

(Compare chapter 2 of the deliverable of alcohol)

Basis of the analysis are publications that report results on experimental studies with performance tests related to driving abilities and that were performed under the influence of a drug.

2.1.1 Selection criteria

The following excluding and including criteria were observed

2.1.1.1 Exclusion criteria

(1) The study is set up non-experimentally.

(2) The study investigates only variables which are not connected to performance abilities needed to drive a vehicle safely.

(3) Only animals serve as subjects, not humans.

(4) Drugs are administered by other application than oral.

(5) Less than 6 subjects have participated in the study.

(6) The investigated population included dependents.

(7) Subjects of age ≤16 years.

(8) Wash-out phases in cross-over studies at least 5 fold of half-life.

2.1.1.2 Inclusion criteria

(1) The study must use a control group design.

(2) A drug-only treatment must be applied and no influencing factors integrated like for example subjects under stress, special occupational groups like only athletes, abnormal conditions like tests in high regions, etc.

(3) Own experimental data have to be reported.

(4) Drug concentration in blood must be able to be calculated.

(5) The study must be published in or after 1994.

The last inclusion criterion makes sense, since the review of literature on medicine effects of Berghaus [1997] included studies up to 1993. Of course we even gathered studies before 1993 if they were found and not included in the old panel.

2.1.2 Literature search

Concerning literature search the routine procedure was observed. In detail:

(1) Computer searches in relevant data bases.

(2) Tables of contents and abstracts of relevant scientific journals.

(3) The publications of authors, of whom more than one study was included into the literature pool.

(4) References to utilizable papers in reviews, processed literature and non-experimental publications.

In a pilot study we searched in different databases like for example MEDLINE, EMBASE, PubMed, Cochrane Library, PsychINFO and in further databases that are provided by the German Central library for Medicine, Cologne like for example WebOPAC, MedPilot and Science Citation Index. Analyzing and weighting the results we decided to search basically in PubMed (key words: driving, psychomotor function, attention, visual perception, vigilance, reaction psychometric, impairment, performance) and completed the citations by relevant scientific journals (selected according to the references in the ICADTS congress books), by reviews, reports and bibliographical references (like for example Lutz et al. [2003], Moskowitz and Wilkinson [2004], Carson [2006], Verster et al. [2009]) and by the reference lists of publications already included in the literature pool.

2.2 Processing of the relevant literature – the database

(Compare chapter 3 of deliverable alcohol)

2.2.1 Basic structure of the database

Data were extracted using a predesigned data abstraction form. In principle all important information (variables) of the study was extracted by means of Microsoft Access, especially data on:

- The reference including source (author, publication year, ...)
- The sample (number, gender, age, health .... of subjects)
- The methodology including quality criteria (study design, control of other factors that could influence the test results, controlling for other agents, ...)
- Statistical information (kind of control group, kind of statistical evaluation, statistical significance level, ...)
- Information about the drug administered (agent, dose, time of day, frequency of administrations, ...)
- Measurement of performance, tasks (kind of tests, time-span between administration and starting the test, ...)
- Results, parameters of all the tests that were performed (statistical significance of the results, (5%-level))

For a detailed description of variables, their categorisation and rules for the categorisation see appendix 6.1.

For an exhaustive explanation of the processing with examples and screenshots of the input fields of Microsoft Access we would like to refer to the Alcohol Report, especially to the publications (3.1.1), the findings (3.1.2), the classification of the tasks and parameters (3.3) including the categorical classification system (3.3.1) and the multidimensional classification system (3.3.2) and, finally, to the classification of results (3.4).

2.2.2 Special aspects of the meta-analysis on medicines and illegal drugs

One basic aspect of Task 1.1 should be the correlation of performance deficits with substance concentrations. Therefore we had to think about the technique of allocating concentrations to the test results (effects) measured. By an earlier study [Berghaus 1997] and by a screening of the newly gathered publications we realized that only very few studies specified concentrations. In addition those publications that indicated concentrations differed in the

point in time taking blood for the measurement (before, during or after the test battery), in the medium in which the concentration was measured (blood, serum/plasma) or in the technique of measurement. Hence this approach was unusable.

Alternatively we had to calculate concentrations based on pharmacokinetic data. But since there exist no internationally acclaimed pharmacokinetic data in form of time-dependent concentration courses for different doses of an agent we had to gather ourselves publications of studies in that concentrations were measured in defined times after application of a drug, in defined dose and that indicate the weight of the subjects and the concentrations for individual subjects. This procedure required more time as anticipated since in almost all cases it could not be judged from the title of the publication or from an abstract given in a database if the publication itself comprises the necessary data. Hence all the potentially relevant publications had to be purchased and controlled concerning completeness of relevant information. By means of some hundred pharmacokinetic publications appropriate data was established by curve fitting of the empirical values given in the publications (see chapter 7). This evaluation resulted in time-dependent concentration gradients for drugs standardized for a defined dose (standard dose) and a standard weight of the user of 70 kg (standard gradient).

Concerning the individual experiment the mean concentration has to be calculated on the basis of the standard gradient according to the dose applied, the mean weight of the subjects and the time span between administration of the drug and the time of testing performance.

Before giving the calculation formula some explanations to the constituting variables ´mean weight´, ´dose´ and ´time span between administration of the drug and the time of testing performance´ are necessary. Unfortunately in by far most of the publications (about 85%) of the earlier study [Berghaus 1997] indications of weights were missing. The same holds true by screening of the newly gathered studies. Hence we used standard weights of 60 kg for women and 72 kg for men for all experiments, weights that were averages of the weights indicated in the older studies with indications. In a few experiments (<10%) the dose of the drug was not given as mg but indicated as mg per kg body weight. To be able to include even those studies we converted values from mg/kg in mg by using the number of women and number of men of the sample and the standard weights for women and men. If indications on gender were missing we used the sample size and 66 kg. Finally relating to the point in time after administration of the drug for which the concentration is calculated. Unfortunately the duration of a single performance test or even the test battery is mentioned only in very few studies. Therefore we had to calculate the concentrations for the starting point in time to treat all the experiments in a similar manner.

Calculation formula

Ct = ((dose/standdose)*normconct)*(70/ ((nw*60 + nm*72)/(nw + nm)))

dose: dose of individual experiment (mg)
standdose: dose for which the standard gradient is calculated (mg)
normconct: concentration of the standard gradient for t = time span between administration and start of performance test battery (ng/mL serum)
nw: number of women in the experiment
nm: number of men in the experiment

To give an example:

Variables of the individual test: 6 mg administered; 15 women 10 men; t = 1.5 h
According to the standard gradient: standdose 3 mg; normconct (for 1.5 hour p.a.) 45 ng/mL
Formula: (6/3 * 45) * (70/((15*60 + 10*72)/(15 + 10))) = (2*45) * 70/((900 + 720)/25)
= 90 * 70/64.8
= 90 * 1.08 = 97 ng/mL

2.2.3 Statistical evaluations

The calculations and the curve fitting of the empirical data concerning the concentration-dependent evaluation of impairment were performed with SPSS 17.0. The curve fitting of the empirical data concerning the time-dependent impairment were performed according to the technique described in chapter 7.

3 RESULTS

3.1 General results and kind of presenting findings on individual agents

3.1.1 General results

3.1.1.1 Results of the literature search

The first problem we had to solve was: Which groups of medicines should be integrated in the analysis. At first we thought that in the time-period between 1993 and 2007 there would only be a manageable number of studies but starting the bibliographic screening it quickly became clear that too many publications exist to search for in the predetermined time and given budget. Therefore after some time of searching and encoding, in the first step we concentrated on those groups of medicines of which it was known that they were of great relevance for traffic safety, namely

- **Antipsychotics**
- **Anxiolytics**
- **Hypnotics/sedatives**
- **Antidepressants**
- **Antihistamines.**

In the second step we concentrated the bibliographic search on the question on which agents of the above mentioned groups of medicines we surely would gather at least 10 studies (we guessed that from a statistical point of view at least 10 studies would be necessary to establish dose- and time-dependent dynamics). After selecting a pool of agents that, in connection with the studies already extracted for the earlier analysis [Berghaus 1997], eventually could fulfill this criteria, we searched for these agents and encoded the copied studies. After some time we realized that it would be even claim too much time and manpower to gather, to select and to extract information on all studies published on some of the agents.

Therefore in the third step we concentrated our bibliographic search on those agents that seemed to be underrepresented or for which we not yet had gathered 10 studies or for which there were no studies in the earlier evaluation because the agent was not on the market (as for example zaleplon, fexofenadine) whereas we stopped the bibliographic search for those studies with many publications like for example diazepam or lorazepam. Hence, finally we had a representative pool of studies for about 33 pharmaceutical agents.

Of course, we had to act in accordance with the provided frequency of publications on medicines in the literature and could for example not analyze most of the newer developed agents because only few studies were published.

The above described literature search strategies for studies since 1994 led, in combination with the literature search for pharmacokinetic studies to the screening of by far more than 20.000 bibliographical references.

After analysing the title of the publication and/or reading the abstract and after selecting the obviously irrelevant studies that were copied we identified within DRUID about **1470 potentially eligible experimental studies, 861 concerning performance dynamics and 609 concerning pharmacokinetics.**

After carefully reading the studies about 900 studies had to be excluded. Hence about 570 studies could be included.

The reasons for excluding studies are multifariously and could not listed in figures because at most there was more than one reason to exclude a study but of course we stopped the further analysis if we found the first exclusion criteria. The following list of exclusion criteria found may be of interest:

- Missing description of essential variables like for example statistical significance of performance impairment, level of statistical significance, …
- Missing description of variables necessary for calculation of concentrations like for example time span between administration and start of tests, …
- Additional influencing factors like for example performance tests with subjects of special profession (competitive athletes, …), in special locations (simulated height, …), in subjects with other “treatments” (noise exposure, sleep deprivation, …), experiments with subjects with former abuse or addiction
- Time between two experiments was too short (<5 fold half-life)
- Preoperative use of agents

3.1.1.2 Data base and selection of studies for the meta-analysis of performance effects

Including the 812 encoded studies with 26.296 effects (results of performed tests) of the earlier meta-analysis [Berghaus 1997]

a total of 1086 studies with 38.819 effects built up the first data pool for the meta-analytic approach to medicines.

This pool comprised about 250 different agents. As mentioned above not all the agents showed a sufficient frequency to be analyzed meta-analytically. Selecting those substances with a sufficient number of studies

718 studies with 33 agents remained of which 19.271 effects were measured.

But further selections according to the kind and frequency of administrations, to the subjects and to the kind of tests were necessary.

Concerning the kind of administration about 90% of effects were measured using **oral administration**. Hence we had to restrict our analysis on this kind of administration.

With regard to subjects and frequency of administration one can differentiate the type of the experimental study in essence into:

- Studies in healthy subjects
  - with single administration,
  - with multiple administrations and
- Studies in patients with multiple administrations.

Even if multiple administrations in healthy individuals and especially in patients represent reality by far better than the single administration, a meta-analytic approach to the evaluation of multiple administrations is impossible since there exist only very few studies for each agent and in addition the few studies are very heterogeneous with respect to the design and other, the results influencing aspects so that they can not be summarized meaningfully.

The principle aim of multiple administrations in healthy subjects is to elucidate the adaptation of the organism to the negative effects of the medicines. The shortcomings with respect to the meta-analytic evaluation can be listed as follows:

- Too few studies per agent
- Heterogeneity of these few studies with respect to the test design:
  - Dose administered (between and within experiments)
  - Period of time of administration (days, weeks, months, …)
  - Frequency of administration per day
  - Period of time between the last administration and start of the battery of tests
- Difficulties concerning the design:
  - Compliance of the subjects
  - Missing control of the behaviour of subjects and especially the use of additional drugs in the time span between the administrations (cannot be standardized)

- In addition: usual variability of the test design as in single administration

Even more reasons must be listed concerning multiple administrations in patients:

- Too few studies per agent/disease
- Heterogeneity of these few studies in regard to the test design
    - Disease
        - Intensity
        - Acute, chronic
        - Previous duration
    - Patients
        - Gender
        - Age
        - Compliance (especially outpatients)
        - Additional use of alcohol, illegal drugs
        - Behaviour during therapy (especially: additional use of drugs)
        - Additional diseases
    - Medical therapy
        - Medicines (sort and combinations)
        - Duration (single, days, weeks, months, years)
        - Doses (between and within experiments)
        - Modification of medicinal therapy
        - Preceding standardization on a single agent
        - Additional medicines
    - Additional nonmedical therapy
    - Control groups
        - Healthy people
        - Patients themselves before medicinal treatment
        - Patients themselves in an earlier state of medicinal treatment
        - Patients without (medicinal) treatment
        - Patients with other treatments
- In addition: usual variability of the test design concerning single or multiple administrations

Hence, multiple administrations can not be evaluated meta-analytically. Therefore we will review the results of appropriate studies in short and restrict the meta-analysis to **single administration in healthy subjects.**

A further restriction is related to the age of the subjects. There are only few studies concerning older people. Since, in addition, the kinetics in older individuals can be in part very different from kinetics in younger people and since there are even only a handful of kinetic studies we only could integrate studies in the analysis using **subjects <60 years**.

Finally we concentrated on the **measurement of human performance** and selected effects measured as for example physiological variables, subjective impressions, self ratings of probands or measurements of non performance behaviour, in part, because such effects were recorded seldom for most agents in comparison to performance measures, and, in part, because the interpretation of results of such variables in relation to safe driving often is difficult or impossible.

Summerized, the following meta-analysis will be restricted to experimental studies with

- **oral administration,**
- **single administration,**
- **in healthy subjects,**
- **<60 years,**
- **performance tests.**

Overall 605 studies with 13.191 effects fulfilled these prerequisites and built up our data base.

3.1.1.3 Some general results of the meta-analysis

In the following we would like to characterize the data base of encoded experimental studies. Due to the multitude of variables it will be impossible to report on all aspects that may be of interest. Therefore we will concentrate on those aspects that are important with respect to the interpretation of the results.

Table 1 lists up the 33 agents for which we could gather enough studies to try a meta-analytic evaluation. The medicines are classified according to the ATC-code (Anatomic-Therapeutic-Chemical Classification-System).

Table 1: Meta-analytically evaluated agents classified according to the ATC-code.

		Studies	Effects
3.2	**N05 Psycholeptics**		
	3.2.1 N05A Antipsychotics		
	3.2.1.1 N05AD01 Haloperidol	10	228
	3.2.1.2 N05AL01 Sulpiride	8	86
	3.2.1.3 R06AD02 Promethazine	11	236
	3.2.2 N05B Anxiolytics		
	3.2.2.1 N05BA04 Oxazepam	26	377
	3.2.2.2 N05BA06 Lorazepam	68	1244
	3.2.2.3 N05BA08 Bromazepam	9	202
	3.2.2.4 N05BA12 Alprazolam	21	354
	3.2.2.5 N05BA01 Diazepam	103	2104
	3.2.2.6 N05BA02 Chlordiazepoxide	9	101
	3.2.2.7 N05BA09 Clobazam	16	287
	3.2.2.8 N05BC01 Meprobamate	17	313
	3.2.2.9 N05BE01 Buspirone	16	341
	3.2.3 N05C Hypnotics and sedatives		
	3.2.3.1 N05CD05 Triazolam	46	1305
	3.2.3.2 N05CD09 Brotizolam	6	78
	3.2.3.3 N05CD06 Lormetazepam	13	161
	3.2.3.4 N05CD07 Temazepam	30	695
	3.2.3.5 N05CD01 Flurazepam	22	203
	3.2.3.6 N05CD02 Nitrazepam	44	417
	3.2.3.7 N05CD03 Flunitrazepam	29	491
	3.2.3.8 N05CF01 Zopiclone	21	331
	3.2.3.9 N05CF02 Zolpidem	31	857
	3.2.3.10 N05CF03 Zaleplon	12	350
3.3	**N06 Psychoanaleptics**		
	3.3.1 N06A Antidepressants		
	3.3.1.1 N06AA02 Imipramine	13	210
	3.3.1.2 N06AA09 Amitriptyline	32	475
	3.3.1.3 N06AB03 Fluoxetine	5	150
	3.3.1.4 N06AB05 Paroxetine	6	118
	3.3.1.5 N06AX03 Mianserin	8	145
	3.3.1.6 N06AX05 Trazodone	8	146
3.4	**R06 Antihistamines**		
	3.4.1 R06A Antihistamines for systemic use		
	3.4.1.1 R06AA02 Diphenhydramine	28	481

3.4.1.3	R06AX07 Triprolidine	14	233
3.4.1.5	R06AX12 Terfenadine	16	259
3.1.4.6	R06AX13 Loratadine	13	213
3.1.4.7	R06AX26 Fexofenadine	5	170

At most benzodiazepines

By far most of the effects could be gathered for tranquilizers (40% of the 13.191 effects) and hypnotics/sedatives (37%). Hence, especially the effects of benzodiazepines were described at most. Even if we could not gather 10 studies for every agent listed in the table an evaluation seemed possible. For fexofenadine we interrupted the search after having screened 5 studies without encoding it because no single effect out of 170 described was statistically significant impaired.

At most men

Concerning the gender of the subjects at most men were included in the experiments: 43% of the 11.334 effects for which the gender was declared were performed without women, whereas only 7% were performed without men.

At most younger people

The average maximum age of subjects was 36.3 years (±8.9 years). 70% of the effects with given maximum age of the subjects (10.720) were measured in subjects ≤40 years.

Starting time of test batteries at most till 7 hours p.a.

Since by far most of the studies started at a defined hour after applying the medicament we categorized the originally encoded minutes in hours by summarizing 0 to 59 minutes to 1, 60 to 119 minutes to 2 and so on. Hence, the indication "1" means that the test started in the first hour post administration (p.a.). Even if, of course, the starting time of tests depended to some degree on the agent overall most of the effects were measured till 7 hours p.a. whereas only 7.1% of the tests started later than 12 hours p.a. Already this table showed that there are "gaps" in research: some hours like 6, 8, 10 revealed essentially fewer effects than the hours 7, 9, 11. Only 0.6% of the effects are measured later than 30 hours p.a.

Table 2: Distribution of starting times of test batteries post administration.

Hours p.a.	Number of effects	Percent	Cumulative percent
1	875	6.6	6.6
2	3059	23.2	29.8
3	2070	15.7	45.5
4	1598	12.1	57.6
5	1386	10.5	68.1
6	649	4.9	73.1
7	991	7.5	80.6
8	153	1.2	81.7
9	634	4.8	86.5
10	192	1.5	88.0
11	494	3.7	91.7
12	149	1.1	92.9
15	357	2.7	95.6
18	137	1.0	96.6
24	117	0.9	97.5
≥ 24	330	2.5	100.0
Overall	13191	100.0	

Aspects of attention are at most tested

An interesting aspect was the question concerning the performance areas that were tested by the researchers. The following table showed that attention was the performance area that was by far most performed. Including the divided attention about 30% of the effects resulted from tests that measure attention. The next frequent area was the en- and decoding followed by reaction, visual functions and psychomotor tasks.

Concerning our technique of evaluating the results of the meta-analysis, we would like to point out already here to the fact that a detailed analysis dependent on the different performance areas will be impossible. Since the data have to be differed according to the agents, to the dose administered and to the time course p.a. the frequencies within the statistical cells would be too small after an additional differentiation into performance areas.

Table 3: Distribution of performance areas.

Performance area	Number of effects	Percent
Tracking	866	6.6
Psychomotor tasks	1688	12.8
Reaction	1794	13.6
Visual functions	1737	13.2
Driving behaviour	469	3.6
Attention	3518	26.7
Divided attention	454	3.4
En- and decoding	2665	20.2
Overall	13191	100.0

Shortcomings of quality

According to the description of work for Task 1.1 the meta-analysis should be weighted for the methodological standards of the studies included. Therefore the results of variables that describe the quality of studies are of special interest. Variables like for example the number of subjects included, the kind of determining the sample size etc. as well as the "missing values" for variables like age, gender of subjects etc. are indications of the degree of quality.

The following figures (percent of all effects) may give an impression on the quality of the studies:

- Only 4.1% information on the method to determine the sample size,
- Only 2.1% describe the driving habits of subjects,
- Only 21% information on the profession of subjects,
- 24.4% without information on the randomization,
- 34% without information if the tests were practiced before real tests,
- 14% no information on number of males and females,
- 18% without information on the age of subjects.

An essential quality criterion is the sample size with which an effect is measured. The appropriate distribution indicated that at most 12 subjects (27%) and secondly 10 subjects (16%) were used. **70% of the effects were measured with fewer than 16 subjects**. One does not need to go deep in statistics to realize that fewer than 16 subjects are by far too few to make a decision with a certain safety, especially because almost all studies measure not

only a single effect (target variable) but up to 15. Hence, it goes without saying, that only a few studies used adaption techniques for the level of statistical significance.

All in all the information presented elucidate that taking into account these shortcomings of the experimental methodology it will be impossible to include only those studies that demonstrate a certain degree of quality. We probably could select only a few studies.

In contrast, to reach reasonably sufficient numbers of effects for the individual agents, we had to include not only effects that tested against placebo (97%) but those effects too that tested against blank value (3%) and even 12% of effects that used a comparison group without matching were comprised (84% cross-over, 4% matched pairs) to increase our data base.

3.1.2 Method of presenting the results of the individual agents

On the one hand due to the multitude of variables encoded it would be impossible to report on all aspects that could be evaluated. On the other hand, as demonstrated in the foregoing chapter, only the oral single administration to healthy subjects was described in the published experiments so frequently that it could be analysed meta-analytically. Hence we had to concentrate on the three main topics:

(1) dose- and time-dependent dynamics in healthy subjects with single oral administration

(2) concentration-dependent dynamics in healthy subjects with single oral administration and

(3) multiple oral administrations in healthy subjects and patients.

In the chapter at hand we would like to elucidate the techniques of reporting and illustrating the results of the more than 30 medicinal agents. In this way we avoid frequent replications and are able to concentrate in chapter 3 on a compressed exposure of the characteristics of the individual agents. In the following we will use the hypnotic/sedative flunitrazepam as an example.

3.1.2.1 Dose- and time-dependent dynamics in healthy subjects with single oral administration

<u>Empirical data: selection of doses that will be analysed</u>

The pool of published experimental studies with flunitrazepam consisted of 29 studies with 491 effects (results of performance tests). Due to pharmacological knowledge, the degree of

effects of an agent depends on the dose. Hence we could, of course, not merge all 491 effects to establish a time dependent dynamic curve but had to differ according to the doses under which the effects were measured. The following table demonstrates that doses between 0.5 mg and 4 mg were administered.

Table 4: Flunitrazepam, experimentally tested doses.

Dose (mg)	Number of effects	%
.5	28	5.7
.6	2	.4
.8	23	4.7
1.0	165	33.6
1.2	7	1.4
1.25	45	9.2
1.3	4	.8
2.0	195	39.7
4.0	22	4.5
All effects	**491**	**100**

Since we intended to categorize the time after administration in 12 classes and since every time class should include at least 10 effects, it is obvious that only for doses 1 and 2 mg there were enough effects to calculate time dependent dynamics.

Empirical data: time-dependent impairment

The next table (Table 5) shows the distribution of statistically significant reduced effects in dependence of time after administration differed for the doses 1 and 2 mg. We arranged the time p.a. in 1 hour classes ($0 \leq x < 1$, $1 \leq x < 2$, etc.) till 12 hours p.a. and categorized times later than 12 hours p.a. in broader classes since only very few tests were conducted in this period of time. Such a time-dependent distribution of impaired effects builds up the basic table with respect to all agents investigated: The upper number of a small box defines the percentage of statistically significant impaired effects in that hour, the lower line the total number of performance effects measured. Hence, to give an example, in our pool of experiments in the first hour there existed 3 effects of which 67% were statistically significant impaired. Likewise in the second hour after administration of 1 mg flunitrazepam 23 results of performance tests were on hand of which 65% were statistically significant reduced. The raw data of doses that could be arranged in time-dependent figures are given in the appendix.

Empirical data: illustration of time-dependent impairment

Since it is too difficult to imagine the time course of these data from such a table we arranged the data in a bar chart (in the figure we omitted the data for time spans more than 24 hours after administration because there were only very few data and, in addition, if data exist, these data were distributed over very different times). Now one can observe some typical aspects of the dynamics in the bar chart better than in the table like for example the declining impairment with time. But there remain some unavoidable disadvantages typical for empirical data. On the one hand there are hours without any test carried out. On the other hand the percentages between closed-by time classes vary, of course, due to special aspects of the experimental design by different working groups. Furthermore there are in part hours in which only very few tests were conducted so that the percentages of statistically significant reduced results vary considerably if a single test more or less is statistically significant impaired (for example period of time -18 hours p.a. for 2 mg dose).

Table 5: Flunitrazepam, time-dependent impairment for two doses (1 mg and 2 mg).

N05CD03 Flunitrazepam (Hypnotic/sedative) **dose dependent dynamics**																
Time post administration (h)	**-1**	**-2**	**-3**	**-4**	**-5**	**-6**	**-7**	**-8**	**-9**	**-10**	**-11**	**-12**	**-15**	**-18**	**-24**	**≥24**	∑ test results studies
N05CD03 Flunitrazepam (1 mg)	**67** **3**	**65** **23**	**33** **18**	**25** **16**	**19** **16**	**-** **-**	**0** **12**	**-** **-**	**0** **12**	**-** **-**	**17** **46**	**0** **3**	**0** **12**	**-** **-**	**-** **-**	**25** **4**	**165** **16**
N05CD03 Flunitrazepam (2 mg)	**78** **9**	**63** **27**	**90** **20**	**41** **17**	**77** **22**	**67** **9**	**29** **14**	**-** **-**	**32** **22**	**11** **9**	**28** **25**	**25** **8**	**50** **6**	**100** **1**	- -	**17** **6**	**195** **13**

Upper line of a small box: Percentage of statistically significant impaired performance effects.

Lower line: Total number of performance effects.

Column ∑ : upper line: sum of all test results in a line; lower line: number of studies.

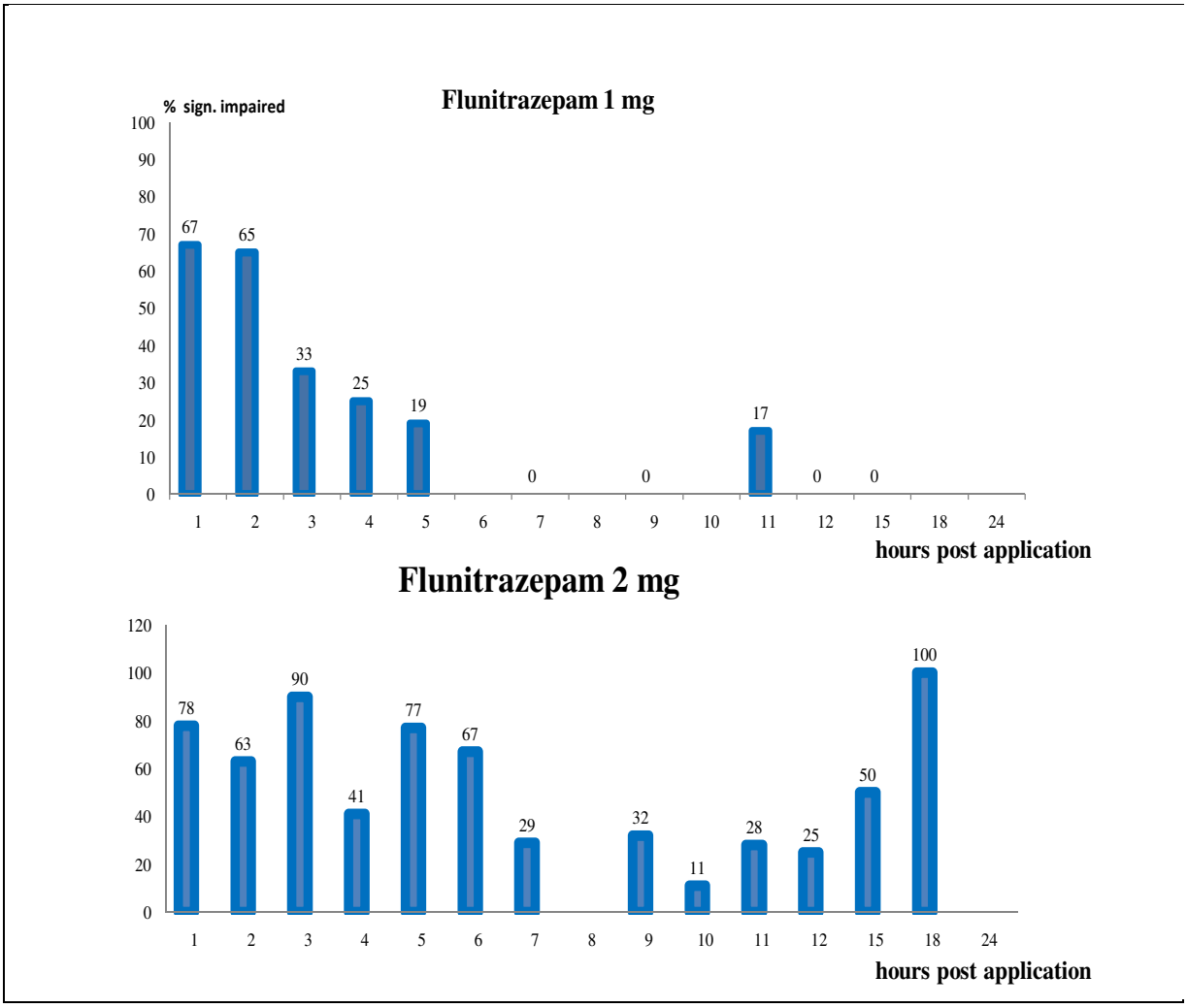

Figure 1: Flunitrazepam, time-dependent impairment for two doses (1 mg and 2 mg).

New approach by fitting the empirical data: preparing tasks

In such a situation a curve fitting seems to be a meaningful support in order to overcome these disadvantages. Assuming that the course of impairment will be strongly determined by the effects of the different agents and by recognizing the similarity of distributions of the time-dependent concentration curves with the time-dependent scatter plots of performance impairment we were convinced that the same curve fitting technique for dynamics as used for calculating kinetics would be useful (compare chapter 7 on pharmakocinetics).

An essential task was the standardization of the fitting procedure in order to compensate some essential influencing aspects on the results before calculating dynamics. If such a standardized method is elaborated it especially will be possible to compare parameters calculated on the fitting curves of different medicinal agents.

- We omitted the data for times later than 15 hours p.a. because there are no or only very few studies and effects measured in these spaces of time for almost all of the medicinal agents. In addition, with ascending time spans between administration of the medicament and start of tests it often is very difficult to control the behaviour of the subjects in the meantime especially if they were allowed to stay at home post administration (use of other drugs, etc.). Hence this procedure was necessary for standardizing reasons of the curve fitting technique between the several agents.

- We screened the data for outliers. That means we analyzed in detail the effects in a time class in which there was an abnormal percentage of statistically significant impaired tests compared to the proximate time classes. For example with 1 mg flunitrazepam in the 11th hour p.a. there were 17% statistically significant impaired effects whereas in the earlier and later class the percentage was 0. Overall 9 studies reported 46 effects (8 impaired) in the relevant time class. All but one showed only very few statistically significant impaired test results. Only one study describes 5 out of 6 effects as impaired. Such a result was very exceptional and seems to be based on special circumstances of the test design. Therefore we omitted this study and there remained 40 effects with 3 (7.5%) results impaired. It is clear that we were very cautious concerning the elimination of outliers and that we will mention the elimination in the appropriate agents. We did not designate the authors of such a study in order to avoid a negative image for those research groups. The abnormal results were not necessary a consequence of a bad research but could be due to special influencing factors.

- We merged the results of close-by time classes if the number of effects in a single class was smaller than 10. Herewith it should be assured that the percentages of statistically significant impaired tests will be calculated on a broader number of cases. As an example the 1 mg dose from the table: instead of two time classes, the first class ‘<1 hour’ (67% of 3 effects statistically significant reduced) and the second class ‘1 hour up to <2 hours’ (65% of 23 effects statistically significant reduced) we build up one class ‘0 up to <2 hours’ with 26 effects of which 65% were statistically significant impaired. Another example was the classes ‘-12 hours’ and ‘-15 hours’ of the 2 mg dose: there were only 8 respectively 6 effects measured. We joint the classes so that there were 14 effects with 5 (36%) statistically significant reduced. If necessary, we even merged 3 proximate time classes to reach a population number of at least 10 effects in the new built class.

- In spite of the merging of time classes to establish sufficient population numbers there were considerable differences concerning the number of effects within the merged time classes due to the predetermined figures in the publications. To account for these differences we weighted

the empirical data before integrating it in the curve fitting technique. In essence the number of effects, the number of studies on which the effects are based and the number of performance areas established by the effects are quality criteria: the more studies, the more effects and the more performance categories are integrated in a time class the broader is the information of this class and hence the higher should be the loading of it.

Concerning the number of effects and the number of studies we ordered the numbers in an ascending order, built up clusters of neighboring numbers and allotted weighting 1 to the smallest cluster (at most the smallest third of all data), weighting 2 to the medium cluster and the weighting 3 to the highest cluster of the ranking. With respect to the driving-relevant performance main categories (8) we allotted weighting 1 if only 1 or 2 categories were included, loading 2 for 3,4 or 5 categories and loading 3 for 6, 7 and 8 categories. Then we built up the sum of the 3 weightings (studies, effects, performance areas) and finally allotted the weighting 1 to the sum 3 or 4, weighting 2 to the sum 5or 6 and weighing 3 to the sum 7, 8 or 9.

<u>New approach by fitting the empirical data: completion</u>

After these preparing tasks we fitted the empirical data according to the technique described in chapter 7. The outcome of fitting empirical data as described above can be seen in the following chart.

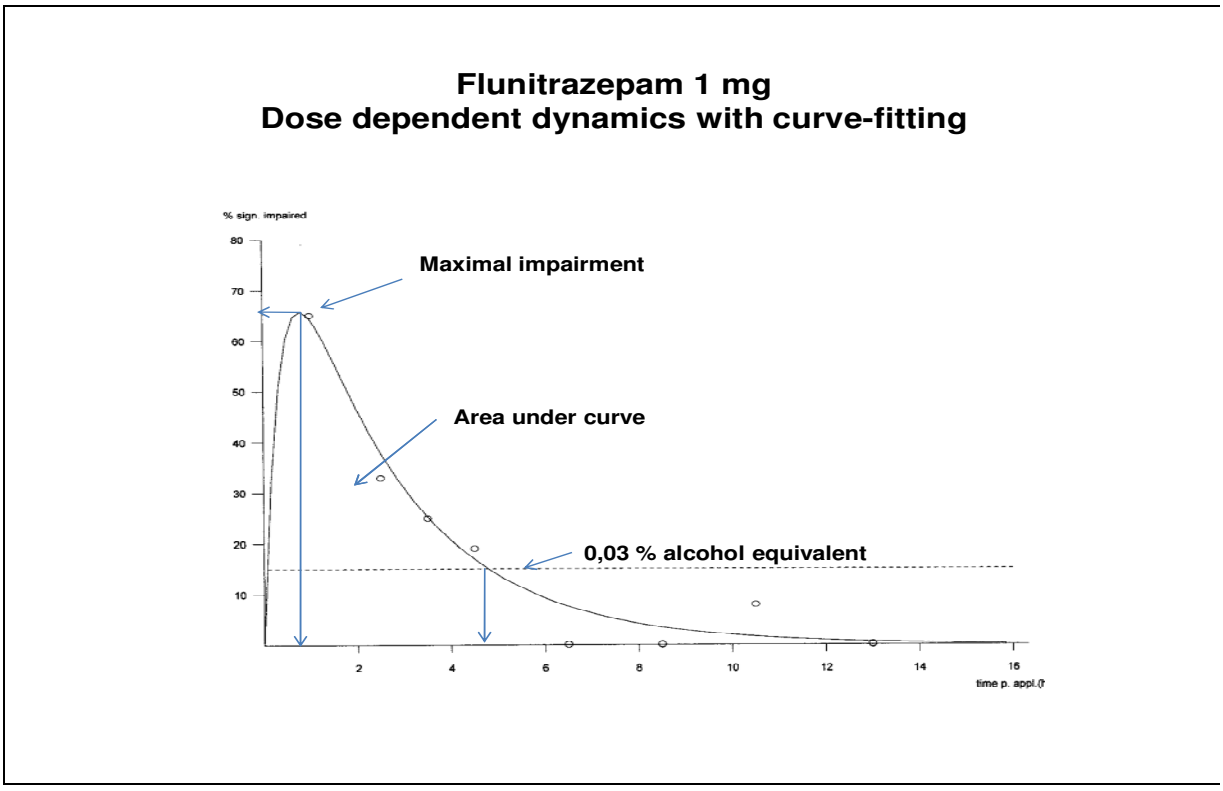

Figure 2: Flunitrazepam, time-dependent impairment with curve fitting.

The small circles define the empirical data, the curve shows the fitting. By comparing figures of the raw data given in the appendix and the small circles one can recognize the kind of merging of neighbored time classes and the selection of outliers. As explained in chapter 7 on pharmacokinetics the fitting curve is the best one in approximating the original data according to the pharmacokinetic model. It is obvious that the fitting for flunitrazepam 1 mg seems to be a good one because all the circles are situated near the curve. The irregularities of the distribution of the empirical data will be balanced. Hence, in contrast to the bar chart, the characteristics of the performance curve clearly emerge after the fitting: Immediately post application the impairment increases up to the maximum which is located about one hour p.a. About 65% of effects are statistically significant impaired during the maximum impairment. Then the curve decreases till zero about 14 hours p. a.

Such a pharmacologically based fitting of empirical data makes it possible for the first time to indicate very important information on impairment for medicinal agents on a very broad pool of experiments, information on the one hand for physicians that prescribe medicaments and for patients using the medicaments and on the other hand to compare different medicaments with respect to their degree of impairment.

It goes without saying that such an approximation was only meaningful for agents that clearly determine the effects. That means on the other hand that for agents with active metabolites (like for example flurazepam) or for agents of that the distribution of effects are determined not only by the dose but even by other influencing factors (like for example the time of administration (“hang-over”)) such a curve fitting was not meaningful. We will mention such influencing factors in the appropriate chapters.

It is even obvious that the empirical data of some agents were better approximated by the curve fitting than other ones. The quality of approximation depended, apart from other influencing factors, on the number of studies and effects that can be integrated in an analysis: The higher the number of studies and effects the better in general the approximation. Therefore it often was difficult to handle agents for that only very few studies and effects could be integrated. Especially if only few time classes showed sufficient high population numbers it was very difficult to construct adequate approximation curves. We indicated results that are based on too few or very few data by brackets. Furthermore it seemed that the dose of an agent determines the quality of approximation: with ascending doses the approximations in general will be better, probably due to the fact that more and more performance areas will be impaired with ascending doses.

New approach by fitting the empirical data: calculation of characteristics based on the curve fitting

The curve fitting provides the opportunity to read characteristics out of the curve. Some essential information was marked in figure 2 in addition to the empirical data and the fitting curve:

- point of time and percentage of maximal impairment
- line of 0,03% alcohol equivalent
- point of time when the curve crosses the 0,03% equivalent
- degree of impairment (area under curve)

The importance of *point of time and percentage of maximal impairment* is obvious.

The *0,03% alcohol equivalent* is a straight line parallel to the x-axis. Its deduction, logic and importance will be elucidated by the following figure.

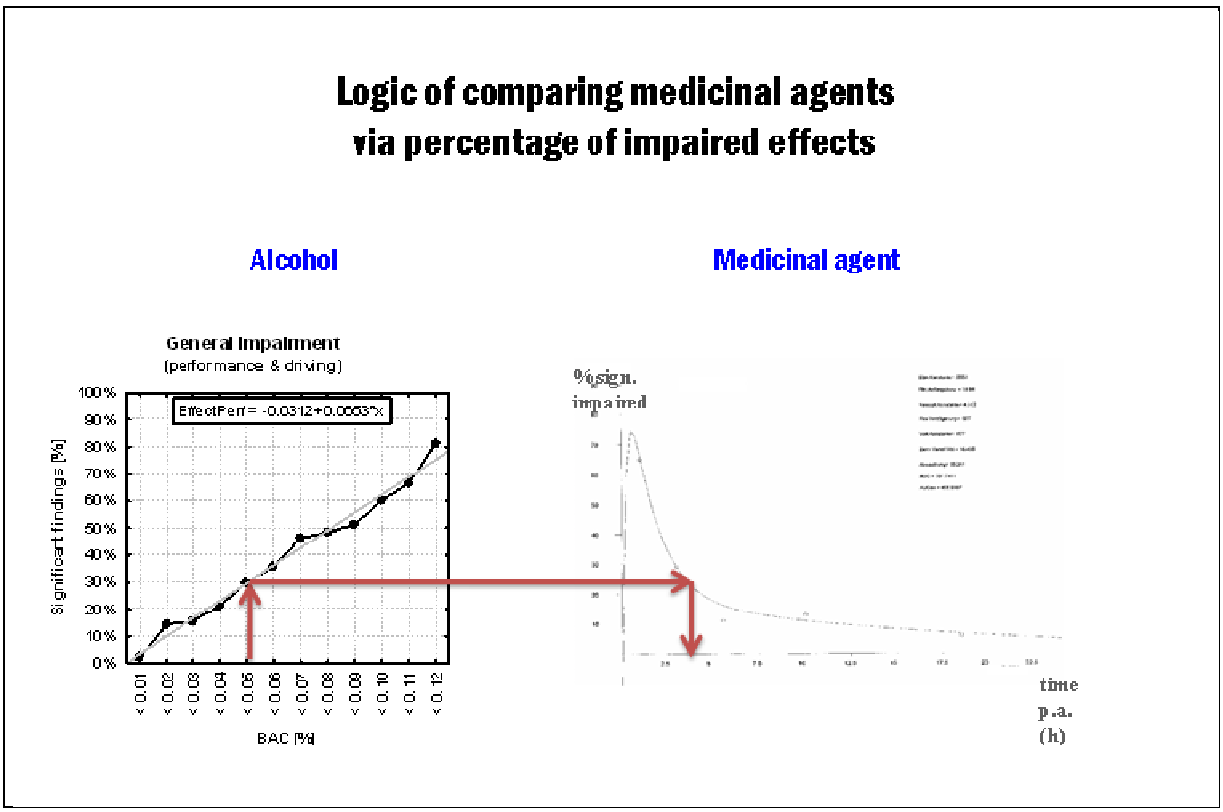

Figure 3: Logic of comparing medicinal agents via percentage of impaired effects.

Probably not each concentration of a substance leads to impairment. Especially in the late elimination phase, there may be measurable a certain low concentration of a dangerous agent but in general there will not be an impairment based on this concentration. Such an 'effect limit' is, at least in German legislation, for alcohol a BAC of 0.03%. That means, in legal

praxis, that it is not assumed that alcohol lower than 0.03% is the cause for a crash in a driver at fault. In the meta-analysis of alcohol it was demonstrated that 0.03% alcohol is associated with a percentage of about 15% statistically significant impaired effects (compare later). Since experimental studies on medicinal agents use the same design especially the same performance tests it seems likely that even for medicinal agents the percentage of 15% will be an indication for an 'effect limit'. Hence the 0,03% alcohol equivalent corresponding to 15% impaired effect could be used as a parameter on which information on the duration of impairment can be based. Therefore fitting curves above 15% statistically significant impaired effects characterize impairment and the point in time when the fitting curve crosses the 15% deficit line in essence indicates the end of the impairment period.

The maximal impairment of an agent is without doubt a very important parameter to guess the danger of a medicament. But this maximum may exist over a short period of time or a long period of time. To cover this aspect we calculated the *'area under curve'*. The importance of the 'area under curve' (AUC), originally a pharmacological parameter for an agent, is explained in the chapter on pharmacokinetics. We modified the calculation of this parameter a little bit to make it more appropriate to the concept of impairment: in place of calculating it with the zero line (x-axis) we choose the 0.03% alcohol equivalent line as lower limit, that means the 15% statistically significant impairment, a limit below which there is in general no indication for an appreciable impairment. Hence the AUC is the integral (summation) of impairment > 15% over time. Agents that show a long period of impairment under 15% in the late elimination phase are not overestimated using this modification. Hence, in the context of traffic safety of medicaments the AUC enables a comparison of the degree of impairment within an agent (dose) and between different substances: the higher the value of this parameter the larger the degree of impairment in terms of the sum of impairment over time. Thus this parameter tries to represent in one single parameter what is normally represented by the intensity (magnitude of statistically significant impaired effects) and the time period of impairment.

Unfortunately there is no possibility to measure the variability of the fitting curve by, for example, a standard deviation as it is usual with curve fitting of empirical kinetic data. Since one has no metered values for individual points of time (kinetics) but percentages for classes of time (dynamics) we had to consider other opportunities to give at least an impression on the variation of the parameters. Surely it would be meaningful to calculate within one time class the mean and standard deviation of percentages of effects of the different studies. But on the one hand in many cases only few percentages built up the mean percentage and on the

other hand in many cases the percentages within one time class varied between 0 and 100 so that the calculation of a standard deviation would create too high values. Therefore we introduced the following procedure: if, for example, within one time class 35 (50%) effects of 70 effects were statistically significant impaired we assumed that 31, that means the original 35 minus 10% (rounded up), were statistically significant impaired and hence took a percentage of 44 (31 of 70) as the value of this time class for a lower curve fitting. Analog, we took 39 (35 plus 10%), that means 56% as percentage for a higher curve fitting. By this procedure (assumption that 10% less or 10% more effects would be statistically significant impaired) for every time class existed higher and lower percentages. Then we fitted the lower and higher percentages creating a lower and a higher curve of that we calculated the same parameters as for the original curve. It is important to bear in mind that the calculated higher and lower parameters are no standard deviations but only serve to get an impression on the variation of the data.

3.1.2.2 Concentration dependent dynamics in healthy subjects with single oral administration

Time- and dose-dependent dynamics are interesting information for physicians and patients because their estimation of the danger of an agent had to be based on the dose of the medicament and the time after application. From a pharmacological and forensic point of view concentration-dependent dynamics may even be of interest. Since we calculated the concentration of an agent for the time point of the start of the test battery we were able to correlate these concentrations with the intensity of performance impairments. Besides the additional information themselves the additional evaluation based on concentrations realizes several advantages in comparison with the exclusive dose- and time-dependent analysis of dynamics. At first, even data for those doses that were not analyzable time-dependently due to too small population numbers could be integrated. On the one hand this means that all effects could be used and hence the concentration-dependent analysis could be based on essentially more data than the dose- and time-dependent analysis. Therefore results of the concentration-dependent analysis could be judged as more safe. On the other hand some agents that could not be evaluated time-dependently could be analyzed concentration-dependently and even higher doses for that at most there were no sufficiently high population numbers were saved for the analysis. Secondly the additional concentration-dependent evaluation provided the opportunity to control results of the time-dependent curve fitting via comparison of concentrations calculated from the approximated time-dependent curves and the

concentration-dependent curve itself. Thus, to give only one example, outliers could be recognized or confirmed.

Concerning the correlation between concentration and degree of impairment a preliminary remark seems to be necessary. For intra-individual purposes it is obvious that for a defined point in time after administration a higher dose of an agent will produce a higher concentration and in general – if the agent shows an impairment at all – even a higher degree of performance impairment. From an inter-individual point of view this fact does not need to be valid. The degree of effects depends essentially on the addiction of the user to the agent. Since we combine the results of different studies we compare the performance of different groups of subjects so that there is not necessarily a positive correlation between concentrations and degrees of impairments. But since the subjects are healthy and consequently do not use medicaments it is to be assumed that a concentration effect will be realized anyhow.

With regard to the technique of the concentration-dependent evaluation at first we inspected closely the concentrations calculated and categorized them in equally spaced classes the number of which we chose according to the overall number of effects. The raw data of concentration classes are given in the appendix. The methodological approach by curve fitting of the raw data was the same as for the time-dependent analysis. Hence, before starting the curve fitting we had to standardize the data as follows:

- In most of the agents the climb gradient during absorption was very steep. Therefore the concentration changed within a few minutes and the concentration for the starting point of a test battery would not reflect the concentration during the test procedure. Since, on the other hand, the measurement of effects during the absorption was very rare and due to comparison reasons we analyzed for all agents only the effects measured after the time point of the maximum of concentration given by the pharmacological tables. By inspecting the raw data we recognized that for all agents measurements of performance were done sufficiently frequent up to defined concentration classes. Above these defined concentration classes only very few studies measured performance and in addition there were essential gaps between the concentration classes so that it was impossible to allocate these data meaningfully (example: the majority of measurements of performance were done up to 60-70 ng/mL and the next measurement for 110 ng/mL). Furthermore percentages of impaired tests measured under very high concentrations in part fluctuated considerably due to the small population numbers without the need that this fluctuation represents the reality. Therefore we omitted the results for such high concentrations. As it was seen in the figures, omitting the effects measured

under high concentrations did not change the power of the conclusions drawn because the essential part of the concentration continuum was the part in the mainstream of the regression curve.

- Similar to the procedure concerning the dose and time dependent dynamics we ordered the data in a cross-tables, eliminated outliers, combined neighboring concentration classes to get a frequency of at least 20 effects in each cell and weighted the data. With regard to reality we completed in general the data by adding the value "0% statistically significant impaired effects" for the virtual concentration zero with weight 9. Exceptions will be mentioned in the appropriate chapters.

The absorption-elimination method of approximation of the time dependent dynamics could of course not be used with the concentration data. A screening of the scatter plots of the different agents and a screening of the results of the approximation techniques of the SPSS statistical program revealed that in essence only 2 methods were in line with the original data: the linear and the quadratic curve fitting. The essential area for approximation (see later) was the part of the concentration-impairment curve in that the value was situated that will be equivalent to 0,05% alcohol, that means in general the medium part of concentrations. This part was always best approximated by a linear or a quadratic approximation. Hence we chose one of these approximations according to visual decision. By giving the R^2 and statistical significance of the F value an estimation of the quality of the approximation will be possible.

The following figure, the quadratic curve fitting for the empirical values of flunitrazepam, illustrates the procedure. At first it is to be seen, as it was expected, that the percentages of statistically significant impaired effects increase with increasing concentrations (circles for empirical data). The approximation was quite good. Applying the logic of comparing medicinal agents with alcohol as explained in the foregoing paragraph we calculated with the aid of the quadratic approximation equation the concentration for 30% impaired effects that means 5.4 ng/mL. According to the meta-analysis on alcohol the 30% level was associated with an alcohol concentration of 0,05%. Hence, the parameter we calculated could be named as 0,05% alcohol equivalent (ng/mL).

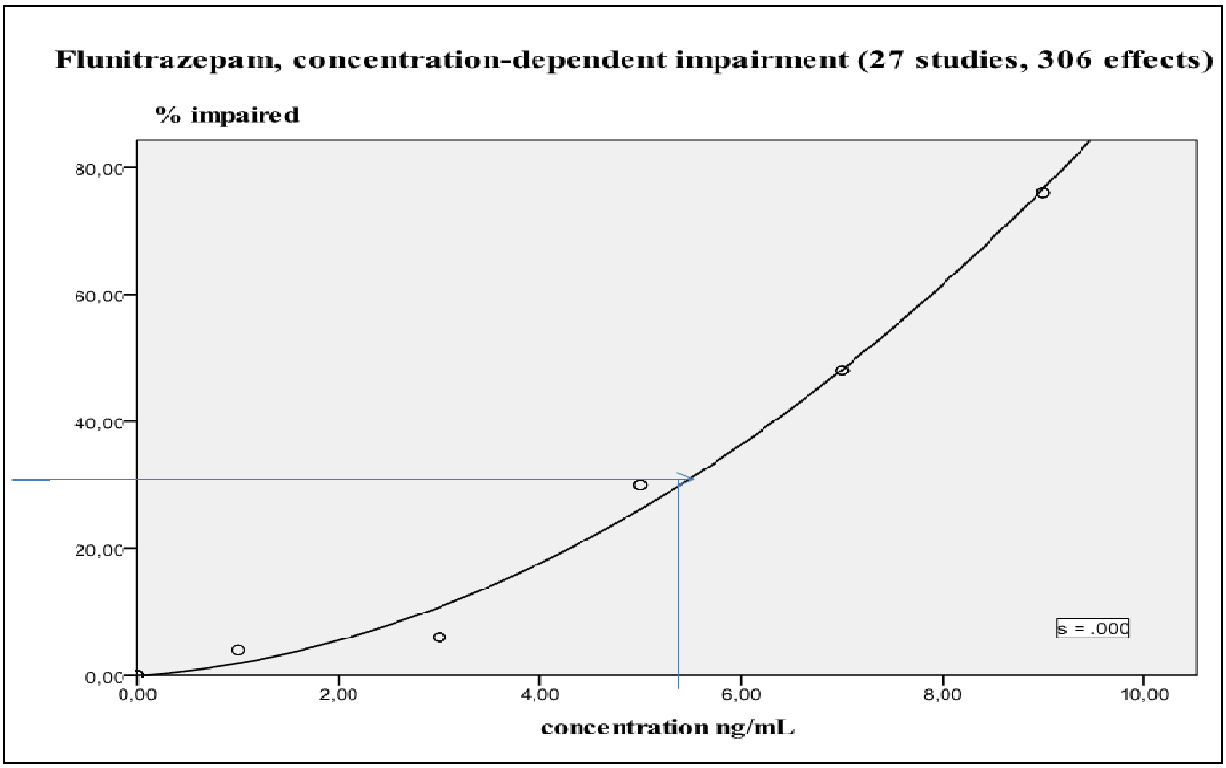

Figure 4: Flunitrazepam, concentration-dependent impairment with quadratic curve fitting (°: empirical points; —: quadratic curve fitting; statistical significance 0.000; R^2 = .993).

3.1.2.3 Illustration of results in chapters on the individual agents

Besides the dose- and time-dependent dynamic curves and the concentration-dependent dynamic curves we will present the results in the chapters on the individual agents in a comprehensive table as follows:

Table 6: Flunitrazepam, summary of results.

Summary **Single administration**	**N05CD03 Flunitrazepam**	
Number of studies	29	
Number of effects	491	
Checked doses (mg)	0.5 - 4.0	
Recommended dose (mg)	0.5 - 1	
Tabularly evaluable doses (mg)	1	2
No. studies / no. effects	15 / 155	11 / 176
Max. sign. impaired test results (%)	66 (60 - 98)	92 (81 - 100)
Hour p.a. of maximum impairment	0.75 (0.50 - 1.0)	2.25 (2.0 - 2.25)
Alcohol equivalence of max. imp. (%)	>0,08	>0,08
Duration p.a. until <15% impairment (h)	5.0 (3.75 - 7.75)	14.0 (12.75 - 15.25)

Degree of impairment	115 (85 - 177)	461 (374 - 562)
0,05% alcohol equ. (ng/mL)	5.4 (5.0 - 5.8)	
% of max. rec. dose (mg)	70 of 1 (65 - 75)	

The definition of the abbreviations is as follows:

'*Number of studies***'** denotes the number of studies of our selection (single oral application to healthy subjects, age <60, crossover design).

'*Number of effects***'** indicates the number of performance tests carried out in the before mentioned number of studies.

'*Checked doses (mg)***'** denote the range of doses that was tested in the studies.

'*Recommended dose (mg)***'** is the normal therapeutic dosage given to an adult patient for the main indication of the medicament during initial ambulant treatment. The indications were made in daily doses that were administered in several quantities (for example for anxiolytics) or in single doses (for example hypnotics sedatives). Recommended doses for medicaments are adapted from the Rote Liste®, an acclaimed, in Germany yearly published information manual for physicians and for meprobamate from ch.oddb.org/de/gcc/fachinfo/swissmedicnr/23851. Comparing the recommended doses with the checked doses one can realize if the recommended dose really was tested in experiments at most.

'*Tabularly evaluable doses (mg)***'** denote the dose or the doses for which there are enough effects to calculate a fitting curve.

'*No. studies/no. effects***'** designate the number of studies and the number of effects for the tabularly evaluable dose on which the following parameters are based. As mentioned above, these figures are smaller than the figures of raw data in the appendix due to the restriction to times p.a. till 15 hours and due to the selection of outliers.

'Max. sign. impaired test results (%)' indicates the maximum of the fitting curve and, in brackets, the figures for the variation ("below" and "above" curve) as described earlier.

'Hour p.a. of maximum impairment' identifies the hour with variation when the maximum of impairment emerges.

'Alcohol equivalence of max. imp.(%)' distinguishes the equivalent alcohol class of the percentage of maximum impairment. The limits are rounded values from the meta-analysis on alcohol (general impairment, performance and driving). Due to the underlying technique

(volatility of empirical results, approximation, etc.), it is clear that we could not give a single figure but only present the following classes of equivalence.

Table 7: Percentage of impaired effects and equivalent alcohol concentrations.

Impaired effects (%)	Concentration class alcohol (%)
<15	<0.03
15 up to ≤30	0.03 up to ≤0.05
30 up to ≤50	0.05 up to ≤0.08
>50	>0.08

'Duration p.a. until <15% impairment (h)' defines the time period in hours till the fitting curve will decrease lower than 15% statistically significant impaired effects.

'Degree of impairment' indicates the area between the approximation curve and the 15% impairment line as a measure for the danger of a medicament as explained above (AUC).

'0,5% alc. equ (ng/mL)' gives the 0.05% alcohol equivalent concentration of the agent.

'% of max. rec. dose (mg)': Apart from some toxicologists most people probably will not be able to evaluate the impact of the given alcohol-equivalent concentrations in ng/mL of a medicament. Therefore, in addition, we tried another approach to elucidate these concentrations by relating the values to the maximal concentration produced by the recommended dose. To give an example: we used 1 mg as the recommended single dose for flunitrazepam. According to the kinetic curve of flunitrazepam, 7.7 ng/mL is the maximal concentration reached by a single administration of 1 mg (maximal concentration for a person weighting 70 kg). Hence, the 0,5% alcohol equivalent (5.4 ng/mL) counts for 70% of 7.7 ng/mL. In other words: about 70% of the recommended dose will lead to a maximum concentration that is equivalent to the effect of 0,5% alcohol. Hence the lower the percentage the more dangerous will be the medicament in its normal dose in terms of performance deficits.

Of course, the percentage calculated depended essentially on the dose that is taken as "recommended" for single administration. In case that a single dose was recommended by the manufacturers (Rote Liste® as reference) we took of course this dose. It was difficult to define a single dose as "recommended" if only areas of daily doses were reported (for example 50-150 mg/day) without announcing quantities for single doses. If there were no further information we had to define single doses by ourselves. Especially if we compared the degree of impairment between agents we announced the recommended single doses that we chose. It goes without saying that our decision on the single dose is not mandatory and only

serves as lead. It is left to the reader to choose his own dose and to calculate the related percentage according to the kinetics of this dose.

3.1.2.4 Multiple oral administrations to healthy subjects and patients

As revealed in the first part of this chapter, studies with multiple administrations to healthy subjects or patients are very seldom for most of the medicinal agents and are not comparable due to the heterogeneity of the design, especially the different doses administered, the different periods of application, different control groups and further influencing factors. Therefore it was impossible to handle these categories of studies meta-analytically. Hence we had to restrict on reviewing appropriate studies with respect to adaptation of the impairments (healthy subjects) and with respect to a complete reduction of the impairment in comparison to healthy controls. Since the results for different agents were very similar to a large extent on the one hand we refer to reviews and on the other hand we restrained from telling the same in every chapter but discussed some general aspects like for example the question of serum concentrations and multiple administrations in a separate chapter (3.6).

3.1.2.5 Summary and comparison of the agents of the different groups of medicaments

In addition to the tables with profiles of the individual agents we summarized the results on a group of agents at the end of the chapter and tried to compare the agents of the group. Since such a comparison may concern very different aspects and it would expand the length of our report too much we concentrated on the comparison of the degree of performance impairment relevant for patients or physicians.

For reasons of extent of the report it also would be impossible to compare our results based on the completely new approach with traditional reviews on medicaments or groups of medicaments. Therefore we only mention in part those reviews.

3.1.2.6 Interpretation of the parameters calculated

We guess it very important to hint already in this chapter to the necessity of correct interpretation of the parameters calculated. Of course, one always should bear in mind that the interpretation of the data only hold true for the context of the experimental design given in the selected experimental studies. Especially we would like to hint on the following aspects.

The parameters calculated on the basis of the time-dependent analysis only were valid for the doses announced as “tabularly evaluable doses”. Administering lower or higher doses, especially supra-therapeutic dosages, may lead to completely other degrees of impairment.

Time-dependent parameters as well as concentration-dependent parameters are valid only for single, oral administration to healthy people ≤60 years (at most younger people). That means for example that concentrations calculated are no longer valid if one takes into account multiple administrations to healthy subjects (adaption) or patients (adaption and interaction of effects of a medicament with effects of disease).

If results were based on only few effects and, in addition, if there are heterogeneities concerning the time-dependent distribution of effects then we indicated this fact by giving the values in brackets.

3.2 N05 Psycholeptics

3.2.1 N05A Antipsychotics

Antipsychotics, frequently named neuroleptics, are mainly used in the treatment of acute and chronic schizophrenia. Further indications are the following (dependent on the pharmakologic agents): acute manic syndromes (e.g. haloperidol), acute agitation (e.g. haloperidol), organic psychosis (e.g. haloperidol), depressive disorders without effectiveness of classic antidepressants (e.g. sulpiride), sedation/sleep disorders (e.g. promethazine), allergic disease (e.g. promethazine with antihistamine effects).

Antipsychotics as a heterogeneous group can be classified into different categories:

- According to the Red List®:
    - Phenothiazines, e.g .promethazine
    - Other tricyclic neuroleptics, e.g. chlorprothixene, flupentixole
    - Butyrophenones, e.g. haloperidol
    - Other/Atypical neuroleptics, e.g. amisulpride, clozapine, risperidone, sulpiride
    - Depot agents
- According to the ICADTS Drug List 2007 (compare Appendix I, page 530, 531 in Verster et al. (eds.) [2009]):
    - Phenothiazines (different chemical subtypes), e.g. promethazine
    - Butyrophenones, e.g. haloperidol
    - Indoles, e.g. sertindole
    - Thioxanthenes, e.g. flupentixol
    - Diphenylbutylpiperidines, e.g. fluspirilene

- Diazepines and related agents, e.g. clozapine, olanzapine
- Benzamides, e.g. sulpiride
- Lithium
- Other antipsychotics, e.g. risperidone

It is obvious that patients without an adequate treatment are not fit to drive.

Due to the low frequencies of publications for antipsychotics only three substances could be selected for a detailed analysis. Unfortunately especially for the modern antipsychotics there were no sufficient data.

In contrast to other classes of agents with regard to antipsychotics there are a lot of experimental studies with patients. But by far most of these studies aim at demonstrating an improvement of special performance areas in the course of medicinal therapy. On the whole, the majority of studies with schizophrenic patients reports improvement of both cognitive functions and attention together with clinical recovery in the course of neuroleptic treatment [e.g. meta-analysis of Woodward et al. 2005]. On the other hand, there are also reports on a lacking cognitive improvement despite clinical recovery from psychosis: for example González-Blanch et al. [2008] did not observe an improvement of cognitive performance in neuro-cognitive tests for attention, visuomotor speed, declarative memory, working memory and executive function after a 6-week-treatment of first-episode non-affective psychosis with either haloperidol, risperidone or olanzapine. The patients only showed practice effects in psychological testing. In the following we do not cite the improvement studies but concentrate on the few studies testing patients against placebo or control groups.

3.2.1.1 N05AD01 Haloperidol

(N05AD Butyrophenone derivative)

Single administration to healthy subjects

Overall 10 studies with 228 effects built up the basis for the meta-analytical approach to haloperidol. Doses between .5 mg and 10 mg were administered to the subjects. The 3 mg dose with 106 effects measured (82 effects up to 15 hours p.a.) was the most frequently experimentally tested one.

After application of 3 mg haloperidol the 20 effects measured up to the 4th hour p.a. showed no single statistically significant impaired one but at the 5th hour 44% of 25 effects indicated a statistically significant reduction in performance. Even if the number of effects was very low

with respect to a valid construction of a time-dependent impairment curve the course is to be seen, even if, of course, the curve could have been started earlier than about 3 hours p.a. as explained in the discussion. The maximum impairment concentrates in the 5th hour, it exceeds only for a short time the 30% level, and it was to be seen about the same time as the maximum of the concentration curve. It takes more than 10 hours till the impairment curve crosses the 15% line.

Concerning the concentration-dependent analysis only 86 effects after the maximum of the concentration curve (5.75 hours p.a.) could be integrated in the analysis. In addition there was no continuity in the population numbers of the different concentration classes and the %-impairment distributions between the concentration classes were heterogeneous. Therefore we had to restrict from establishing a concentration-dependent impairment curve. Overall the percentages of statistically significant reduced tests in the different concentration classes of the elimination phase did not exceed 20 up to a concentration of 2 ng/mL. Only 11 effects measured between 3,2 and 3,4 ng/mL presented a percentage of 27.

Haloperidol 3 mg, time-dependent impairment (5 studies, 82 effects)

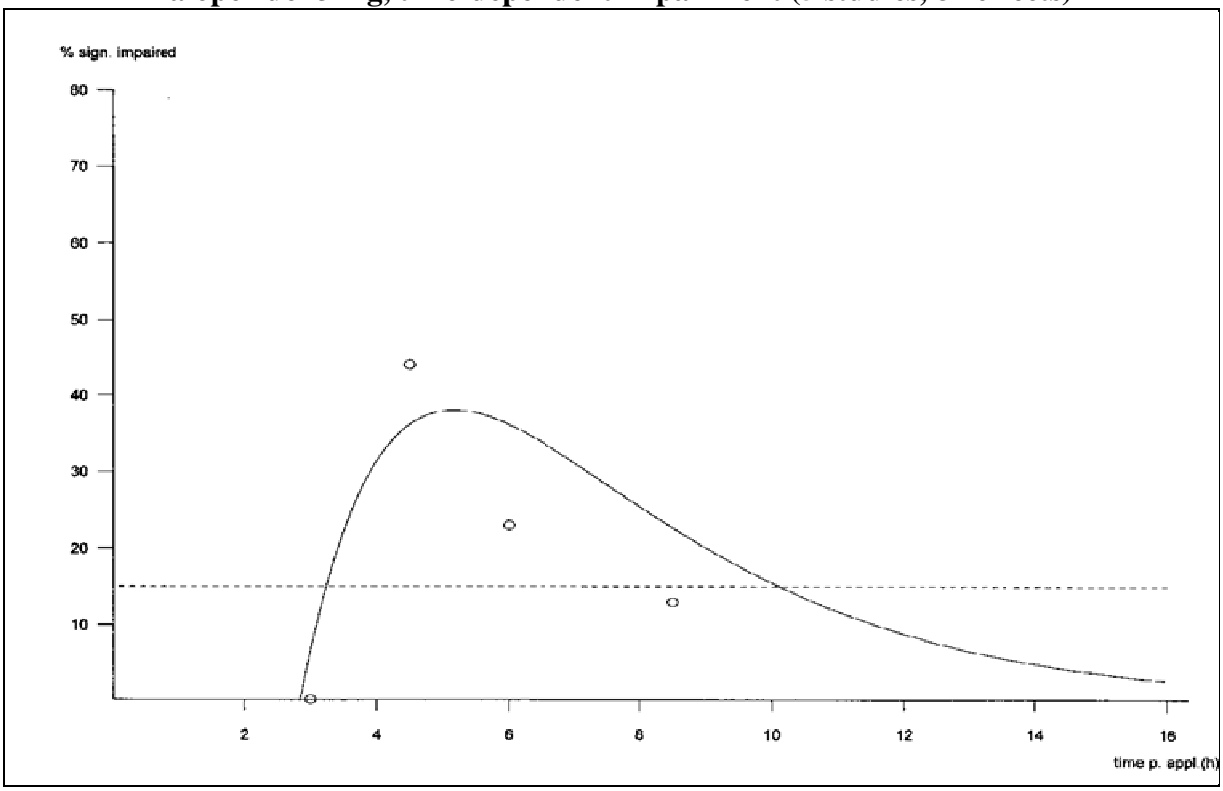

Figure 5: Haloperidol 3 mg, time-dependent impairment.

Table 8: Haloperidol, summary of results.

Summary	***N05AD Butyrophenone derivates***

Single administration	N05AD01 Haloperidol
Number of studies	10
Number of effects	228
Checked doses (mg)	.5 - 10
Recommended dose (mg)	1 - 20 / day
Tabularly evaluable doses (mg)	3
No. studies / no. effects	5 / 82
Max. sign. impaired test results (%)	38 (31 - 44)
Hour p.a. of maximum impairment	5.25 (5.0 - 5.25)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08
Duration p.a. until <15% impairment (h)	10.25 (8.5 - 11.5)
Degree of impairment	93 (50 - 138)
0,05% alcohol equ. (ng/mL)	too few effects
% of max. rec. dose (mg)	only low correlation

Multiple administrations to healthy subjects

Clayton et al. [1972] tested 100 subjects with a dose of 5 x 0.5 mg within a period of 36 hours. There were no statistically significant effects in real driving tests.

Summary multiple administrations: No statistically significant impairment, but not enough data available.

Administration to patients

Many recently published studies compare the effect of antipsychotic treatment with modern atypical substances to haloperidol as the main representative of typical APDs.

In contrast to the atypical APD olanzapine, a 6-month treatment of early phase schizophrenic patients with haloperidol showed negative effects on procedural learning which were not yet present after a treatment of 6 weeks [Purdon et al. 2003]. Patients with schizophrenia who received haloperidol in a steady-state dosage (10.4 mg/day, no blood concentrations given) and were tested before discharge from hospital showed statistically significant worse results in psychomotor tests compared to both healthy controls and patients under the atypical neuroleptic risperidone [Soyka et al. 2005]. The individuals underwent a standard test battery (visual perception, attention, reaction time, sensorimotor performance); only 5% passed all

subtests without any major failure. Keefe et al. [2006] found no statistically significant difference between either low-dose haloperidol (ca. 5 mg/day) or olanzapine (ca. 11 mg/day) with regard to neurocognitive status of first-episode schizophrenic patients (n=263) after a long-term treatment of 52 weeks or 104 weeks. Both antipsychotic agents appeared to improve neurocognitive functioning, olanzapine only was superior to haloperidol after short treatment intervals of 12 weeks and 24 weeks. The haloperidol group did not show statistically significant cognitive improvement after 12 weeks.

Meta-analytic results indicate that the overall cognitive function improves while on haloperidol for a longer time period. Similar to the results of a single application in healthy subjects only high doses greater than 24 mg per day seem to have negative effects in single tests [Woodward et al. 2007].

Summary patients: performance was improved during therapy but performance deficits continue over weeks/months (effects of psychosis probable).

3.2.1.2 N05AL01 Sulpiride

(N05AL Benzamide)

Single administration to healthy subjects

Concerning sulpiride 8 publications with 86 effects and doses testing between 100 and 400 mg could be integrated in the analysis. These 8 publications disseminated on only 4 working groups of which 2 groups account for 75 effects. The 400 mg dose was the at most experimentally tested one (73 effects). But since 4 of the 5 publications of this mg-group stem from only one working group the interpretation has to be done very cautious. Only 4% of these effects showed statistically significant impaired results. There was no time-dependence or concentration-dependence of impairment. It is obvious that a curve fitting was not possible.

Table 9: Sulpiride, summary of results.

Summary **Single administration**	***N05AL Benzamides*** **N05AL01 Sulpiride**
Number of studies	8
Number of effects	86
Checked doses (mg)	100 - 400
Recommended dose (mg)	50 - 300 / day
Tabularly evaluable doses (mg)	400 *)
No. studies / no. effects	5 / 73

Max. sign. impaired test results (%)	<10
Hour p.a. of maximum impairment	no
Alcohol equivalence of max. imp. (%)	<0,03
Duration p.a. until <15% impairment (h)	0
Degree of impairment	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached

*): no curve fitting due to minor impairment and too few effects

Multiple administrations to healthy subjects

Two older studies [Seppälä 1976, Liljequist et al. 1975] tested a daily dosis of 150 mg sulpiride in 24 probands over a period of 14 days. In a battery of psychomotor tests (among others attention, concentration, learning, memory) a slight tendency to impaired results was found, but statistically significant performance deficits could not be detected.

Summary multiple administrations: No statistically significant impairment, but not enough data available.

Administration to patients

No studies on hand.

Summary patients: No studies on hand.

3.2.1.3 R06AD02 Promethazine

(R06AD Phenothiazine derivative)

Single administration to healthy subjects

With 11 studies and 236 effects for promethazine we could gather almost as much studies and effects as for haloperidol. Doses between 20 and 50 mg were tested of which the 25 mg dose with 141 effects was the most frequently analysed one. Since 30 mg with 77 effects was a near by dose we merged the two doses so that we could base our time-dependent analysis on 11 studies with 215 effects.

The maximum of deficits was situated around 5 hours p.a. Even if the fitting curve did not reach the maximum of the empirical data (due to a relatively low percentage of statistically significant impaired effects at the 5th hour p.a., but of 5 studies for this time-span an outlier

could not be identified) the amount of impairment reached 65%. The maximum of the fitting curve emerged about two hours later than the maximum of the concentration of the agent in serum which is a hint that the maximum of impairment should be earlier than about 5 hours p.a.

With respect to the concentration dependent analysis effects measured ≥2.75 hours p.a. were included in the analysis. According to the quadratic approximation curve (R^2 = .977) about 53% of the therapeutic dose of 25 mg was necessary to reach the 0,05% alcohol equivalent. Even the equivalent concentration calculated supported the empirically based assumption that the fitting curve should be more concentrated and should essentially start immediately p.a. and being steeper during the elimination phase.

Promethazine 25 and 30 mg, time-dependent impairment (11 studies, 215 effects)

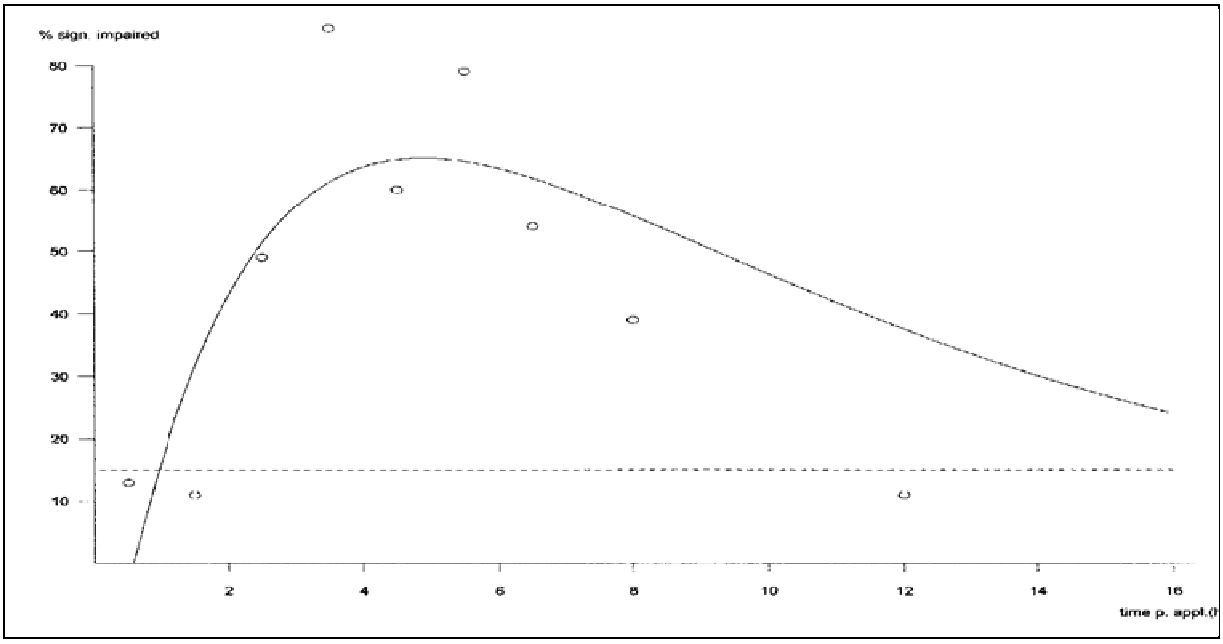

Figure 6: Promethazine 25 and 30 mg, time-dependent impairment.

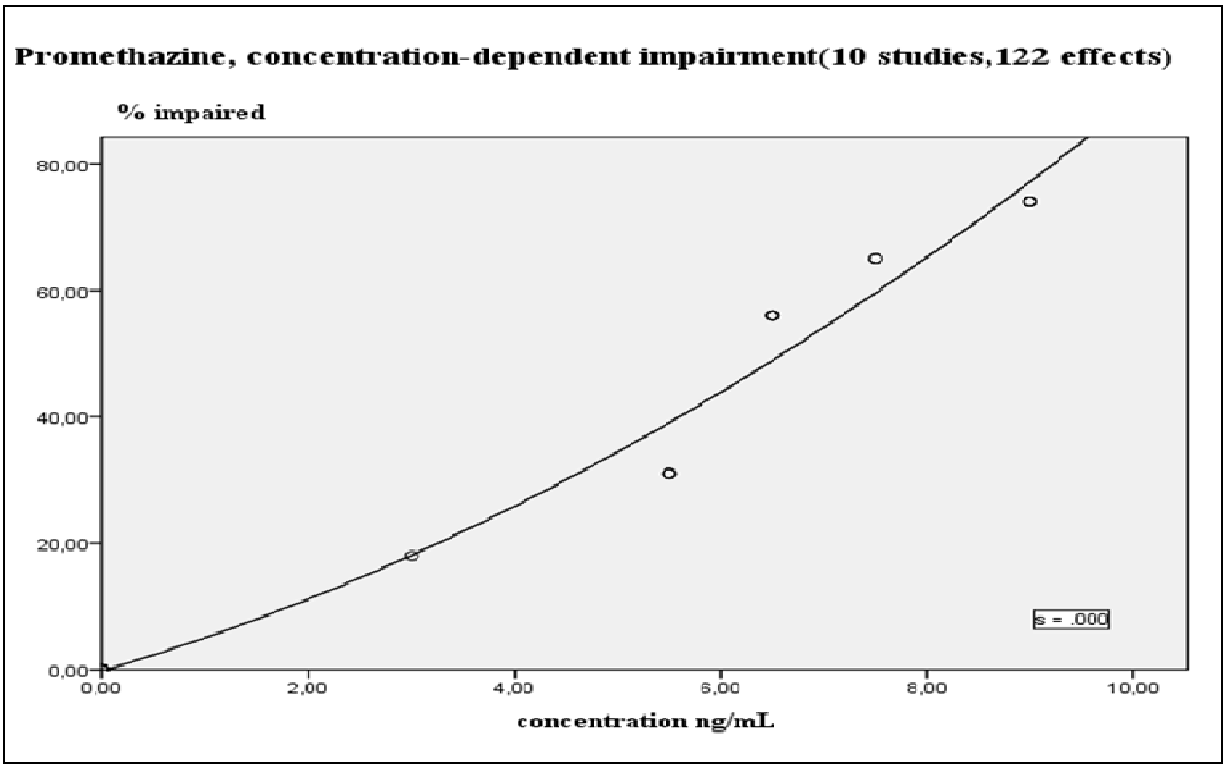

Figure 7: Promethazine, concentration-dependent impairment.

Table 10: Promethazine, summary of results.

Summary **Single administration**	***R06AD Phenothiazine derivates*** **R06AD02 Promethazine**
Number of studies	11
Number of effects	236
Checked doses (mg)	20 - 50
Recommended dose (mg)	25
Tabularly evaluable doses (mg)	25, 30
No. studies / no. effects	11 / 215
Max. sign. impaired test results (%)	(65) probably higher ((56 - 73))
Hour p.a. of maximum impairment	(5.0) probably earlier ((4.75 - 5.75))
Alcohol equivalence of max. imp. (%)	>0,08
Duration p.a. until <15% impairment (h)	(20.25) probably earlier ((20.25 - >24))
Degree of impairment	491 (405 - 880)
0,05% alcohol equ. (ng/mL)	4.5 (3.9 - 5.4)
% of max. rec. dose (mg)	53 of 25 (46 - 64)

Multiple administrations to healthy subjects

In contrast to the experiments with a single dose in healthy subjects in a study of Hindmarch and Parrott [1978] 10 subjects were administered 25 mg as an evening dose over a period of 4 days. Tests on the next morning revealed no statistically significant impairment.

Summary multiple administrations: No statistically significant impairment, but not enough data available.

Administration to patients

No studies on hand.

Summary multiple administrations: no data at hand

3.2.1.4 Comparison of Profiles N05A Antipsychotics

Single administration to healthy subjects

There is a clear distinction between the 3 agents we could analyze. Sulpiride is not associated with performance impairment. Of the two other agents haloperidol of dose 3 mg has by far fewer driving related performance deficits than promethazine of dose 25 or 30 mg. The comparison of all parameters calculated showed by far higher impairment for promethazine than for haloperidol. Whereas haloperidol has only a concentrated maximum of about 40% in a relatively short period of time, promethazine showed an extended time-range with essential deficits. Hence the degree of impairment of promethazine is about the five-fold of that of haloperidol. Only half of the recommended dose of promethazine is necessary to reach the 0,05% alcohol equivalent.

Multiple administrations to healthy subjects

In contrast to the single administration statistically significant impairment could not be found for any of the 3 agents investigated. However, this finding is due to the lack of enough data. There are only few studies on multiple administrations to healthy subjects. At least for haloperidol and promethazine impairment has to be expected in the initial phase of a treatment.

Table 11: Comparison of profiles: N05 Psycholeptics: N05A Antipsychotics.

Agent	***N05AD Butyrophenone derivates*** **N05AD01 Haloperidol**	***N05AL Benzamides*** **N05AL01 Sulpiride**	***R06AD Phenothiazine derivates*** **R06AD02 Promethazine**
Number of studies	10	8	11
Number of effects	228	86	236
Checked doses (mg)	.5 - 10	100 - 400	20 - 50
Recommended dose (mg)	1 - 20 / day	50 - 300 / day	25
Tabularly evaluable doses (mg)	3	400 *)	25, 30
No. studies / no. effects	5 / 82	5 / 73	11 / 215
Max. sign. impaired test results (%)	38 (31 - 44)	<10	(65) probably higher ((56 - 73))
Hour p.a. of maximum impairment	5.25 (5.0 - 5.25)	No	(5.0) probably earlier ((4.75 - 5.75))
Alcohol equivalence of max. imp. (%)	0,05 - 0,08	<0,03	>0,08
Duration p.a. until <15% impairment (h)	10.25 (8.5 - 11.5)	0	(20.25) probably earlier ((20.25 - >24))
Degree of impairment	93 (50 - 138)	0	491 (405 - 880)
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	too few effects only low correlation	not reached	4.5 (3.9 - 5.4) 53 of 25 (46 - 64)
Adaption	No stat. significant impairment, but not enough data available	No stat. significant impairment, but not enough data available	No stat. significant impairment, but not enough data available
Results in patients	Performance was improved during therapy, but performance deficits continue over weeks/months	No studies at hand	No studies at hand

*): no curve fitting due to minor impairment and too few effects

Administration to patients

Haloperidol improves the performance during therapy but performance deficits continue over weeks/months. This is most probably an effect of the underlying disease/psychosis. For sulpiride and promethazine we did not find appropriate studies on patients against healthy controls. Generally, it must be supposed that in particular in the initial phase of an antipsychotic medication driving ability is not given. Not before one or two weeks at the earliest, a steady state and stabilization can be expected. In these cases the driving ability has to be assessed in each single case in dependence on multiple influencing factors including not only the type and dosage of medication but also the development of psychosis and the personality of the patient.

In comparison to “typical” antipsychotic drugs (APDs), such as haloperidol, modern “atypical” antipsychotic drugs, such as clozapine, olanzapine, quetiapine and risperidone, provide a modest benefit to cognitive function in schizophrenic patients [meta-analyses of Woodward et al. 2005 and 2007, 41 studies]. The first meta-analysis that included only reports from comparisons of typical and atypical APDs that randomly assigned patients to treatment revealed that atypicals were superior to typicals at improving overall cognitive functions. Specific improvements were observed in the learning and processing speed domains. A second meta-analysis used all prospective studies regardless of whether or not participants were randomly assigned to treatment. Here, all cognitive domains demonstrated statistically significant improvement on atypical APD medications. There were several statistically significant differences between the above mentioned atypical APDs with regard to attention and verbal fluency. However, the authors regard these findings as preliminary and state that no medication with atypical APDs appeared superior or inferior to the other medications in overall cognitive function. They emphasize the small magnitude of the observed changes due to the medication with atypical APDs (0.2 to 0.4 standard deviations) in relation to the huge cognitive deficits of schizophrenic patients due to their disease (more than a standard deviation below healthy controls in most of the neuropsychological tests). Practice effects in cases of repeated testing may be seen as a problem [Goldberg et al. 2007: similar improvement in an APD group and a healthy control group]. However, study results indicate that the cognitive improvements under atypical APDs increase with the duration of the treatment (baseline, 6 weeks, 6 months) [Sharma 2003]. It must be mentioned, that a recently published great multicenter study with 817 schizophrenic patients [Keefe et al. 2007] could not demonstrate a benefit in neurocognition of modern atypical antipsychotic drugs

(olanzapine, quetiapine, risperidone) in comparison to the older generation (perphenazine) after 2 months and up to 18 months of treatment. After 2 months and 6 months all substances showed small cognitive improvements without statistically significant differences; after 18 months perphenazine was superior to olanzapine and risperidone. The authors suppose various reasons for their unusual study results such as the great number of patients, the lower dosage of "older" antipsychotics and minimal exclusion criteria ("real-world" features and no artificial study design).

In summary, it has to be considered that most of the patients suffering from schizophrenic or associated psychosis need neuroleptic treatment to achieve a (nearly) "normal" status which is almost always better than without medication even if side effects occur. In Germany, an acute episode or severe chronic status of schizophrenia is not compatible with driving ability and an adequate medication is the prerequisite for a positive assessment of driving ability.

3.2.2 N05B Anxiolytics

Anxiolytics – also called tranquilizers – are mainly used for the treatment of anxiety and mental stress. Furthermore, they serve as additional medication in acute mania and depression.

At present, the by far most frequently prescribed drugs from this class belong to the benzodiazepines. These benzodiazepines show rather similar pharmacodynamic properties, but differ considerably with regard to their pharmacokinetic characteristics. In particular the half-life and thus the action time varies. The classification of benzodiazepines used as anxiolytics includes the following main substances (see also chapter 3.2.3 on hypnotics/ sedatives):

- Intermediate half-life (6-24 h): oxazepam, lorazepam, bromazepam, alprazolam.
- Long half-life (>24 h): diazepam, chlordiazepoxide, clobazam.

The main risks result from the sedative side effects (main effect, see hypnotics) and the possible development of dependency.

The smaller group of "other anxiolytics" consists of meprobamate and buspirone. In Germany, meprobamate belongs to the list of narcotic drugs and its prescription is not allowed. Buspirone is the main "other" drug and is prescribed with an increasing frequency. It

has an intermediate action time and the effects are different from the benzodiazepines (delayed anxiolytic effect after ca. 10-14 days, no development of dependency).

3.2.2.1 N05BA04 Oxazepam

(N05BA Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

Overall 26 studies with 377 effects and doses tested between 10 mg and 90 mg could be selected as basis for the meta-analytic approach. A sufficient number of effects to construct an approximation curve to the empirical data were given for 15 mg and 30 mg.

Concerning the 15 mg dose a continuous panel of data was given up to the 6th hour p.a. After this time period there was measured only 1 effect in the 9th hour that showed no statistically significant decline. Usually we restrict from using data less than 10 effects for one time class, But since all effects for doses ≥30 mg at this period of time indicated no sole statistically significant impairment and in order to be able to fit an adequate curve we used the 0% for the 8th hour with respect to the value for the 30 mg dose. The curve-fitting illustrates the maximum impairment (41%) at the 2nd hour. About 8 hours p.a. the curve dropped below the 15% limit.

The time-dependent analysis for the 30 mg dose revealed statistically significant impaired effects up to 5 hours p.a. The maximum of the curve fitted was situated a little bit later than for the 15 mg dose and even the deficits were higher (52%). Hence the period of time till the 15% level was longer and the degree of impairment higher.

With respect to the concentration dependence for the period of time ≥2.5 hours p.a. we had to exclude one study as an outlier because almost all effects were not statistically significant impaired, contrary to all other studies. Without this study sufficiently high numbers of effects were to be seen up to 500 ng/mL. Thereafter only a single study tested performance under different concentrations. Therefore we calculated the linear curve-fitting without this study. The appropriate approximation (R^2 = .676) was not good (there was no hint for an outlier especially concerning the low value in category 400 ng/mL) so that the interpretation should be only cautiously. It showed the 30% limit at 330 ng/mL. This was in good agreement with the time-dependent analysis of 30 mg but according to the 360 ng/mL value the 15 mg curve should not have reached the 30% level.

Oxazepam 15 mg, time-dependent impairment (8 studies, 118 effects)

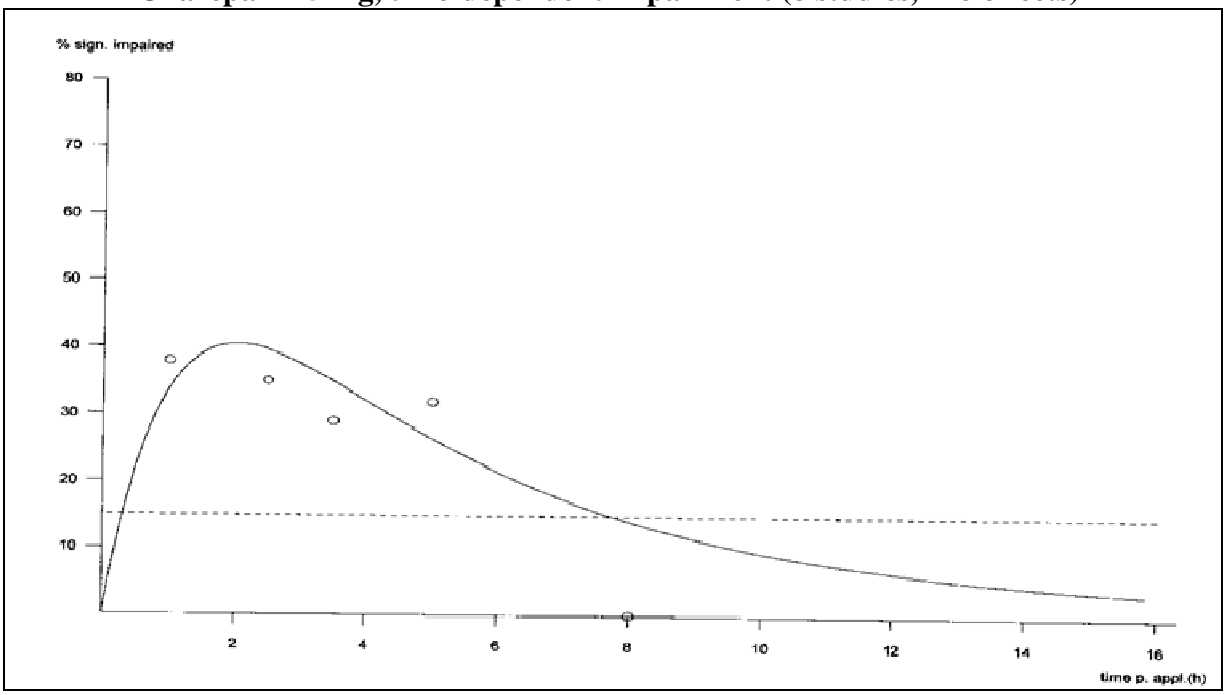

Figure 8: Oxazepam 15 mg, time-dependent impairment.

Oxazepam 30 mg, time dependent impairment (11 studies, 115 effects)

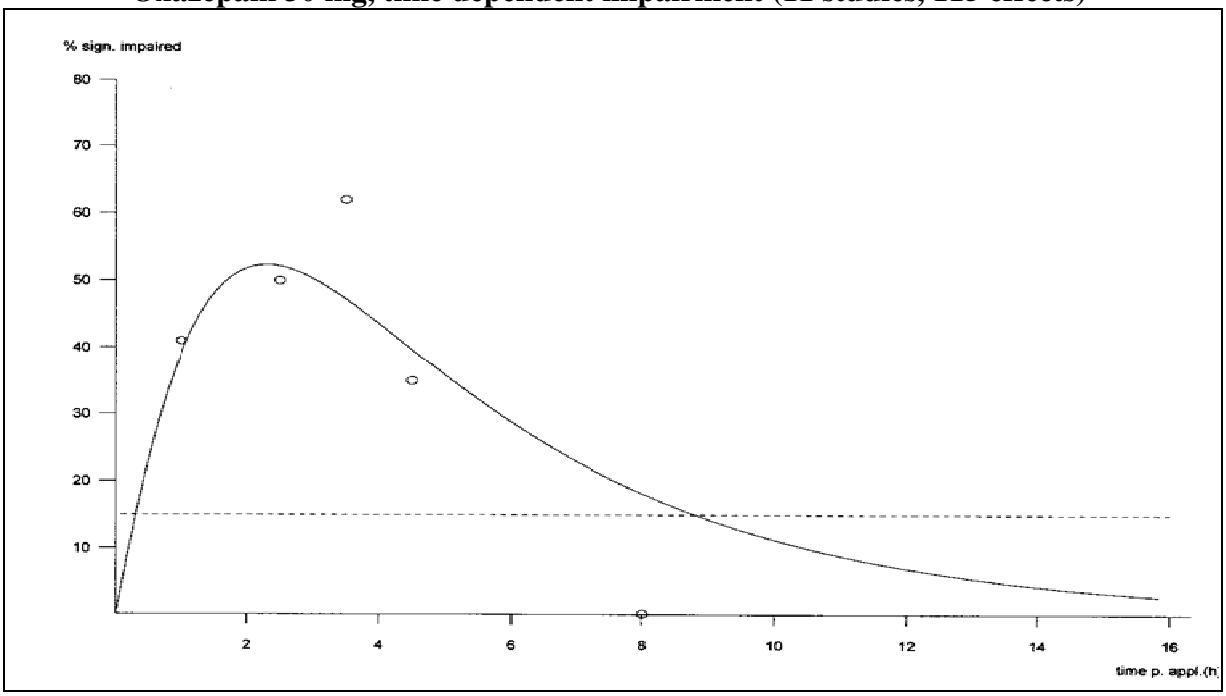

Figure 9: Oxazepam 30 mg, time-dependent impairment.

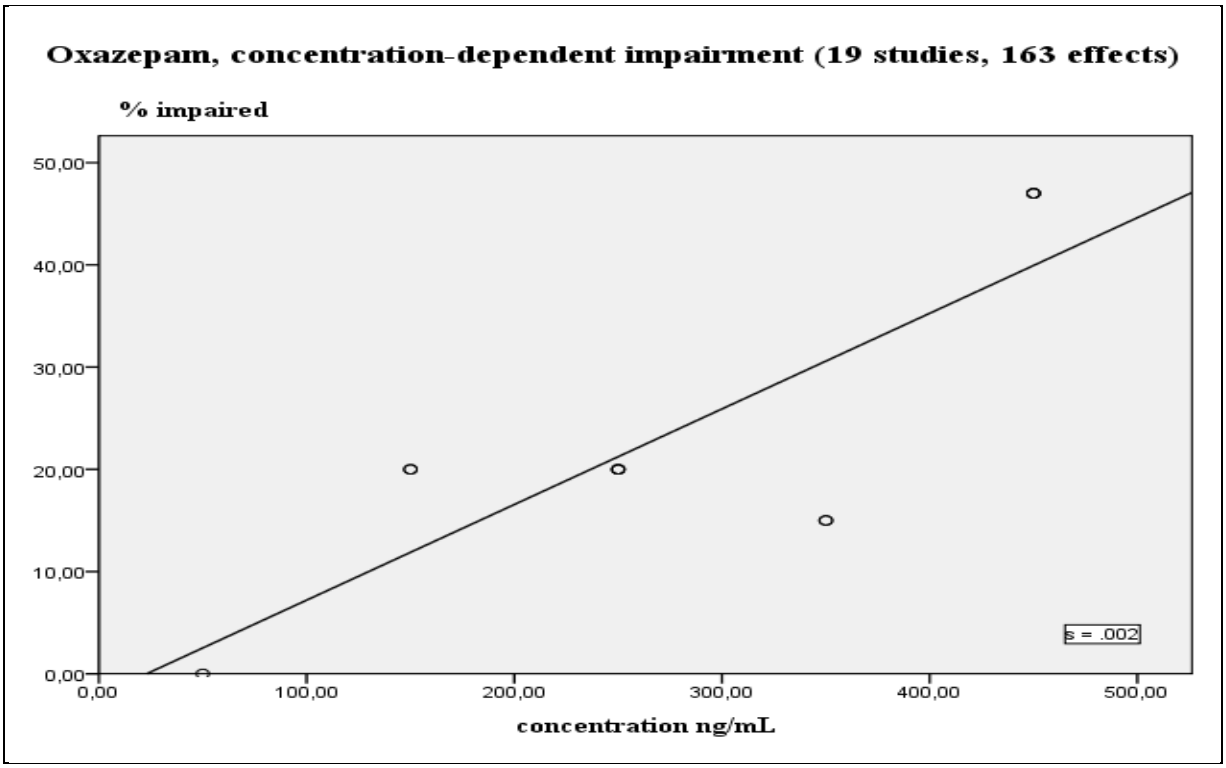

Figure 10: Oxazepam, concentration-dependent impairment.

Table 12: Oxazepam, summary of results.

Summary **Single administration**	**N05BA04 Oxazepam**	
Number of studies	26	
Number of effects	377	
Checked doses (mg)	10 - 90	
Recommended dose (mg)	10 - 30 / day	
Tabularly evaluable doses (mg)	15	30
No. studies / no. effects	8 / 118	11 / 115
Max. sign. impaired test results (%)	41 (34 - 46)	52 (46 - 61)
Hour p.a. of maximum impairment	2.0 (1.25 - 2.0)	2.25 (2.25 - 2.5)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08	>0,08
Duration p.a. until <15% impairment (h)	7.75 (7.75 - 11.5)	9.0 (9.0 - 10.0)
Degree of impairment	104 (89 - 121)	170 (142 - 235)
0,05% alcohol equ. (ng/mL)	(330) ((300 - 390))	
% of max. rec. dose (mg)	(218) of 10 ((199 - 258))	

Multiple administrations to healthy subjects

Multiple administrations of oxazepam in various studies demonstrated the development of tolerance towards performance reducing effects, however, there was no complete restitution and the primary level of performance could not be reached again. The testing period lasted up to 3 weeks. The placebo level was observed not before termination of oxazepam treatment. The results were gained in both psychophysical tests and driving tests [Ghoneim et al. 1986, Lilequist et al. 1979, Laurell and Törnros 1986, Hindmarch et al. 1990, Volkerts et al. 1992 and 1993, van Laar et al. 1993].

Summary multiple administrations: Development of tolerance after weeks, but impaired performance compared to placebo level.

Administration to patients

Only few data were available. Evening doses of oxazepam (15 mg or 30 mg) for 5 days or 7 days, respectively, did not cause impairment in tests on the following morning/day. Only the reaction time could be impaired [Feldmeier and Kapp 1983, Fischbach 1983, Bliwise et al. 1984].

Summary patients: No sufficient data, apparently slight impairment.

3.2.2.2 N05BA06 Lorazepam

(N05BA Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

68 studies with 1244 effects and doses tested between .5 mg and 9.0 mg could be integrated in the analysis. Sufficient numbers of effects to built up a time-dependent impairment curve were on hand for doses 1, 2 and 2.5 mg.

The impairment curve for 1 mg lorazepam just reached the 30% level after about 2 hours p.a. Accordingly to the relatively high empirical value for the 4th hour p.a. the curve runs a little bit higher than the empirical values for 5 hours and later p.a. The 15% level was crossed 7.5 hours p.a.

As expected, the fitted curves for 2 and 2.5 mg run essentially higher than the 1 mg curve. The maximum impairment for both doses was about 80% and was reached in the 4th hour p.a. But times till the crossing of the 15% level were different (12.5 hours for 2 mg versus 19.75 hours for 2.5 mg) and consequently the degree of impairment was higher for 2.5 mg.

Concerning the concentration-dependent impairment we analysed the data after the concentration maximum 3.0 hours p.a. Up to a concentration of 30 ng/mL the 5 ng/mL concentration classes presented adequate numbers of studies and effects. Because higher doses up to 63 ng/mL were tested only in 2 studies of which one study stood for 28 of the 36 effects measured (almost all effects were statistically significant impaired) and because the number of effects were too low for the different concentration classes we did not include these 2 studies when calculating the linear approximation. The curve fitting (R^2=.834) revealed a concentration of 9 ng/mL equivalent to the 0,05% alcohol impairment. This limit concentration was in good agreement with the 30% lines of the different time-dependent approximations.

Lorazepam 1 mg, time-dependent impairment (18 studies, 175 effects)

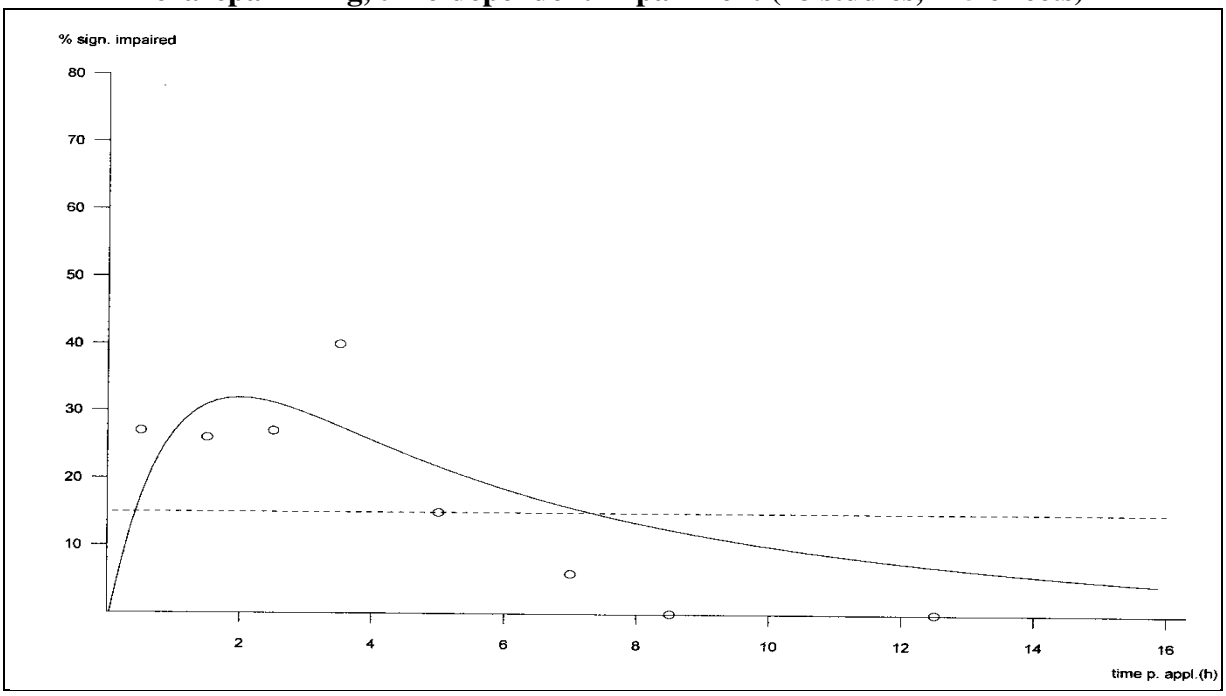

Figure 11: Lorazepam 1 mg, time-dependent impairment.

Lorazepam 2 mg, time-dependent impairment (32 studies, 425 effects)

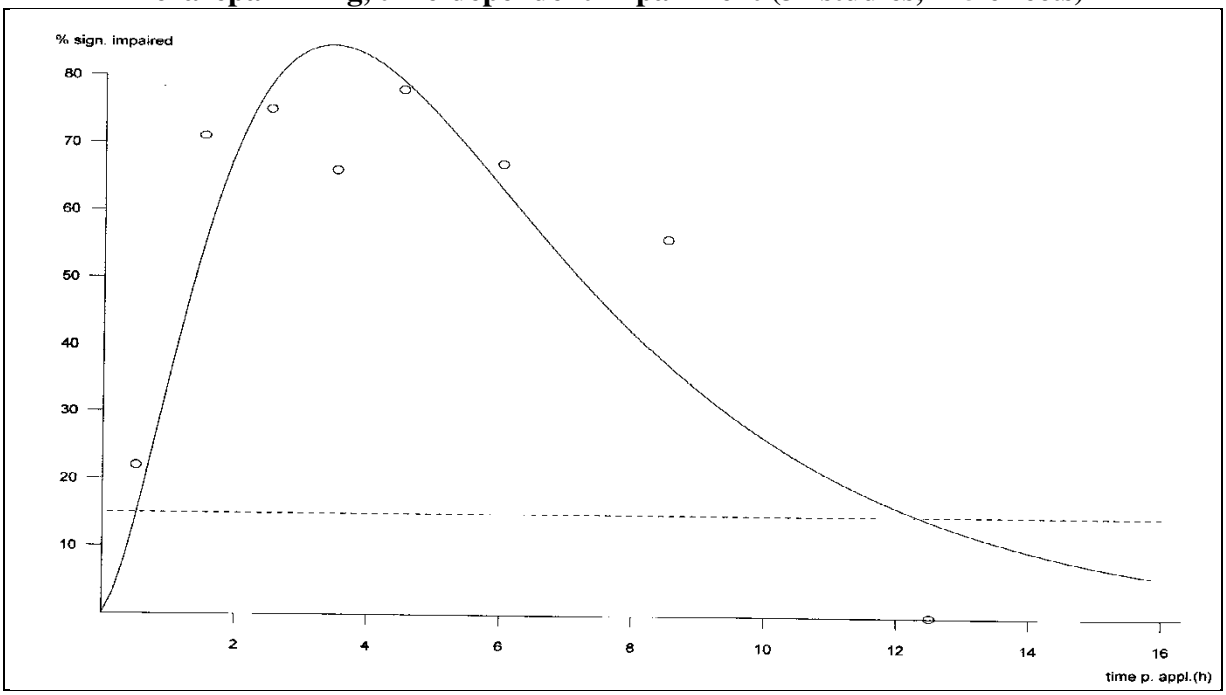

Figure 12: Lorazepam 2 mg, time-dependent impairment.

Lorazepam 2.5 mg, time-dependent impairment (26 studies, 269 effects)

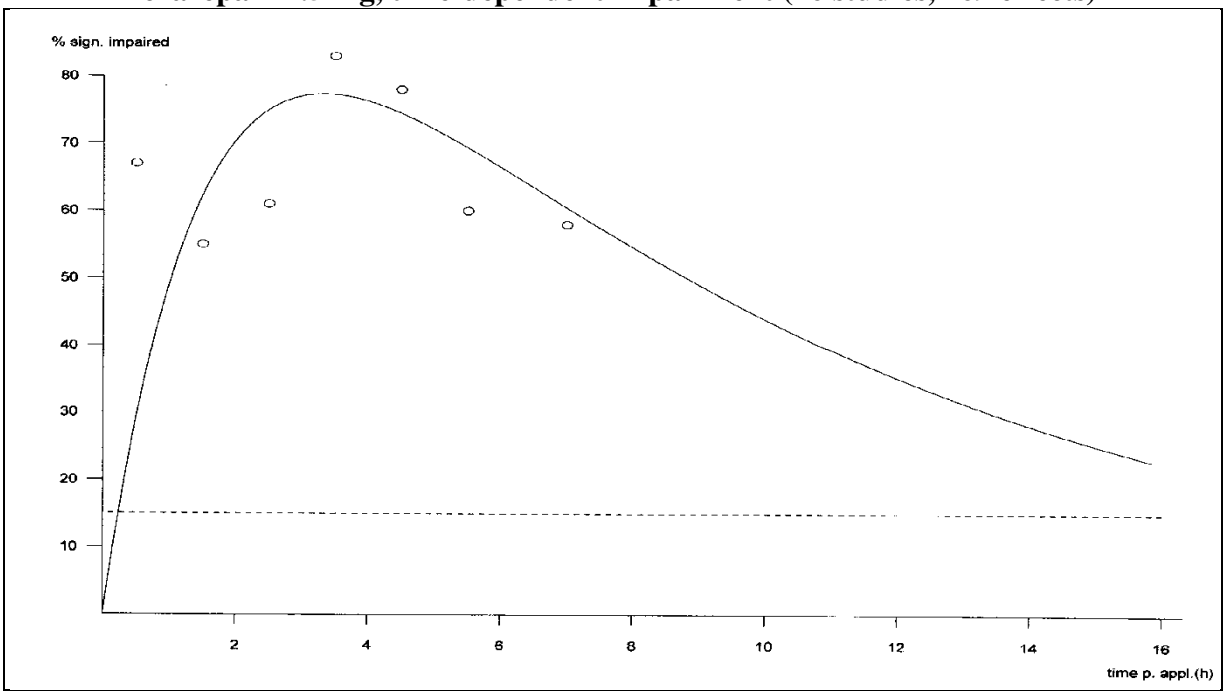

Figure 13: Lorazepam ,2.5 mg, time-dependent impairment.

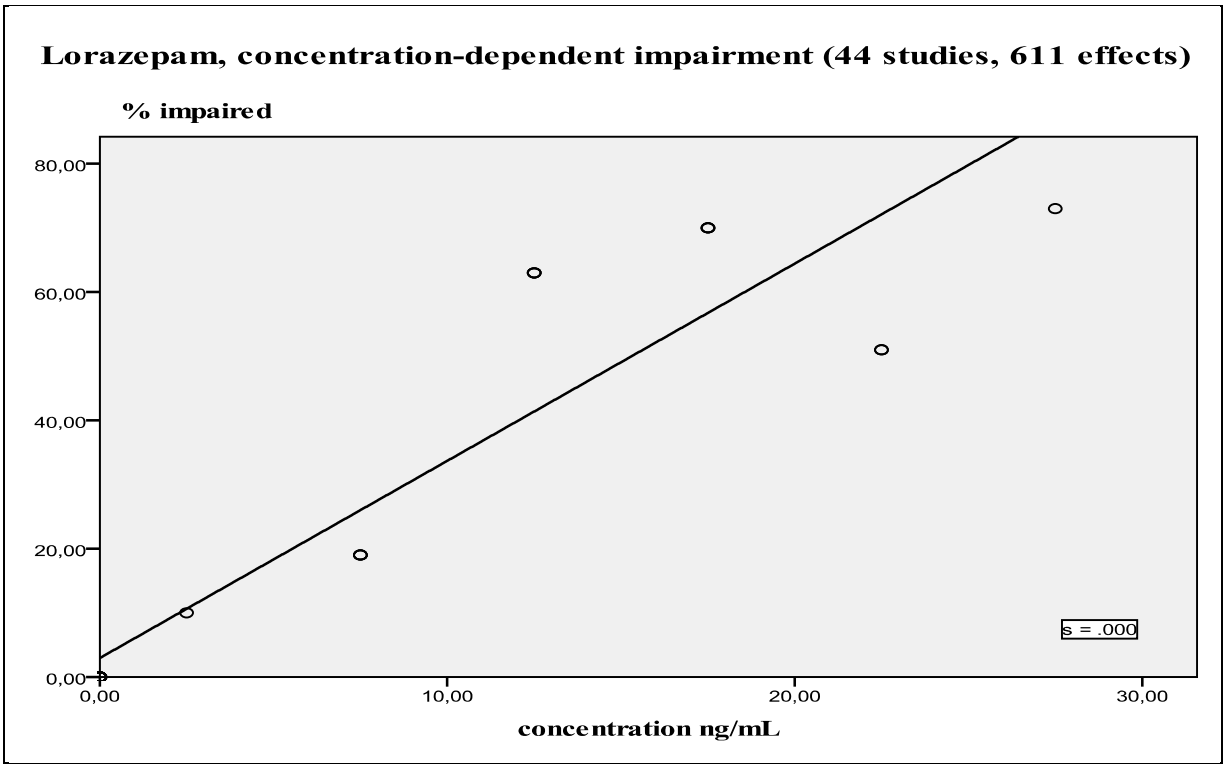

Figure 14: Lorazepam, concentration-dependent impairment.

Table 13: Lorazepam, summary of results.

Summary **Single administration**	**N05BA06 Lorazepam**		
Number of studies	68		
Number of effects	1244		
Checked doses (mg)	0.5 - 9.0		
Recommended dose (mg)	0.5 - 2.5 / day		
Tabularly evaluable doses (mg)	1	2	2.5
No. studies / no. effects	18 /175	32 / 425	26 /269
Max. sign. impaired test results (%)	32 (26 - 40)	85 (70 - 87)	77 (69 - 85)
Hour p.a. of maximum impairment	2.0 (1.25 - 2.25)	3.5 (3.0 - 3.75)	3.25 (3.25 - 3.75)
Alcohol equivalence of max. imp. (%)	0,03 - 0,05	>0,08	>0,08
Duration p.a. until <15% impairment (h)	7.5 (5.75 - 8.0)	12.5 (12.5 - >24)	19.75 (19.75 - >>24)
Degree of impairment	64 (33 - 94)	418 (418 - 707)	571 (527 - 951)
0,05% alcohol equ. (ng/mL)	9 (8 - 10)		
% of max. rec. dose (mg)	126 of 1 (112 - 140)		

Multiple administrations to healthy subjects

There are relatively numerous papers on this substance. Some of them are quoted more detailed in the following. In summary, there is no complete restitution to be expected, but the performance after multiple administrations within a time interval of several days to ca. 1 week is much better than after single administration although the plasma concentrations are reported to be much higher. However, there are still deficits in driving tests after 7 or 8 days of permanent therapy. As it could be expected, the time interval of performance limitations is dependent on the dose (1-6 mg/day) and the time interval between administration and testing (no impairment after 24 hours or more) [Berghaus 1997].

The first administration of lorazepam 2 mg within a 1-week-administration caused marked disturbances of body sway, no changes of the postural sway were noticed 10 hours after the last dose of 1 week's treatment; the effect was stronger than with bromazepam or clobazam [Patat and Foulhoux 1985]. The administration of lorazepam 1 mg twice per day for one week statistically significant increased the reaction time in the beginning, but not in the further course, when daily measurements in healthy male volunteers were conducted on the following morning, at least 9 hours after the last dose [Jurado et al. 1989]. In a 5-day treatment and daily testing of healthy students, lorazepam between 0.5 and 1.5 mg per day did not influence the free recall test and the critical flicker fusion frequency test, but produced statistically significant improvement on the digit symbol substitution test and the choice reaction time test; the improvement occurred around the presumed steady-state plasma lorazepam concentration (day 3); thus, low repeated doses of lorazepam in healthy subjects seemed to improve the psychomotor performance without sedation [Bourin et al. 1994]. Lorazepam 2 mg twice daily for one week statistically significant impaired most of the tested psychomotor functions in healthy male volunteers on day 1, but then after 7 days lorazepam had few psychomotor effects due to the development of tolerance [Vanakoski et al. 2001].

Summary multiple administrations: Marked improvement within 1 week, but no complete tolerance.

Administration to patients

There are a lot of papers on this topic. On the whole, there are hints of a development of tolerance in chronic users, but the placebo level is not always reached and in particular in higher doses an impairment is to be expected up to at least 1 week or longer, also in driving tests [Walsh et al. 1983, O'Hanlon et al. 1995]. If administered a usual evening dose of up to 2 mg, no hang-over effect could be observed neither in single nor in permanent treatment

[McClure et al. 1988, Bonnet and Arand 1999, Saletu et al. 1997]. In an investigation on the development of tolerance in chronic users of lorazepam (1-20 years), there was a clear indication of such a tolerance in comparison with healthy control persons [van Steveninck et al. 1997].

Summary patients: Improvement of performance, but presence of permanent impairment in higher doses possible.

3.2.2.3 N05BA08 Bromazepam

(N05BA Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

Only 9 studies with 202 effects measured and doses between 1.5 and 12 mg could be found for bromazepam in spite of an intensive searching. In addition the material was dominated by 2 research groups that accounted for 162 effects. One of these groups had to be eliminated because all effects were not statistically significant changed even though the measurements were carried out at concentrations at which all other studies showed essential performance deficits. Without the research group excluded there was no dose with a sufficient number of effects to calculate meaningfully a curve fitting. Nevertheless the data were homogeneous. At low doses (1.5 mg) there was no deficit, at 3 mg marginal deficit. At 6 and 12 mg statistically significant impaired effects concentrated in the 2nd and 3rd hour p.a.

It was not meaningful to calculate a concentration-dependent curve fitting since only 92 effects of the after maximum time span (≥1.5 h) were on hand of which 72 effects came from one research group.

It goes without saying that all mentioned information on bromazepam should be treated with caution due to the small data base.

Table 14: Bromazepam, summary of results.

Summary **Single administration**	**N05BA08 Bromazepam**	
Number of studies	9	
Number of effects	202	
Checked doses (mg)	1.5 - 12	
Recommended dose (mg)	3 - 6 / day	
Review doses (mg)	6 *)	12 *)
No. studies / no. effects	4 / 33	3 / 31

Max. sign. impaired test results (%)	(45)	(ca. 75)
Hour p.a. of maximum impairment	(2)	(2 - 3)
Alcohol equivalence of max. imp. (%)	(0,05 - 0,08)	(>0,08)
Duration p.a. until <15% impairment (h)	(3)	no data
Degree of impairment	too few effects	
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	too few effects	

*): no curve fitting due to too few effects

Multiple administrations to healthy subjects

As it was expected, the degree of impairment depended on doses administered. Lower doses up to 3 mg for 8-15 days did not cause statistically significant deficits [Hobi et al. 1981 and 1982, Hindmarch et al. 1990]. The first administration of bromazepam 6 mg within a 1-week-administration caused an increase of the posturographic parameters (body sway), no changes of the postural sway were noticed 10 hours after the last dose of 1 week's treatment; the effect was between that one of lorazepam and clobazam [Patat and Foulhoux 1985]. However, in courses with higher doses up to 18 mg/day complete tolerance was not observed even after longer treatment (1-2 weeks) [Liljequist et al. 1975, Saario 1976, Schaffler and Klausnitzer 1989, Münte et al. 1996].

Summary multiple administrations: No deficits following lower doses, but no complete tolerance with higher doses (at least weeks).

Administration to patients

In comparison to Clobazam 10 mg Bromazepam 15 mg showed no increase of flicker fusion [Ponciano et al. 1981].

Summary patients: Too few data to estimate impairment.

3.2.2.4 N05BA12 Alprazolam

(N05BA Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

As to alprazolam we could gather 21 studies describing 354 effects under doses between .25 and 2.0 mg. Only the 1 mg dose showed a sufficiently high number of effects to calculate a curve fitting.

The impairment curve of the 1 mg dose climbed up to its maximum of about 74% statistically significant reduced effects within 2 hours. Hence the maximum of dynamics corresponded to the maximum of kinetics. It took about 14 hours till the percentage of impairment went below the 15% limit.

The computer aided design of the concentration-dependent impairment curve used effects that were measured after the concentration maximum 2.0 hours p.a. The linear approximation (R^2 = .961) indicated the 0,05% alcohol equivalent at a concentration of 9 ng/mL. This value agreed completely with the limit constructed on the basis of the time-dependent curve. The time-dependent curve crossed the 30% level during the elimination phase at about 9.25 hours p.a. According to the kinetics a concentration of 9 ng/mL existed at this point of time.

Alprazolam 1 mg, time-dependent impairment (11 studies, 130 effects)

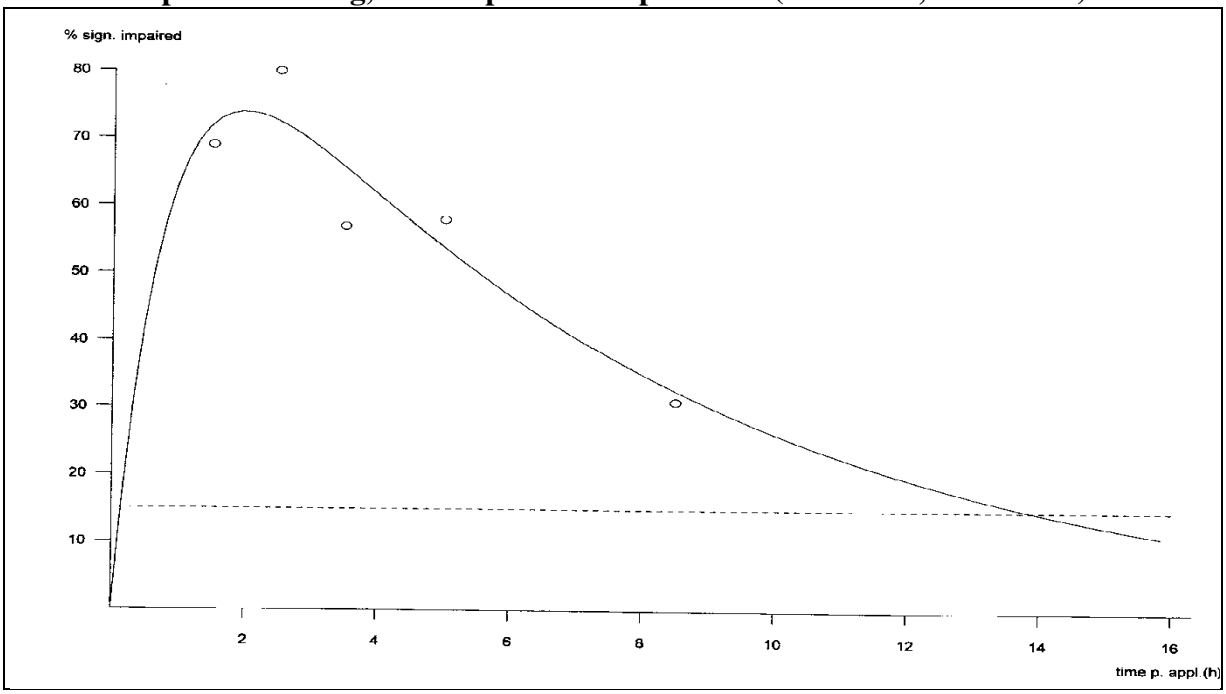

Figure 15: Alprazolam 1 mg, time-dependent impairment.

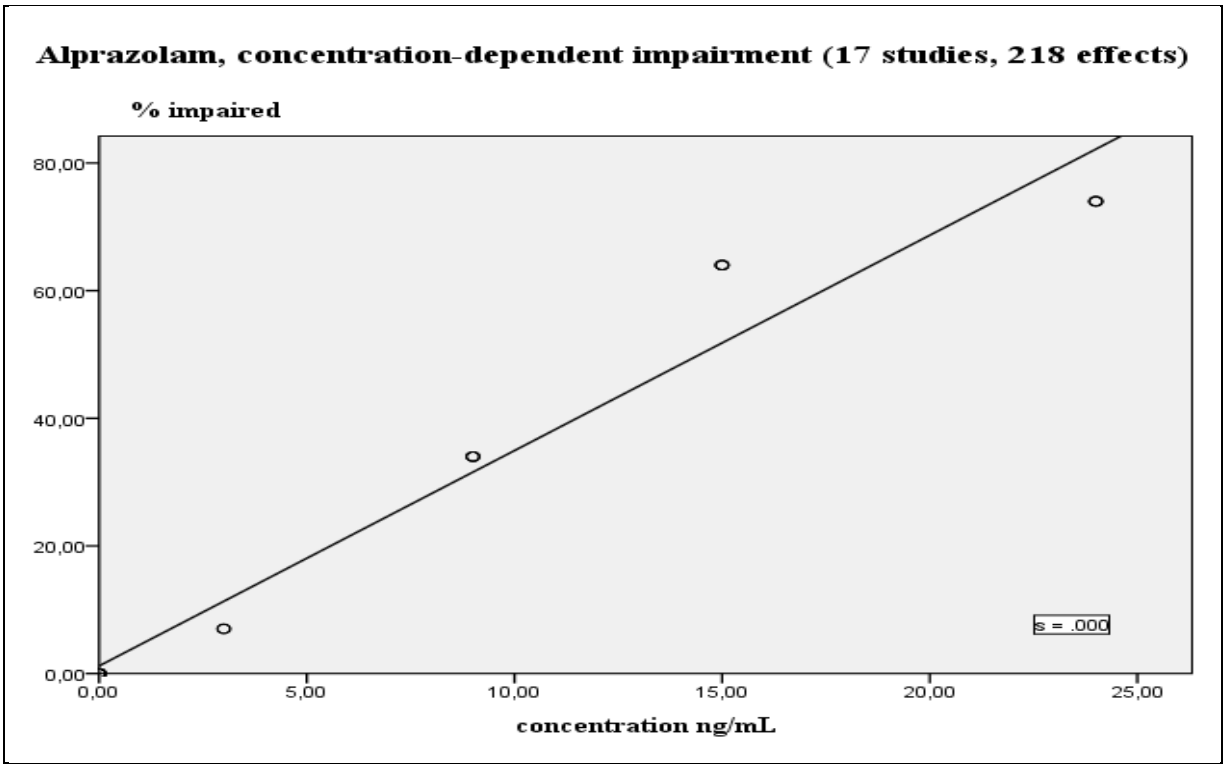

Figure 16: Alprazolam, concentration-dependent impairment.

Table 15: Alprazolam, summary of results.

Summary **Single administration**	**N05BA12 Alprazolam**
Number of studies	21
Number of effects	354
Checked doses (mg)	0.25 - 2.0
Recommenden dose (mg)	0.75 - 1.5 / day
Tabularly evaluable doses (mg)	1
No. studies / no. effects	11 / 130
Max. sign. impaired test results (%)	74 (65 - 85)
Hour p.a. of maximum impairment	2.0 (1.75 - 2.0)
Alcohol equivalence of max. imp. (%)	>0,08
Duration p.a. until <15% impairment (h)	14.0 (11.5 - 16.0)
Degree of impairment	369 (262 - 480)
0,05% alcohol equ. (ng/mL)	9 (8 - 10)
% of max. rec. dose (mg)	118 of 0.50 (105 - 132)

Multiple administrations to healthy subjects

The data available give evidence of a development of tolerance, in particular in younger people. Within one week only little performance deficits persisted at various doses from 0.75 to 2.25 mg/day when compared to placebo (Hindmarch and Gudgeon 1980, Aranko et al. 1985, Subhan et al. 1986, Jurado et al. 1989, Allen et al. 1991). Even in higher doses (4 mg/day), tolerance could be observed after 3-4 days of treatment [Lasher et al. 1991, Smith and Kroboth 1987]: several test parameters were not different from placebo, sedation was markedly reduced despite doubling of concentrations.

Summary multiple administrations: Marked tolerance after several days, persistence of minor deficits up to 1 week.

Administration to patients

There are too few data on patients. One study with anxiety patients [Danjou et al. 1992] found sedation, tiredness and impaired performance shortly (2.5 h) after the first dose of alprazolam 0.75 mg.

Summary patients: Too few data to estimate impairment.

3.2.2.5 N05BA01 Diazepam

(N05BA Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

As to anticipate, most of the publications dealing with experimental studies on effects of agents on performance existed for diazepam because many studies with other agents used diazepam as a positive control. Overall 103 studies describing 2104 effects built up the basis of our meta-analytic approach to diazepam but there are far more experimental studies on diazepam which were not integrated for reasons we mentioned in chapter 2 “material and method”. Doses between 5 mg and 40 mg were tested. Doses 5, 10, 15 and 20 mg emerged with more than 250 effects each whereas the other doses showed maximal numbers of effects of about 50. Due to the multitude of studies and effects the data are quite homogeneous and demonstrate some typical facts concerning the correlation between ascending doses and concentrations and the degree of impairment.

Concerning the time-dependent analysis on 5 mg and 10 mg we had to exclude one study with above average numbers of s statistically ignificant impaired effects in relation to the other

studies with a comparable design (dose, time of starting the performance tests). In addition for the 10 mg dose 9 effects measured in the 10th hour p.a. had to be eliminated due to the high percentage of impaired effects contrary to the time span before the 10th hour and after the 10th hour.

The curve fitting to the empirical data was in general satisfying and the results illustrated very fine the increasing deficits with ascending doses. The maximum of impaired test results climbed from 23% for 5 mg to 74% for 20 mg, the degree of impairment from 17 to 171 and the alcohol equivalent from 0,03-0,05 to >0,08%. Even the duration p.a. till the 15% level increased from 4.5 hours to 6.25 hours p.a. whereas the hour of maximum impairment concentrated about 1 hour p.a. for all doses.

Concerning the concentration-dependent impairment we analysed the data after the concentration maximum ≥1 hour p.a. Up to 700 ng/mL there was a continuous and high frequency of empirical data to calculate the approximation. The linear curve-fitting (R^2 = .979) approximated the data very closely. The 30% level was calculated at 320 ng/mL. With regard to the volatility of the kinetics this value is in good agreement with the 30% thresholds derived from the time-dependent curve fittings: the impairment curve for 5 mg did not reach the 30% level and for doses 10, 15, 20 mg the appropriate values were 270, 330 and 360 ng/mL.

Even if there are metabolitesof diazepam the results could be explained exclusively by the effects of diazepam itself.

Diazepam 5 mg, time-dependent impairment (36 studies, 333 effects)

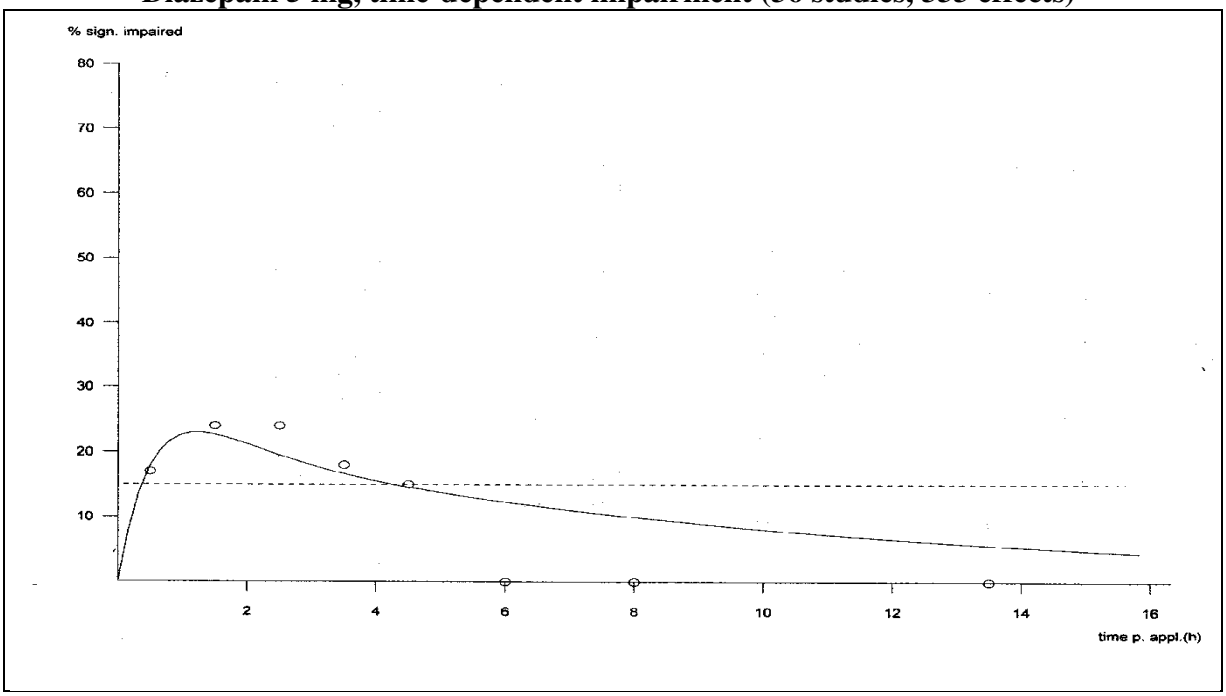

Figure 17: Diazepam 5 mg, time-dependent impairment.

Diazepam 10 mg, time-dependent impairment (53 studies, 756 effects)

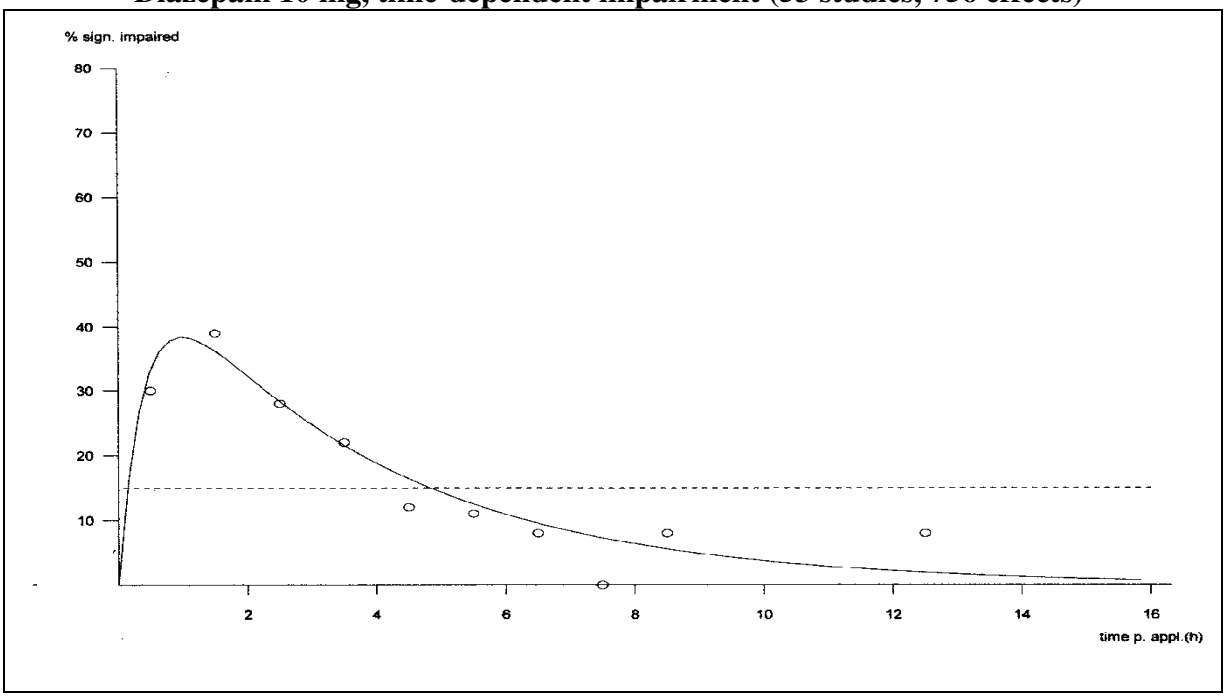

Figure 18: Diazepam 10 mg, time-dependent impairment.

Diazepam 15 mg, time-dependent impairment (18 studies, 444 effects)

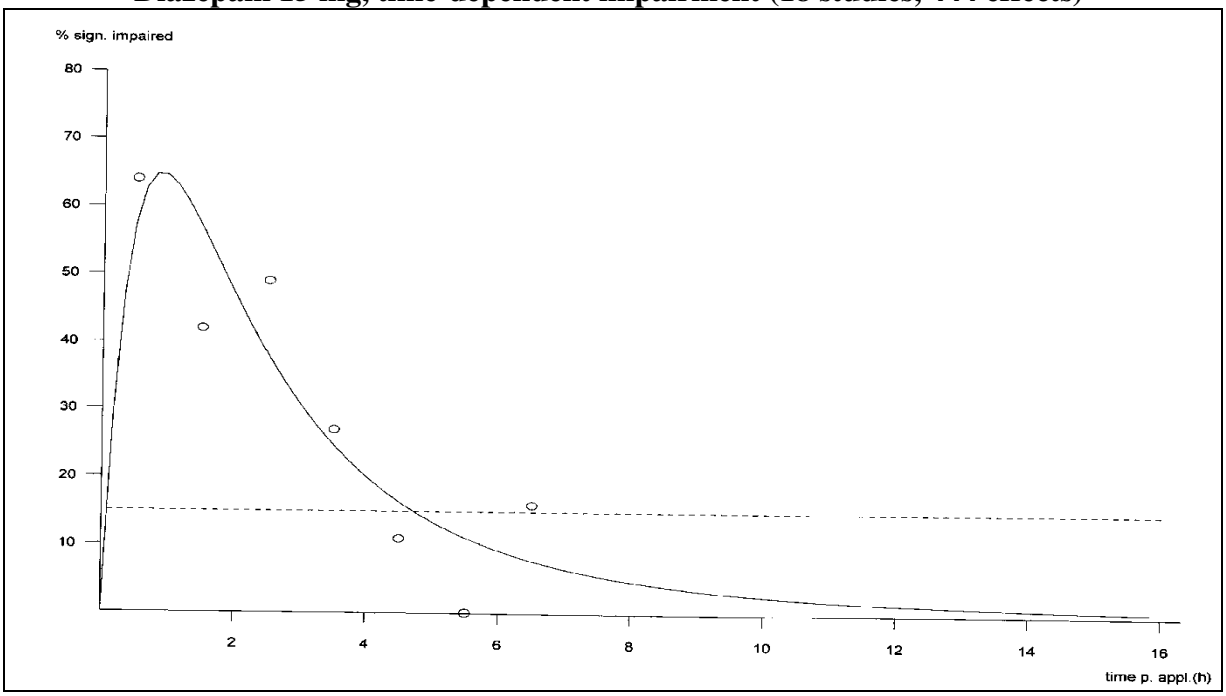

Figure 19: Diazepam 15 mg, time-dependent impairment.

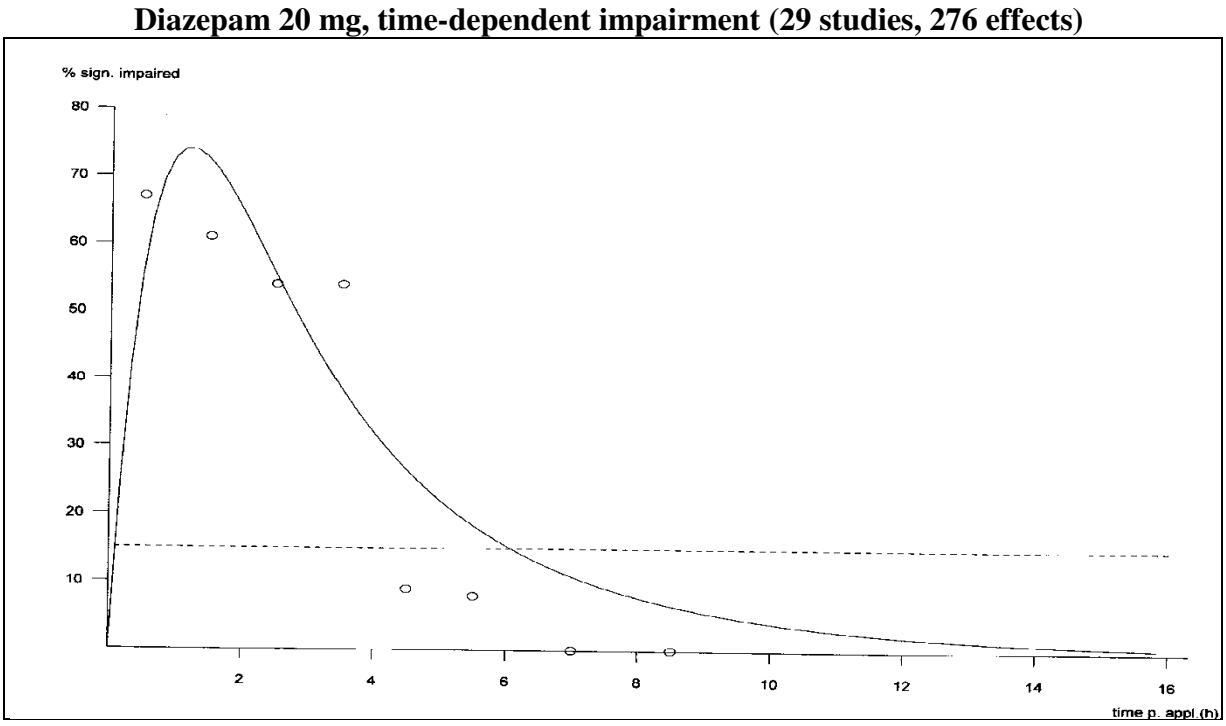

Figure 20: Diazepam 20 mg, time-dependent impairment.

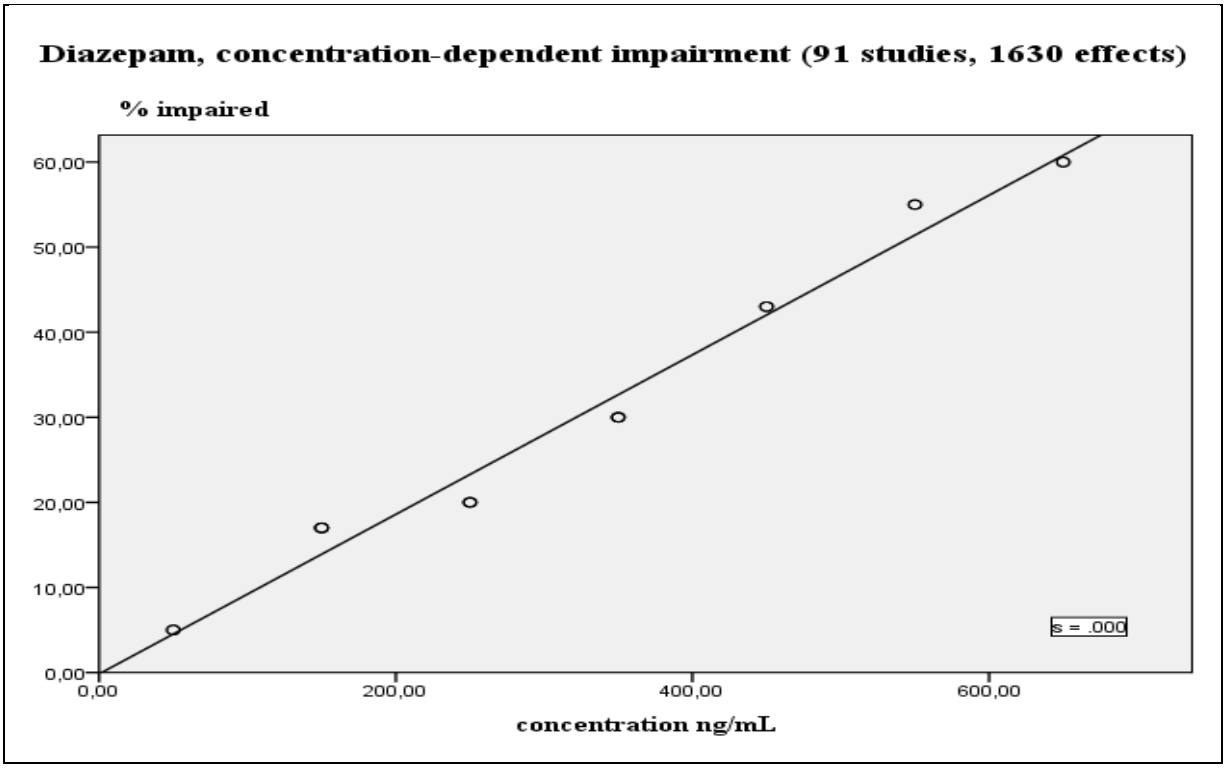

Figure 21: Diazepam, concentration-dependent impairment.

Table 16: Diazepam, summary of results.

Summary **Single administration**	**N05BA01 Diazepam**			
Number of studies	103			
Number of effects	2104			
Checked doses (mg)	2 - 40			
Recommended dose (mg)	5 - 20 / day			
Tabularly evaluable doses (mg)	5	10	15	20
No. studies / no. effects	36 /333	53 / 756	18 / 444	29 / 276
Max. sign. impaired test results (%)	23 (21 - 26)	38 (35 - 40)	64 (57 - 70)	74 (62 - 82)
Hour p.a. of maximum impairment	1.25 (1.25 - 1.25)	1.0 (1.0 - 1.25)	0.75 (0.5 - 1.0)	1.25 (1.0 - 1.25)
Alcohol equivalence of max. imp. (%)	0,03 - 0,05	0,05 - 0,08	>0,08	>0,08
Duration p.a. until <15% impairment (h)	4.5 (3.25 - 6.5)	5.0 (4.25 - 7.75)	4.75 (4.5 - 5.75)	6.25 (6.25 - 7.25)
Degree of impairment	17 (11 - 36)	57 (44 - 84)	112 (88 - 135)	171 (142 - 211)
0,05% alcohol equ. (ng/mL)	320 (290 - 370)			
% of max. rec. dose (mg)	97 of 10 (88 - 112)			

Multiple administrations to healthy subjects

Similar to the single administration there were on hand a considerable number of studies on the multiple administration of diazepam under various conditions (dose, types of tests, time interval between administration and tests etc.). Two reviews reported the following quintessence: Among 23 studies with 172 test results up to a treatment interval of 1 week (daily dose 6-30 mg), no dependence on the dose could be stated. The percentage of statistically significant impaired test results was between 41% (2 h after application) and 0% (after 24 h), on an average around 29%. Among further 5 studies with 56 test results with a treatment period between 1 week and 1 month (daily dose 10-15 mg), the percentage of statistically significant impaired test results was still between 26 and 50% (ca. 4 h after application), the average was again 29%. These results demonstrated that even after long-term administration statistically significant performance impairments have to be considered [Berghaus 1997]. Correspondingly, complete tolerance towards impairing effects cannot be

expected, at least not within one week and probably even not within one month [Berghaus 1997].

Summary multiple administrations: Improvement in the first week, but no complete tolerance. Impairment always possible (>1 month).

Administration to patients

The above mentioned aspects for multiple administrations to healthy subjects seemed also to be valid for patients. In anxiety patients a long-lasting reduction of performance is to be considered. After 2 to 4 weeks of treatment a tendency of minor impairment was observed (daily doses of 3 x 5 mg and 3 x 10 mg) [Lutz et al. 2003]. In comparison to patients without treatment (placebo) the results were heterogeneous, but mainly there were performance deficits in psychophysical tests and driving tests (5 mg-30 mg/day, 2-4 weeks of treatment) [Berghaus 1097].

In comparison to healthy persons there was a higher error rate in driving tests (single dose of 10-20 mg) [deGier et al. 1981].

Summary patients: Delayed performance deficits over weeks and possibly months.

3.2.2.6 N05BA02 Chlordiazepoxide

(N05BA Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

Overall only 9 studies with 101 effects could be analysed for chlordiazepoxide. Doses between 10 and 60 mg were explored. The 10 mg dose dominated clearly with 76 effects measured whereas all other doses only emerged with 25 effects. Unfortunately the results were very heterogeneous. On the one hand, contrary to other agents, 7 test results of different dosages were statistically significant positive. On the other hand the impairment concentrated on the 10 mg dose. Whereas for the 10 mg dose deficits could be presented for 6 hours that means for all hours in which effects were measured, for doses >10 mg only the first hour illustrated some statistically significant impaired effects (2 of 8). The amount of deficits for the 10 mg dose ranged in essence between 9 and 17% (1., 2., 3., 5. hour) whereas there was a deficit of 0% for the 4^{th} and 38% for the 6^{th} hour with at most cell numbers of about 10 effects.

Even the concentration-dependent analysis of effects measured during the after maximum time ≥1.75 h p.a. was strange: 16% of 44 tests measured under concentrations of up to 600 ng/mL were statistically significant impaired whereas 0 of 9 effects measured under concentrations of >600 ng/mL were affected.

The results of chlrodiazepoxid may be determined on the one hand on the few data available but on the other hand on the kinetics that means the metabolite demoxepam. Chlordiazepoxide itself has its maximum concentration about 1.75 hour p.a. and then the concentration declines slowly. In contrast, demoxepam climbs up till 13 hours p.a. Hence the measurement of the chlordiazepoxide concentration will not comprise the impairment dynamics.

Table 17: Chlordiazepoxide, summary of results.

Summary **Single administration**	**N05BA02 Chlordiazepoxide**
Number of studies	9
Number of effects	101
Checked doses (mg)	10 - 60
Recommended dose (mg)	maximal 60 /day
Tabularly evaluable doses (mg)	10 *)
No. studies / no. effects	5 / 76
Max. sign. impaired test results (%)	probably <30
Hour p.a. of maximum impairment	not assignable
Alcohol equivalence of max. imp. (%)	probably 0,03 - 0,05
Duration p.a. until <15% impairment (h)	not assignable
Degree of impairment	not assignable
0,05% alcohol equ. (ng/mL)	not assignable
% of max. rec. dose (mg)	

*): no curve fitting due to too few effects and metabolite demoxepam

Multiple administrations to healthy subjects

There is evidence of slighter impairment in subjects with multiple administrations. In 6 studies with 44 test results and a treatment period up to 1 week (daily dose 10-40 mg), only 4 effects were statistically significant impaired. Similarly, in 3 studies with 17 test results and a treatment interval between 1 week and 1 month (daily dose up to 30 mg), only 2 results were statistically significant impaired [Berghaus 1997].

Summary multiple administrations: Minor impairment up to 1 month.

Administration to patients

No data on hand (statistically significant impairment not probable due to known profile).

Summary patients: No data on hand. Impairment not probable.

3.2.2.7 N05BA09 Clobazam

(N05BA Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

16 studies with 287 effects and doses between 10 and 60 mg could be integrated in the analysis. A sufficient number of effects to try to build up a time-dependent impairment curve were given for 10 and 20 mg. But since there were only a few effects impaired (10 mg) or since the results probably were influenced by metabolites (20 mg) a curve fitting was not meaningful.

For the 10 mg dose statistically significant impaired effects only existed in the 2nd to 4th hour p.a. with averaged 9% of 85 effects. All effects measured later showed no deficits.

Even for the 20 mg dose only few effects measured in the 2nd to 4th hour were reduced (7% of 61). Thereafter no effect was statistically significant impaired for several hours (up to 9 hours p.a.). At the 10th and 11th hour p.a. 11 effects were described by one research group of which 4 effects showed impairments. It was very difficult to present a suitable explanation due to few data, due to the fact that only one research group tested performance during this time span and due to the fact that unfortunately no effects were measured at this time with higher doses. Since the administration of the agent took place at night, a “hang-over could not be excluded.

The percentage of impaired effects in the 2nd to 4th hour p.a. climbed up with doses >20 mg. For 30 to 60 mg combined 30% of 20 effects in the 2nd hour and 56% of 18 effects in the 3rd hour were impaired.

A concentration-dependent view was not meaningful due to the fact that there existed only few effects measured with higher concentrations (>700 ng/mL) whereas for lower concentration classes the percentages fluctuated between 0% and 23% without showing a correlation between concentration and percentage of impaired test results.

Overall the results under higher doses at later time p.a. could be influenced by different kinetics of metabolites Norclobazam and Desmethylclobazam.

Table 18: Clobazam, summary of results.

Summary Single administration	N05BA09 Clobazam	
Number of studies	16	
Number of effects	287	
Checked doses (mg)	10 - 60	
Recommended dose (mg)	20 - 30 / day	
Tabularly evaluable doses (mg)	10 *)	20 *)
No. studies / no. effects	13 /127	10 / 96
Max. sign. impaired test results (%)	<15	<15
Hour p.a. of maximum impairment	2 - 32	3
Alcohol equivalence of max. imp. (%)	<0,03	<0,03
Duration p.a. until <15% impairment (h)	0	0
Degree of impairment	0	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not meaningfully calculable due to few data, metabolites and low correlation	

*): no curve fitting due to too few effects impaired and/or metabolites

Multiple administrations to healthy subjects

In a summarizing evaluation of 10 studies with a treatment period up to 1 week (daily dose 10-30 mg), Berghaus [1997] only found essential performance deficits for the time up to 4 h after the last application (22-56% statistically significant impaired). Beyond this point of time only single deficits were observed. Lutz et al. 2003 did not found statistically significant performance deficits as far as usual doses were applied (10-30 mg), even if higher plasma concentrations were present compared to single application.

Summary multiple administrations: No statistically significant deficits in usual doses and several hours after application, otherwise impairment probable.

Administration to patients

In comparison to patients without treatment (placebo) in 3 greater studies no statistically significant performance deficits could be observed (daily dose 10-40 mg, 2-6 weeks therapy) [Berghaus 1997]. In cases of long-term administration and “normal” doses (20-30 mg/day), clobazam is supposed to be without greater influence on the performance level [Lutz et al. 2003].

Summary patients: No statistically significant deficits.

3.2.2.8 N05BC01 Meprobamate

(N05BC Carbamate, other anxiolytics)

Single administration to healthy subjects

For meprobamate we gathered 17 studies with 313 effects and doses administered between 200 and 3600 mg. Two doses (400 and 800 mg) seemed to show population numbers high enough to analyse the time distribution in detail. Both doses revealed marginal deficits in the 2nd to 4th hour p.a. so that a curve fitting was not meaningful. To learn more about the possible impairment we combined doses of more than 800 mg up to 3600 mg. 104 of these 116 effects distributed up to 15 hours p.a. and every time class with adequate population number presented more than 40% statistically significant impaired effects. That means that the administration of higher doses of meprobamate was combined with essential impairment.

The concentration-dependent breakdown of the effects acknowledged this impression. The quadratic curve fitting (R^2 = .977) of effects measured after the maximum concentration (2.25 hours p.a.) illustrated the 30% level at 29000 ng/mL. Hence, according to the kinetics of meprobamate, a dose of more than 1200 mg was necessary to reach this danger point.

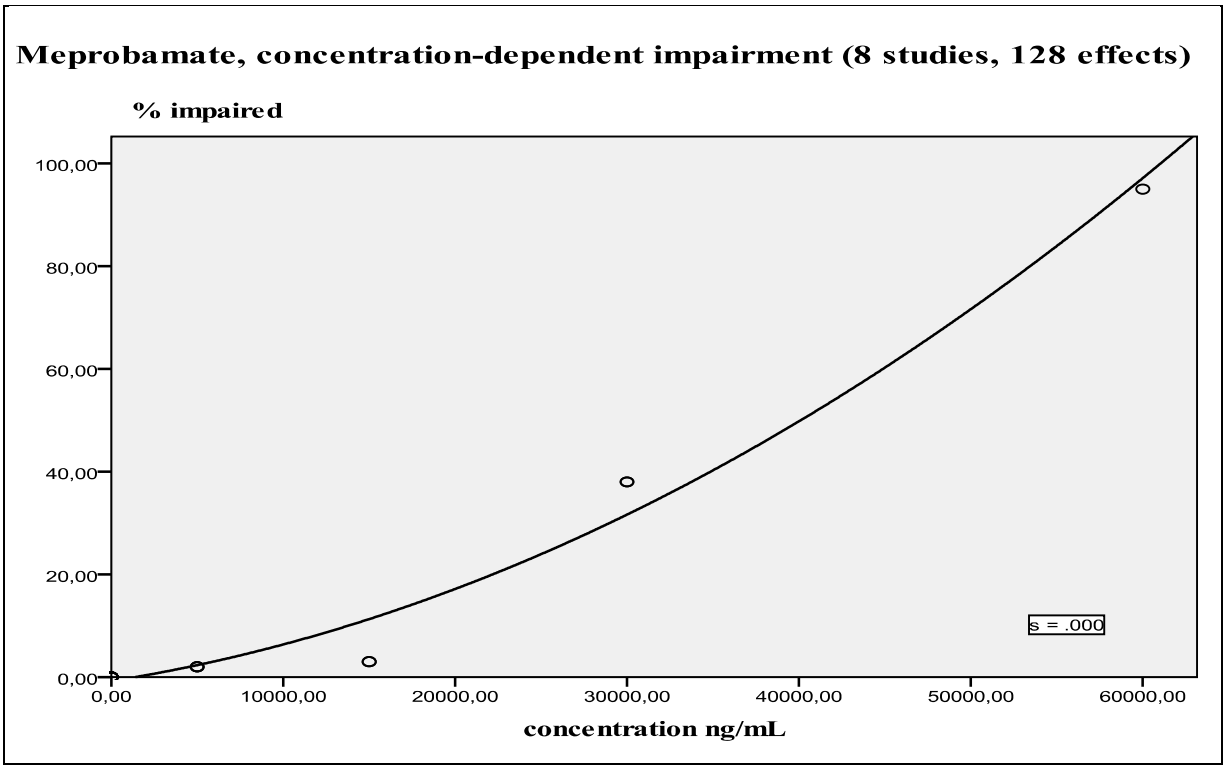

Figure 22: Meprobamate, concentration-dependent impairment.

Table 19: Meprobamate, summary of results.

Summary **Single administration**	***N05BC Carbamates*** **N05BC01 Meprobamate**		
Number of studies	17		
Number of effects	313		
Checked doses (mg)	200 - 3600		
Recommended dose (mg)	1200 - 1600 / day		
Tabularly evaluable doses (mg)	400 *)	800 *)	1200 - 3600 *)
No. studies / no. effects	7 / 79	7 / 82	6 / 104
Max. sign. impaired test results (%)	<15	<15	67 - 75
Hour p.a. of maximum impairment	2 - 4	2	5 - 9
Alcohol equivalence of max. imp. (%)	<0,03	<0,03	>0,08
Duration p.a. until <15% impairment (h)	0	0	probably >24
Degree of impairment	0	0	not calculable
0,05% alcohol equ. (ng/mL)	29000 (25000 - 33000)		
% of max. rec. dose (mg)	326 of 400 (281 - 371)		

*): no curve fitting due to minor impairment or aggregation of doses

Multiple administrations to healthy subjects

The results seem to be heterogeneous and there are only few data. In older investigations [Claridge 1961, Melikian 1961], there were no statistically significant impairments in psychophysical tests after daily doses of 800 and 1200 mg and a treatment period of 3 and 14 days. Loomis and West [1958] found performance impairment in a driving simulator, however, there were only twice applications of 400 mg meprobamate and testing shortly after application, so that this study should be considered with caution.

Summary multiple administrations: No clear deficits.

Administration to patients

In comparison to patients without treatment (placebo), studies revealed no statistically significant performance deficits in patients (1600 mg daily over 6 days) or only partial impairments in higher doses (1800 mg as single administration, testing shortly after application, no deficits with 1200 mg) [Reitan 1957, Jonnsson and Andersen 1960].

Summary patients: No clear deficits.

3.2.2.9 N05BE01 Buspirone

(N05BE Azaspirodecandione derivative, other anxiolytics)

Single administration to healthy subjects

Overall we encoded 16 studies with 341 effects with doses between 5 and 120 mg. At most the 10 mg dose and the 20 mg dose were administered.

Apart from small fluctuations all doses (10, 20 and even the higher doses) only revealed few effects impaired during the 2nd up to the 4th hour p.a. Time classes with sufficient population numbers showed <15% of effects reduced.

Even the concentration-dependent analysis revealed no ascending percentage of impairment up to the maximum concentration tested (14 ng/mL). The percentages fluctuated in essence between 0 and 16% without a correlation to concentrations. Overall only 6% of 332 effects measured ≥1.0 hour p.a. were impaired. Hence there seemed to be no essential impairment following the use of buspirone.

Table 20: Buspirone, summary of results.

Summary **Single administration**	***N05BE Azaspirodecandione derivatives*** **N05BE01 Buspirone**	
Number of studies	16	
Number of effects	341	
Checked doses (mg)	5 - 120	
Recommended dose (mg)	15 - 60 / day	
Tabularly evaluable doses (mg)	10 *)	20 *)
No. studies / no. effects	11 / 130	6 / 88
Max. sign. impaired test results (%)	<10	<10
Hour p.a. of maximum impairment	2 - 4	2 - 4
Alcohol equivalence of max. imp. (%)	<0,03	<0,03
Duration p.a. until <15% impairment (h)	0	0
Degree of impairment	0	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	0.05% equivalent not reached	

*): no curve fitting due to minor impairment and/or too few effects

Multiple administrations to healthy subjects

The results in the summarizing evaluation of Berghaus [1997] on 6 studies were heterogeneous: there was no correlation between the daily dose and the percentage of

statistically significant impaired test results in the interval up to 1 week treatment period. Between 1 week and 1 month there were only few impaired results.

Summary multiple administrations: Minor impairment up to 1 month.

Administration to patients

In comparison to patients without treatment (placebo) no statistically significant impairment could be found with daily doses of 5-20 mg and a therapy time of 4 weeks (memory function, driving test) [Lucki et al. 1987, van Laar et al. 1992].

Summary patients: No impairment.

3.2.2.10 Comparison of anxiolytics

The essential results of the meta-analytical approach, that means the characteristics of the different agents of the anxiolytics were summarized in the following tables with the help of which one can inform on the parameters of an interesting substance.

Table 21: Comparison of profiles: N05B Anxiolytics (N05BA Benzodiazepine derivatives, intermediate half-life).

Agent	N05BA04 Oxazepam	N05BA06 Lorazepam	N05BA08 Bromazepam	N05BA12 Alprazolam
Number of studies	26	68	9	21
Number of effects	377	1244	202	354
Checked doses (mg)	10 - 90	0.5 - 9.0	1.5 - 12	0.25 - 2.0
Recommended dose (mg)	10 - 30 / day	0.5 - 2.5 / day	3 - 6 /day	0.75 - 1.5 / day
Tabularly evaluable doses (mg)	15 30	1 2 2.5	6 *) 12 *)	1
No. studies / no. effects	8 / 118 11 / 115	18 /175 32 / 425 26 /269	4 / 33 3 / 31	11 / 130
Max. sign. impaired test results (%)	41 52 (34 - 46) (46 - 61)	32 85 77 (26 - 40) (70 - 87) (69 - 85)	(45) (ca. 75)	74 (65 - 85)
Hour p.a. of maximum impairment	2.0 2.25 (1.25 - 2.0) (2.25 - 2.5)	2.0 3.5 3.25 (1.25 - 2.25) (3.0 - 3.75) (3.25 - 3.75)	(2) (2 - 3)	2.0 (1.75 - 2.0)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08 >0,08	0,03 - 0,05 >0,08 >0,08	(0,05 - 0,08) (>0,08)	>0,08
Duration p.a. until <15% impairment (h)	7.75 9.0 (7.75 - 11.5) (9.0 - 10.0)	7.5 12.5 19.75 (5.75 - 8.0) (12.5 - >24) (19.75 - >>24)	(3) no data	14.0 (11.5 - 16.0)
Degree of impairment	104 170 (89 - 121) (142 - 235)	64 418 571 (33 - 94) (418 - 707) (527 - 951)	too few effects	369 (262 - 480)
0,05% alcohol equ. (ng/mL)	(330) ((300 - 390))	9 (8 - 10)	too few effects	9 (8 - 10)
% of max. rec. dose (mg)	(218) of 10 ((199 - 258))	126 of 1 (112 - 140)		118 of 0.50 (105 - 132)
Adaption	Development of tolerance after weeks, but impaired performance compared to placebo level	Marked improvement within 1 week, but no complete tolerance	No deficits in lower doses, but no complete tolerance in higher doses (at least weeks)	Marked tolerance after several days, persistence of minor deficits up to 1 week
Results in patients	No sufficient data, apparently slight impairment	Improvement of performance, but presence of permanent impairment in higher doses possible	Too few data to estimate impairment	Too few data to estimate impairment

*): no curve fitting due to too few effects

Table 22: Comparison of profiles: N05B Anxiolytics (N05BA Benzodiazepine derivatives, long half-life).

Agent	N05BA01 Diazepam				N05BA02 Chlordiazepoxide	N05BA09 Clobazam	
Number of studies	103				9	16	
Number of effects	2104				101	287	
Checked doses (mg)	2 - 40				10 - 60	10 - 60	
Recommended dose (mg)	5 - 20 / day				maximal 60 / day	20 - 30 / day	
Tabularly evaluable doses (mg)	5	10	15	20	10 *)	10 *)	20 *)
No. studies / no. effects	36 / 333	53 / 756	18 / 444	29 / 276	5 / 76	13 /127	10 / 96
Max. sign. impaired test results (%)	23 (21 - 26)	38 (35 - 40)	64 (57 - 70)	74 (62 - 82)	probably <30	<15	<15
Hour p.a. of maximum impairment	1.25 (1.25 - 1.25)	1.0 (1.0 - 1.25)	0.75 (0.5 - 1.0)	1.25 (1.0 - 1.25)	not assignable	2 - 3	3
Alcohol equivalence of max. imp. (%)	0,03 - 0,05	0,05 - 0,08	>0,08	>0,08	probably 0,03 - 0,05	<0,03	<0,03
Duration p.a. until <15% impairment (h)	4.5 (3.25 - 6.5)	5.0 (4.25 - 7.75)	4.75 (4.5 - 5.75)	6.25 (6.25 - 7.25)	not assignable	0	0
Degree of impairment	17 (11 - 36)	57 (44 - 84)	112 (88 - 135)	171 (142 - 211)	not assignable	0	0
0,05% alcohol equ. (ng/mL)	320 (290 - 370)				not assignable	not meaningfully calculable due few data, metabolites and low correlation	
% of max. rec. dose (mg)	97 of 10 (88 - 112)						
Adaption	Improvement in the first week, but no complete tolerance. Impairment always possible (>1 month)				Minor impairment up to 1 month	No stat. significant deficits in usual doses and several hours after use, otherwise impairment probable	
Results in patients	Delayed performance deficits over weeks and possibly months				No data on hand, impairment not probable	No stat. significant deficits	

*): no curve fitting due to too few effects and/or metabolites and/or too few effects impaired

Table 23: Comparison of profiles: N05B Anxiolytics (other anxiolytics).

Agent	***N05BC Carbamates*** **N05BC01 Meprobamate**			***N05BE Azaspirodecandione derivatives*** **N05BE01 Buspirone**	
Number of studies	17			16	
Number of effects	313			341	
Checked doses (mg)	200 - 3600			5 - 120	
Recommended dose (mg)	1200 - 1600 /day			15 - 60 / day	
Tabularly evaluable doses (mg)	400 *)	800 *)	1200 - 3600 *)	10 *)	20 *)
No. studies / no. effects	7 / 79	7 / 82	6 / 104	11 / 130	6 / 88
Max. sign. impaired test results (%)	<15	<15	67 - 75	<10	<10
Hour p.a. of maximum impairment	2 - 4	2	5 - 9	2 - 4	2 - 4
Alcohol equivalence of max. imp. (%)	<0,03	<0,03	>0,08	<0,03	<0,03
Duration p.a. until <15% impairment (h)	0	0	probably >24	0	0
Degree of impairment	0	0	not calculable	0	0
0,05% alcohol equ. (ng/mL)	29000 (25000 - 33000)			0,05% equivalent not reached	
% of max. rec. dose (mg)	326 of 400 (281 - 371)				
Adaption	No clear deficits			Minor impairment up to 1 month	
Results in patients	No clear deficits			No impairment	

*): no curve fitting due to minor impairment and/or too few effects and/or metabolites and/or aggregation of doses

In the following we would like to compare results of the different agents. We concentrated on the basic questions of patients, physicians and for traffic safety, namely the question of differences concerning the degree of performance impairment.

Single administration to healthy subjects

It seemed meaningful to differentiate the summarizing comparison in one part dealing with results of different doses within one and the same agent and in a second part describing differences between the agents.

Single administration to healthy subjects: comparison within an agent

Contrary to the antipsychotics, for anxiolytics existed several agents for which more than one dose could be analyzed meta-analytically. This provided the opportunity to compare the deficit profile of ascending doses.

With ascending doses even the degree of impairment raised. This increase could be realized with regard to all parameters calculated: the maximum impairment, the alcohol equivalence and the duration until the percentages of impaired effects get below 15%. Especially the area between the approximation curve and the 15% deficit line as an indication for the degree of impairment, which combines the two aspects degree and duration of impairment, revealed the positive correlation between increasing impairment and increasing dosages. Even if the differences between two neighbored doses were small or even a little bit the other way round (like for the maximum of impaired effects for 2 mg and 2.5 mg lorazepam) the area between the curve and the 15% line revealed a clearly increasing degree of impairment. The positive correlation between dosages and deficits held true for the agents of all groups of substances (benzodiazepines intermediate half-life, benzodiazepines long half-life and other anxiolytics). By the way, the illustrated correlation was, in our opinion, a hint that the meta-analytic approach worked: even if the designs and especially the groups of subjects and dosages administered were completely different between the experimental studies integrated in the analysis, the overall data demonstrated the correlation between impairment and doses as it was to expect according to physiological standards.

The degree of the correlation could be, of course, very different. Whereas for example for oxazepam the parameter “degree of impairment” climbed up only from 104 to 170 from 15 mg dose to 30 mg dose it increased from 64 to 418 for 1 mg doses to 2 mg dose lorazepam. Concerning other agents (clobazam, meprobamate) impairment started with higher doses whereas with low doses no or only marginal deficits could be realized. Contrary to the above

mentioned parameters describing the degree of impairment the time spread of the maximum impairment demonstrated only a fragile correlation in that the time at most increased with higher doses.

Altogether the comparison within several agents clearly demonstrated that after single administration of a medicament to healthy subjects the dose was the essential influencing factor that determined the degree of performance impairment for a special agent.

This result confirmed, transferred to reality, that the rule of "ascending" dosage management is one of the best procedures to use by patients to minimize the danger of performance deficits at the initial therapy with medicaments.

Single administration to healthy subjects: comparison between agents

As mentioned before the extent of performance impairment essentially depended on the dose administered. Hence it was very difficult to compare the degree of performance deficits between different agents because the result of this comparison will be predetermined by the doses chosen for the different agents. Of course, it seemed likely to base the comparison on "recommended doses". But unfortunately the manufacturers of anxiolytics do not indicate single doses but only daily doses and, in addition, no single batch but an interval of doses. To give, however, an impression we took one third of the daily maximum dose as "single" dose and, if necessary, we rounded up this value. Concerning meprobamate we chose 400 mg as "single" dose because this dose was tested at most in kinetic studies. Since for most of the agents parameters could not be calculated meta-analytically for "single" doses the comparison had to be based in essence exclusively on the "0,05% alcohol equivalent".

Within the intermediate half-life benzodiazepines – sufficient information could be gathered for oxazepam, lorazepam and alprazolam – oxazepam seemed to affect the performance to a lesser extent than alprazolam or lorazepam. Only about 105%-140% of a single dose of alprazolam or lorazepam was necessary to reach the 0,05% alcohol equivalent whereas for oxazepam more than 200% had to be administered.

Unfortunately only for diazepam out of the group of long half-life benzodiazepines there was enough information. Hence a comparison was impossible.

The same holds true for other anxiolytics for which parameters only could be calculated for meprobamate.

Comparing agents with sufficient information between groups of anxiolytics there seemed to be a clear distinction in that diazepam, alprazolam and lorazepam affected performance at

most. About one single dose was necessary to reach 0,05% alcohol equivalent. As next agent followed oxazepam of which a two-fold single dose and finally meprobamate of which a three-fold single dose had to be administered.

Table 24: Percentage of doses necessary to reach the 0.05% alcohol equivalent for different anxiolytics.

Agent	**"Single" dose (mg)**	**%-area of 0,05% alcohol equivalence**
diazepam alprazolam lorazepam	10 0.5 1	88 - 112 105 - 132 112 - 140
oxazepam	10	199 - 258
meprobamate	400	281 - 371

Multiple administrations to healthy subjects and patients

With the exception of diazepam there are mainly only a few studies concerning multiple administrations. Predominantly, the interval up to 1 week is covered, the later time period is not sufficiently represented. Thus, the evaluation of an "adaption" is very limited. The results showed that performance deficits may persist in the case of classic benzodiazepines with intermediate and long half-lives. With increasing treatment interval the impairment tends to decrease, but it cannot be excluded even for longer treatment periods. Multiple administration is less critical in substances with slight impairment after single administration (other anxiolytics), but there were only few studies available. Even for multiple administrations an important influencing factor is of course the dose even if there does not exist a direct correlation for many drugs. Regularly, lower/recommended doses over longer times (>1 week) are associated with less or no impairment.

The same principles are applicable to experimental studies with patients. The number of relevant studies was relatively small and partially heterogeneous. The main problem is the high variability of experimental conditions (dose, treatment period, time interval between application and testing etc.) so that it is very difficult to draw reliable conclusions. However, in most of the cases the probability of impairment will decrease with the increasing time of treatment.

3.2.3 N05C Hypnotics and Sedatives

Hypnotics and sedatives include various benzodiazepines with different half-lives and the so-called z-drugs zopiclone, zolpidem and zaleplon. The main pharmacodynamic effects of

benzodiazepines are sedation, anxiolysis, muscle relaxation , the treatment of epilepsy and the induction of sedation in the context of anesthetics.

The main indication of hypnotics and sedatives, however, is insomnia. It is a common disease involving about one third of the general population. The lack of night-time sleep often leads to an increased daytime sleepiness with the possibility of reduced driving abilities (attention, concentration etc.). On the other hand, the treatment of insomnia by hypnotics and sedatives, using long-acting benzodiazepines as sleeping pills, also may cause negative effects (so called hang-over or residual effects) on the day following application of agents at night.

Sedation is the main “side” effect (or better: effect), as it belongs to the fundamental profile of these substances. Hence, concerning the effects of hypnotics, à priori one has to expect that hypnotics/sedatives will impair performance and consequently driver fitness. The degree of sedation depends on the duration of the presence of the drug in blood.

Among benzodiazepines there are substances with short (e.g. brotizolam, triazolam; half-life <6 hours), intermediate (e.g. lormetazepam, temazepam; half-life 6-24 hours) and long half-life (e.g. nitrazepam, flunitrazepam, flurazepam; half-life >24 hours). The z-drugs are newer benzodiazepine receptor agonists with similar effects as benzodiazepines but with shorter half-lives (1-6 hours). Even if sedatives are recommended for short use of only weeks, it must be considered, that the treatment of insomnia frequently takes months or even years and is sometimes irregular so that many patients do not develop tolerance towards the medication.

3.2.3.1 N05CD05 Triazolam

(N05CD Benzodiazepine derivative, short half-life)

Single administration to healthy subjects

46 studies with 1305 effects and doses tested between 0.125 mg and 3 mg could be integrated in the analysis. A sufficient high number of effects to fit the empirical data were given for .25 mg and 0.5 mg.

The time-dependent impairment curve for dose 0.25 mg was based on 34 studies and 528 effects. The curve indicated the maximum percentage of deficits about 2 hour p.a. with 41% and a time period of 6.5 hours till the 15% line was crossed.

The higher dose of .5 mg demonstrated a higher maximum of impairment (71%) about the same time after taking the medicine. Correspondent the period of time to the 15% crossing was about 10 hours and the degree of impairment about the 3-fold as for the 0.25 mg dose.

Concerning the concentration-dependent impairment we analysed the data after the concentration maximum ≥1.25 hours p.a. A continuous and sufficient number of studies and effects were to be seen up to a concentration of 5 ng/mL. For this area the curve calculated fitted the empirical data excellent (R^2 = .996). The 30% equivalent was 1.6 ng/mL. Compared to the 30% thresholds of the time-dependent approximation the time curves should be more concentrated after the maximum.

Triazolam .25 mg, time-dependent impairment (34 studies, 528 effects)

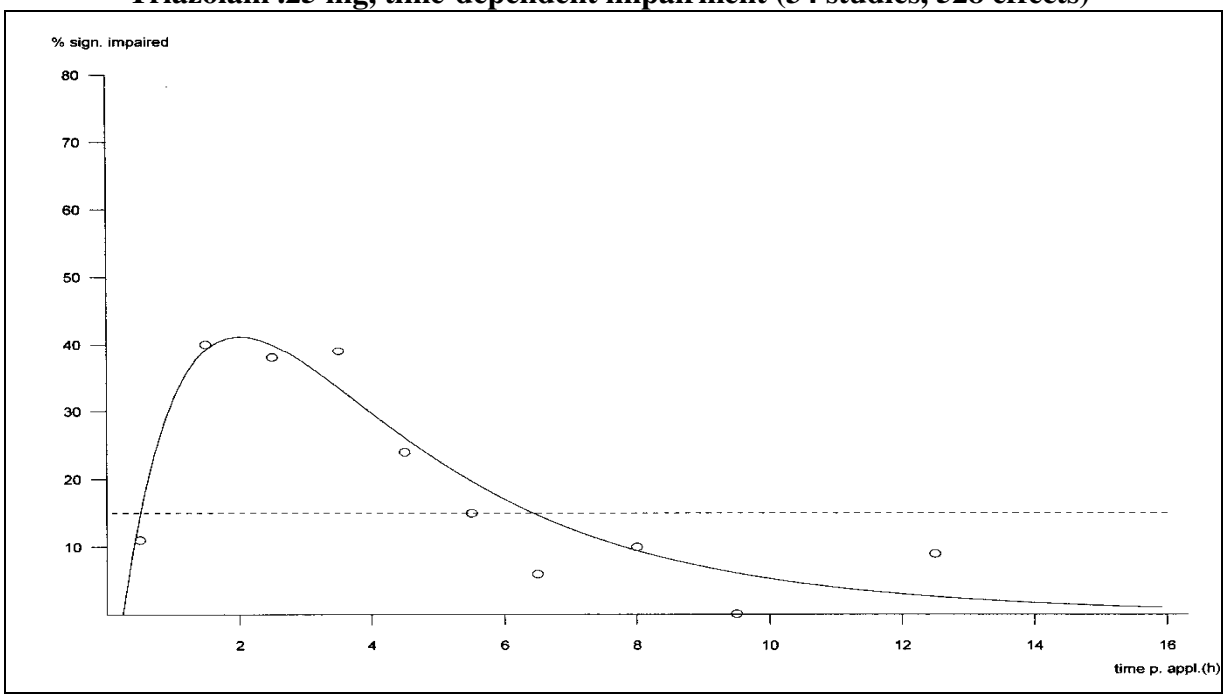

Figure 23: Triazolam .25 mg, time-dependent impairment.

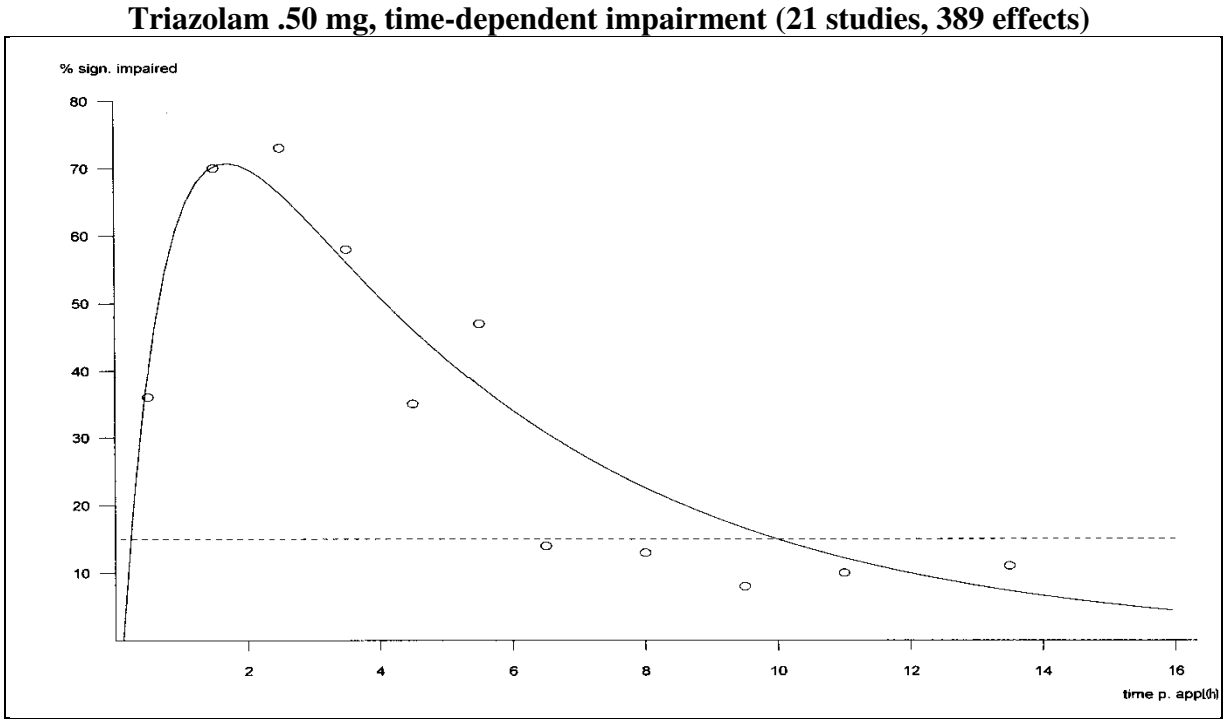

Figure 24: Triazolam .50 mg, time-dependent impairment.

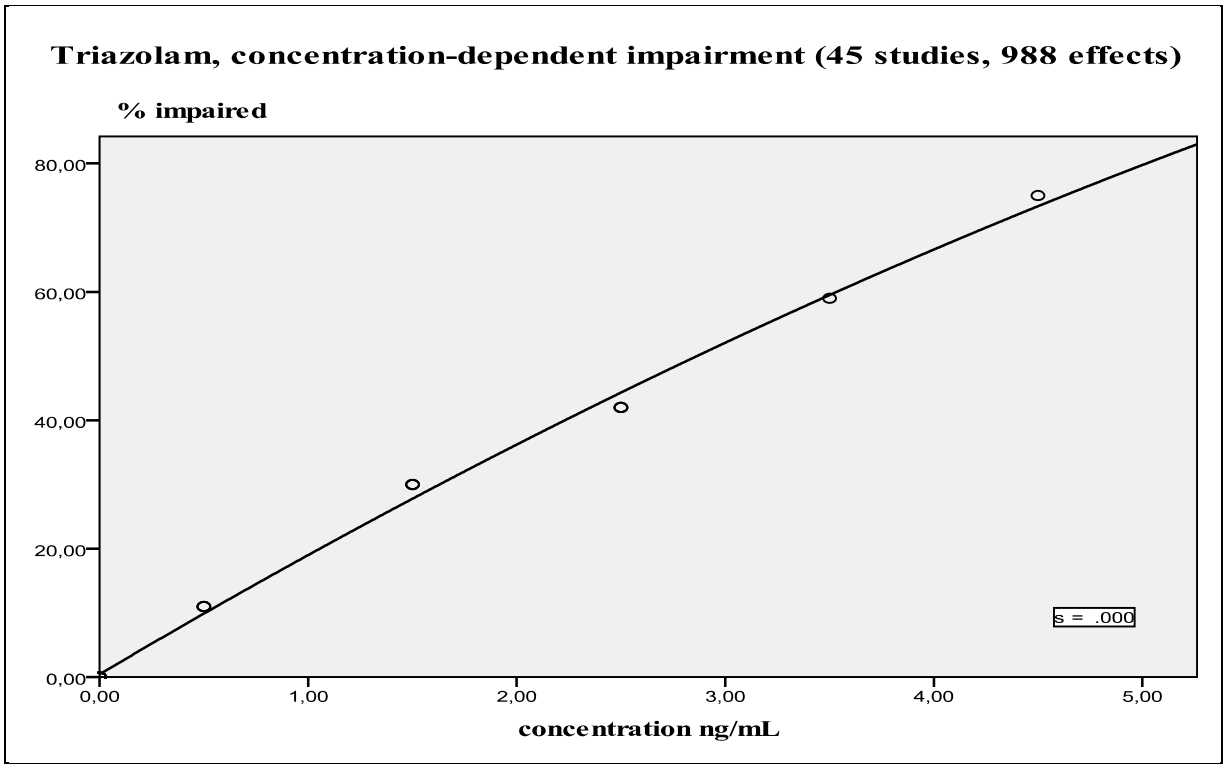

Figure 25: Triazolam,concentration-dependent impairment.

Table 25: Triazolam, summary of results.

Summary **Single administration**	**N05CD05 Triazolam**	
Number of studies	46	
Number of effects	1305	
Checked doses (mg)	.125 - 3.0	
Recommended dose (mg)	0.125 - 0.25	
Tabularly evaluable doses (mg)	0.25	0.50
No. studies / no. effects	34 / 528	21 / 389
Max. sign. impaired test results (%)	41 (37 - 47)	71 (67 - 80)
Hour p.a. of maximum impairment	2.0 (2.0 - 2.0)	1.75 (1.75 - 1.75)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08	>0,08
Duration p.a. until <15% impairment (h)	6.5 (5.75 - 8.25)	10.0 (7.5 - 11.75)
Degree of impairment	89 (65 - 122)	247 (197 - 323)
0,05% alcohol equ. (ng/mL)	1.6 (1.5 - 1.8)	
% of max. rec. dose (mg)	80 of 0.25 (75 - 90)	

Multiple administrations to healthy subjects

In contrast to other benzodiazepines with short half-life, the multiple administrations of triazolam caused, according to 9 studies, statistically significant impairment in about one third of tests up to an interval of 1 week. Even up to 1 month about 10% of results were statistically significant reduced. However, these negative results are probably due to the fact that triazolam was used in relatively high concentrations [Berghaus 1997].

Summary multiple administrations: Triazolam in higher doses leads to relatively strong impairment up to 1 week and sometimes even up to 1 month.

Administration to patients

Based on about 8 studies the percentage of statistically significant impaired effects reduced to half within one week of therapy [Berghaus 1997]. Compared to placebo the therapy with triazolam 0.25 mg – as well as with other hypnotics – improved the sleep quality statistically significant, which was documented by a reduction/normalization of alterations in

polysomnography and EEG as they were typical of patients with sleep disorders and absent in healthy controls [Terzano et al. 2003].

Summary patients: Improvement of performance with therapy but deficits remained.

3.2.3.2 N05CD09 Brotizolam

(N05CD Benzodiazepine derivative, short half-life)

Single administration to healthy subjects

In spite of an intensive literature search we could only gather 6 studies in which 78 effects were described. These effects were measured with doses between 0.1 and 0.5 mg with the highest cell number of 24. Hence a time-dependent approach was impossible. Due to the very small frequencies within the different time categories the results distributed only by chance and hints for maximum of impairment or time span to missing impairment could not be derived from the data.

But a concentration-dependent analysis was possible because almost all effects were measured in the elimination phase. It revealed nice results for the period of time after resorption (≥1.25 hours p.a.). The quadratic approximation was complete ($R^2 = 1.000$, the data had been concentrated into 3 classes due to the minimal population number) and the 30% impairment was reached with 2.8 ng/mL. According to the concentration-dependent impairment curve the 15% impairment level was reached with 1.1 ng/mL that means, according to the kinetic curve, about 9 hours p.a. for the .25 mg dose and about 14 hours for the .5 mg dose. But these results should be discussed with caution due to the few data on which the analysis is based.

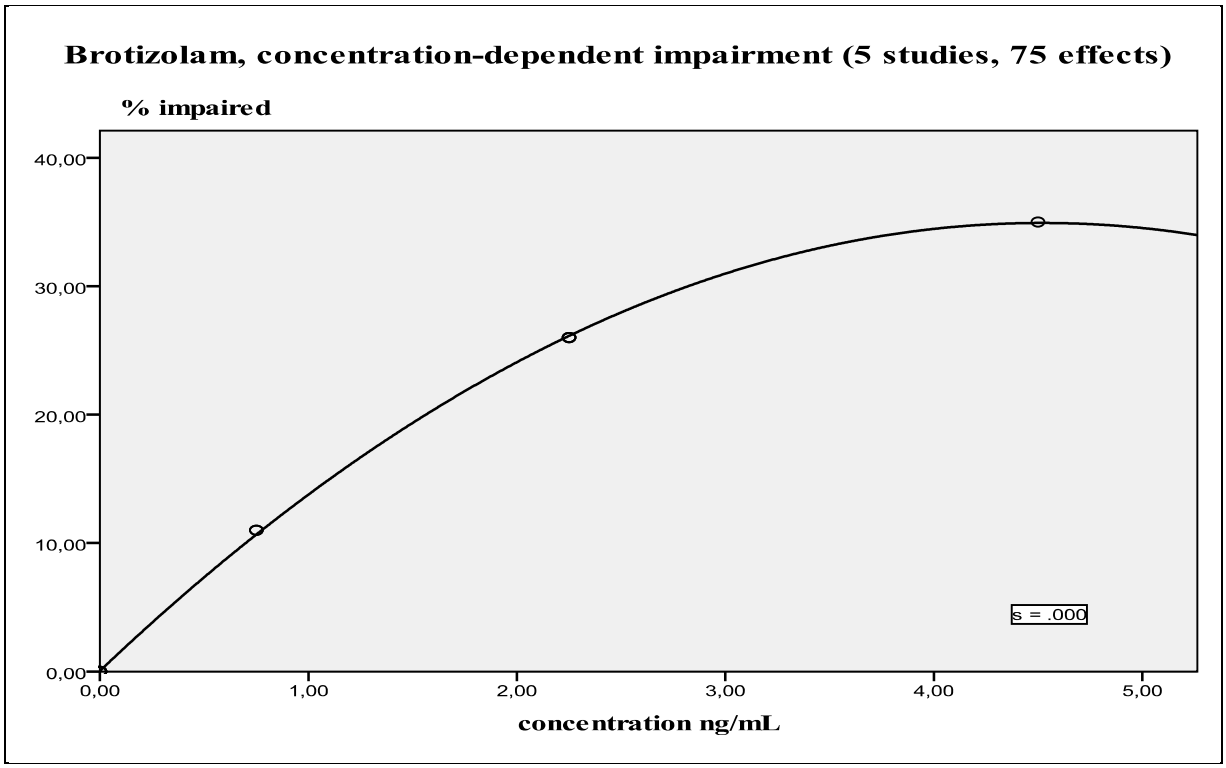

Figure 26: Brotizolam, concentration-dependent impairment.

Table 26: Brotizolam, summary of results.

Summary **Single administration**	**N05CD09 Brotizolam**
Number of studies	6
Number of effects	78
Checked doses (mg)	0.1 - 0.5
Recommended dose (mg) **Tabularly evaluable doses (mg)** **No. studies / no. effects**	0.125 - 0.25 No *)
Max. sign. impaired test results (%)	too few data
Hour p.a. of maximum impairment	too few data
Alcohol equivalence of max. imp. (%)	too few data
Duration p.a. until <15% impairment (h)	probably 9 for 0.25 mg dose
Degree of impairment	too few data
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	(2.8) ((2.3 - 4.5)) (100) of 0.25 ((82 - 161))

*): no curve fitting due to too few data

Multiple administrations to healthy subjects

No accumulation was found within one week following doses of 1 mg/day [Bechtel 1983]. On the next morning, 9.5 hours after the intake of Brotizolam 0,25 mg in the evening, no reduced performance was detected using driving test simulator, even after multiple applications during 3 nights [Törnros u. Laurell 1990]. Further studies revealed similar results [Krueger 1986, Krueger and Müller-Limmroth 1983, Hartse et al. 1983]: neither the administration of brotizolam 0,25 mg for 3 days nor the 4-fold application of brotizolam at doses between 0,25 and 0,5 mg in the evening led to negative effects 7 hours later.

Summary multiple administrations: Brotizolam showed no negative effects under recommended doses.

Administration to patients

In only one study dealing with younger patients with insomnia, no difference was found 9,5 hours after a dose of Brotizolam 0,25 mg or 0,5 mg compared with placebo testing [Roehrs et al. 1983]. In comparison to placebo a therapy with brotizolam 0,25 mg as well as with other hypnotics improved sleep quality statistically significant. Pathological changes in polysomnography and EEG typical for insomniacs and not present in healthy controls were reduced or normalized [Terzano et al. 2003]. Despite improvement of subjective sleep quality, a newer Japanese investigation [Uchimura et al. 2006] using brotizolam 0,25 mg showed mild sleepiness on the following morning as the most frequent side effect. This effect in some patients (3 of 14 persons, 3-day-administration, placebo before and after) exceeded that one after zolpidem 10 mg.

Summary patients: Main side effect in patients is slight sleepiness for at least several days.

3.2.3.3 N05CD06 Lormetazepam

(N05CD Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

13 studies with 161 effects measured with doses between 0.5 and 2.0 mg built up the basis for the evaluation on lormetazepam. The 1 mg dose was the most frequently tested one.

Due to small population numbers within the given classes of time we had to aggregate the data till 15 hours p.a. into 5 classes. The impairment curve illustrated the maximum of about 27% in the first hour p.a. It only took about 4 hours to the 15% level.

The concentration-dependent impairment curve fitted the empirical data not good (≥1.75 hours p.a., R^2 = .846) therefore the results should be interpreted only with caution. It presents the 30% level at a concentration of 9.2 ng/mL. Hence, as expected, the time-dependent impairment curve of the 1 mg dose of lormetazepam did not reach the 30% level in its time course.

Lormetazepam 1 mg, time-dependent impairment (11 studies, 95 effects)

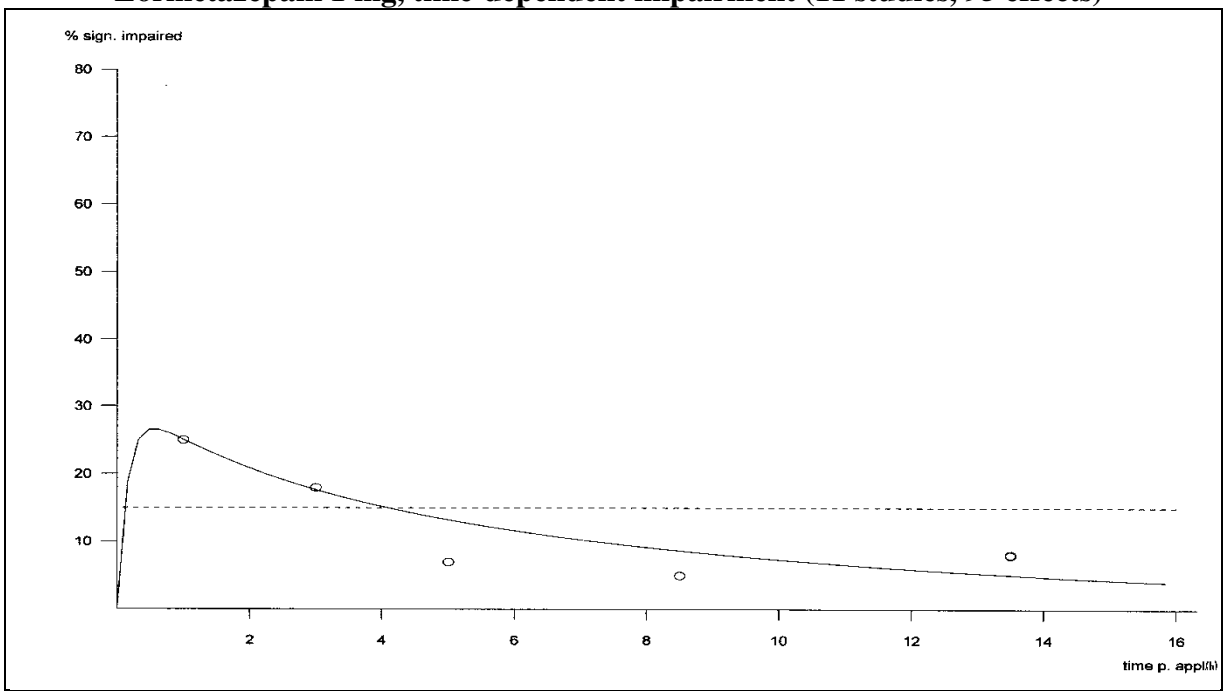

Figure 27: Lormetazepam 1 mg, time-dependent impairment.

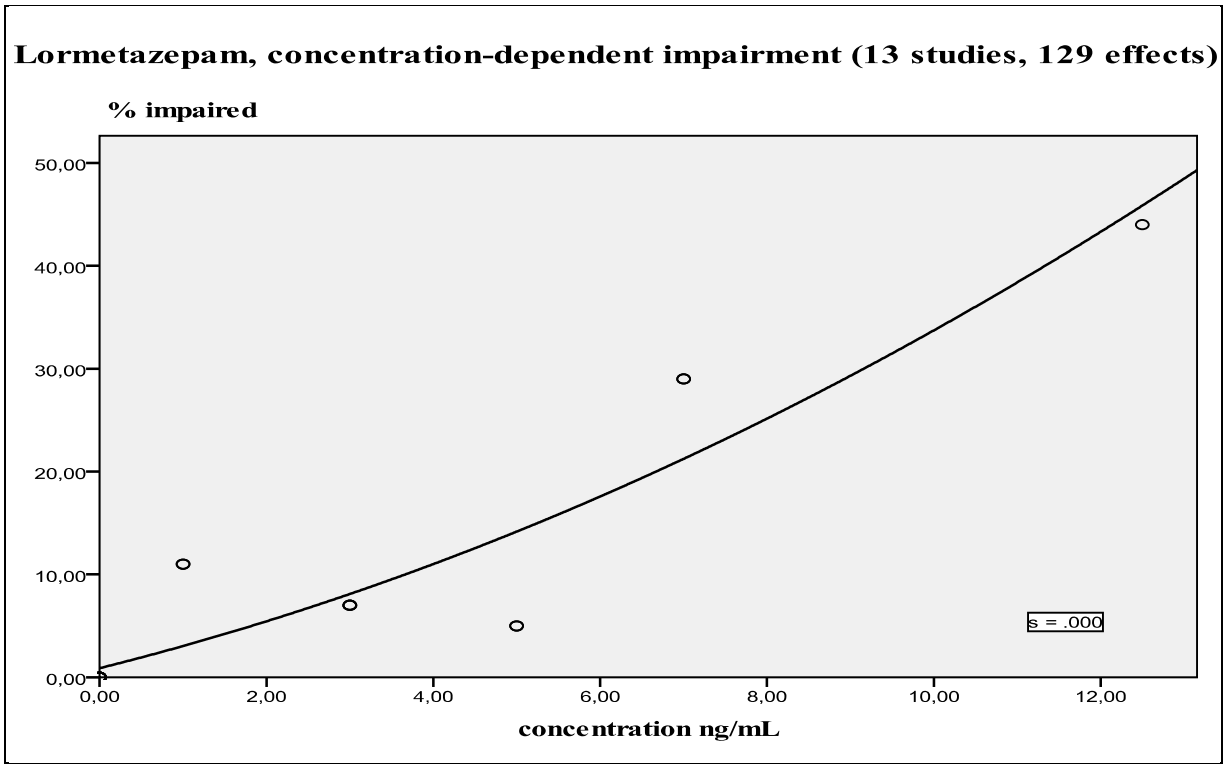

Figure 28: Lormetazepam, concentration-dependent impairment.

Table 27: Lormetazepam, summary of results.

Summary **Single administration**	**N05CD06 Lormetazepam**
Number of studies	13
Number of effects	161
Checked doses (mg)	0.5 - 2.0
Recommended dose (mg)	0.5 - 2.0
Tabularly evaluable doses (mg)	1
No. studies / no. effects	11 / 95
Max. sign. impaired test results (%)	27 (22 - 30)
Hour p.a. of maximum impairment	0.5 (0.5 - 1.25)
Alcohol equivalence of max. imp. (%)	0,03 - 0,05
Duration p.a. until <15% impairment (h)	4.25 (2.0 - 7.75)
Degree of impairment	22 (7 - 48)
0,05% alcohol equ. (ng/mL)	(9.2) ((7.5 - 10.6))
% of max. rec. dose (mg)	(125) of 1 ((102 - 144))

Multiple administrations to healthy subjects

In the first days after a therapy with lormetazepam in the evening (0,5-2 mg), a reduction of performance was noticed frequently in both laboratory testing and driving tests; hangover effects on the following day were observed in single cases [Subhan u. Hindmarch 1983, Roehrs et al. 1984, Volkerts et al. 1992 u. 1993]. In various studies, multiple administration of lormetazepam regularly led to a new increase of performance after approximately one week, possible deficits in the beginning were no longer detectable in driving simulator [Subhan u. Hindmarch 1983, Willumineit u. Neubert 1983]. Partially, an improvement of performance was even found compared to the initial situation, e.g. in tracking tests [Willumineit u. Neubert 1983]. A correlation between plasma concentrations and performance was generally not present [Volkerts et al. 1992 u. 1993].

In contrast to the above mentioned former study results, Iudice et al. [2002] arrived at the conclusion that lormetazepam 1 mg affected neither the psychomotor performance on the following morning nor daytime vigilance or driving performance in young healthy test persons when given in the evening over a period of three days and compared to placebo. A comprehensive test repertoire was applied for the assessment of memory, alertness, reaction time, objective and subjective sleepiness and performance in driving simulator. However, learning effects after an initial testing before study begin could come into consideration.

Summary multiple administrations: Possible impairment up to one week, then full recovery.

Administration to patients

Patients with sleep disorders have been examined seldom. In laboratory tests, by 3 weeks at the latest a normalization of performance was observed after administration of 1 mg or 2,5 mg of lormetazepam in the evening. Deficits of skilfulness persisted the longest time, but then no impairment was existent in numerous subtests already in the beginning [Oswald et al. 1979]. Higher doses of lormetazepam (1 mg vs. 2 mg) seemed to be associated with slightly more severe deficits in driving tests (lateral deviation) up to one week after start of the therapy [Brookhuis et al. 1990]. More recent study data [Staner et al. 2005] concerning patients with insomnia, who received lormetazepam 1 mg in single and repeated doses in the evening for one week and were tested in driving simulator 9-11 hours later on the next day, point to a similar direction: In contrast to zolpidem and placebo, at the time of examination lormetazepam increased the deviation of speed and speed limit, furthermore it caused changes of EEG typical of benzodiazepines which could be interpreted as a prolonged disturbance of central nervous system activation.

Summary patients: In patients, lormetazepam showed impairment for up to several weeks, then normal status can be achieved (comparable to healthy persons).

3.2.3.4 N05CD07 Temazepam

(N05CD Benzodiazepine derivative, intermediate half-life)

Single administration to healthy subjects

Overall 30 studies with 695 effects could be selected from the literature search and the including/excluding technique for the analysis of temazepam. Doses between 5 mg and 60 mg were tested of which the 10 mg and the 20 mg dose showed an adequate population number to try a curve fitting.

The impairment curve of the 10 mg dose indicated only marginal negative effects that did not reach the 15% level. The start of the approximation curve about half an hour p.a. was, of course, a virtual one that exclusively was determined by the technique of curve fitting and must not reflect any physiological reality. As explained in the discussion, the approximation-curve could have been started even earlier but since the first percentage of effects was measured as the highest the approximation technique determines the starting point of the curve as it is shown in the figure.

Concerning the 20 mg dose we had to exclude the data for the period of time between 12 and 15 hours p.a. before approximating the empirical values because all data since the 7^{th} hour up to the 12^{th} hour (77 effects) showed no statistically significant impaired effect whereas for the period between 12 and 15 hours there were 6 of 22 effects statistically significant reduced. This impairment resulted in essence on one research group of which all effects, contrary to all other studies for this period of time, were reduced (a working group that was even an outlier with another agent). The curve fitting of the 20 mg dose seemed to illustrate considerably higher performance reduction than the approximation of the empirical data of the 10 mg dose. Within one hour the impairment climbed up to about 56%. But in comparison to the evaluation of doses >20 mg and especially in comparison to the concentration-dependent evaluation the curve probably was by far too high. Though we are not completely sure that, especially in the first hour, there was an outlier even if there was a research group that evaluated a percentage of impairment above average but on the one hand the impairment of doses >20 mg (145 effects) showed for the first 4 hours p.a. only an impairment of about 50 to 55%. On the other hand the concentration dependent linear curve fitting (≥1.5 hours p.a., R^2 = .947, without the above mentioned outliers) reveals the 30% impairment at 450 ng/mL.

According to the kinetics for 20 mg temazepam this value was not reached (maximum of the mean values about 420 ng/mL). Considering all these information we guessed that the maximum of impairment for the 20 mg dose would be at the second hour with an impairment of about 30% and that the period of time till 15% impairment would be about 4 hours.

Temazepam 10 mg, time-dependent impairment (9 studies, 152 effects)

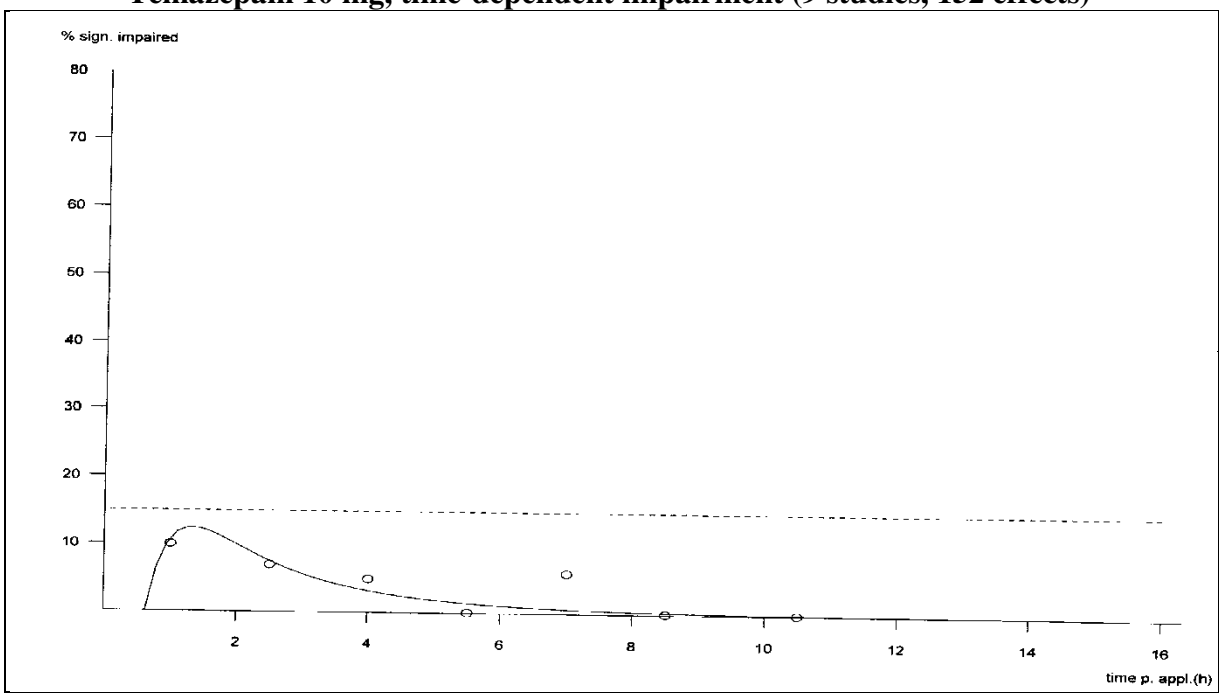

Figure 29: Temazepam 10 mg, time-dependent impairment.

Temazepam 20 mg, time-dependent impairment (12 studies, 251 effects)

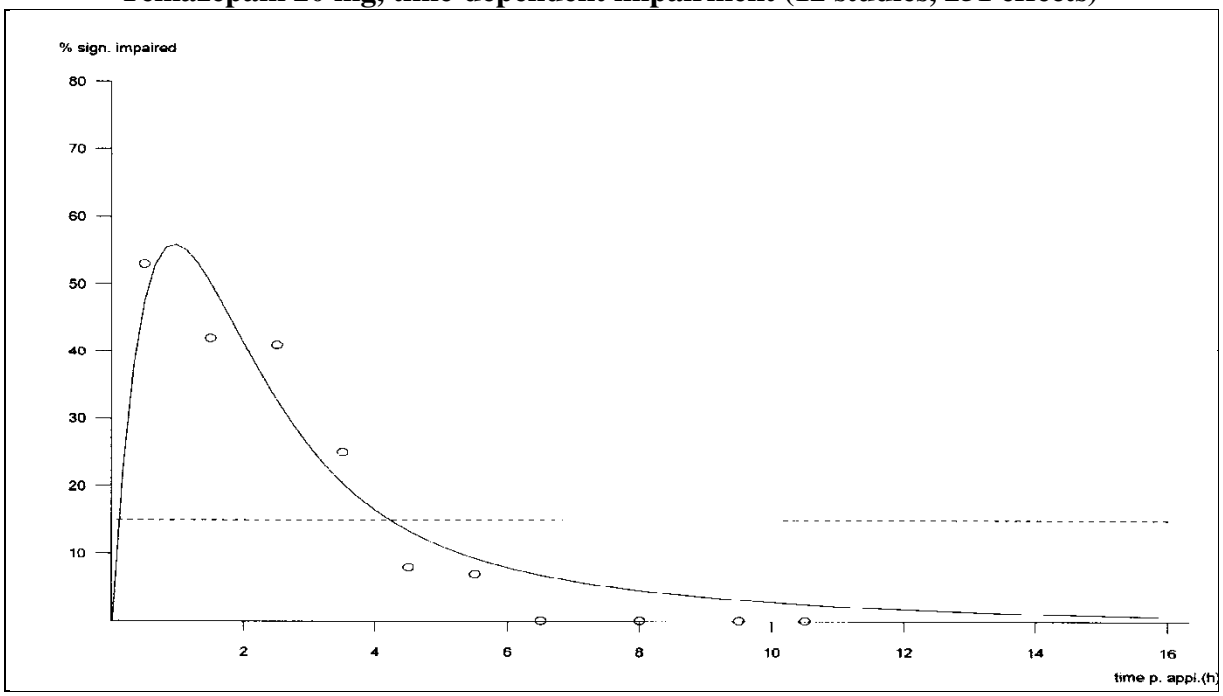

Figure 30: Temazepam 20 mg, time-dependent impairment.

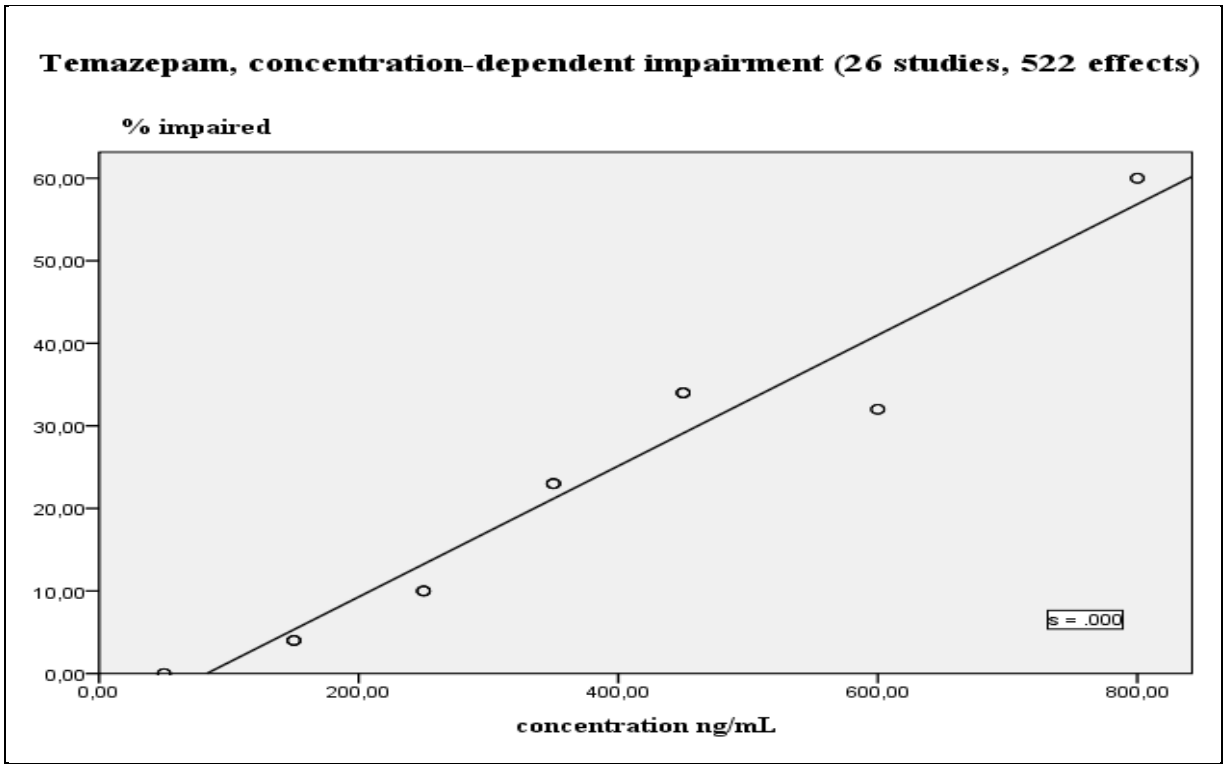

Figure 31: Temazepam, concentration-dependent impairment.

Table 28: Temazepam, summary of results.

Summary **Single administration**	**N05CD07 Temazepam**
Number of studies	30
Number of effects	695
Checked doses (mg)	5 - 60
Recommended dose (mg)	10 - 20
Tabularly evaluable doses (mg)	10 20
No. studies/no. effects	9 / 152 12 / 251
Max. sign. impaired test results (%)	12 probably (7 - 14) approx. 30
Hour p.a. of maximum impairment	1.25 probably (.75 - 1.25) approx. 2
Alcohol equivalence of max. imp. (%)	<0,03 probably approx. 0,05
Duration p.a. until <15% impairment (h)	0 probably (0 - 0) approx. 4
Degree of impairment	0 probably (0 - 0) approx. 40
0,05% alcohol equ. (ng/mL)	450 (390 - 510)
% of max. rec. dose (mg)	106 of 20 (92 - 121)

Multiple administrations to healthy subjects

9 studies indicated that 13% of test results were statistically significant impaired up to 1 week and 4% up to 1 month [Berghaus 1997].

Summary multiple administrations: Impaired test results possible up to 1 month.

Administration to patients

In an investigation on the development of tolerance in chronic users of temazepam (1-20 years), there was no indication of such a tolerance in comparison with healthy control persons [van Steveninck et al. 1997]. With a high interindividual variability, the prescription of temazepam 20 mg to patients with sleep disorders revealed a statistically significant improvement of objective sleep parameters (efficiency of sleep phases, awake periods after sleep onset, sleep efficiency) and of subjective evaluation of sleep quality when compared to placebo; the benzodiazepine effect was there assessed by electro-encephalographic methods and the saccadic movements of the eyes [Tuk et al. 1997]. In a placebo-controlled study with women suffering from insomnia, an intentional late (2 am) administration of a single dose of temazepam 20 mg exhibited no statistically significant deficits of psychomotor performance (memory) or the parameters of driving simulation (speed, reaction time), when tested 5.5 hours after medication. Essential residual effects on the following day were excluded, however, there was a minority of patients with an increased number of collisions in driving simulation which made a late medication not recommendable [Partinen et al. 2003].

Summary patients: The results of patients with temazepam are heterogeneous. There seem to be only little negative effects on driving performance. The development of tolerance was not described.

3.2.3.5 N05CD01 Flurazepam

(N05CD Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

With respect to flurazepam 22 studies with 203 effects and doses tested between 15 and 45 mg were at hand.

In contrast to other agents flurazepam has considerably active metabolites. Whereas N-1-hydroxyethyl-flurazepam demonstrates a very similar time-dependent kinetic comparable to flurazepam the metabolite desalkylflurazepam illustrates a completely other kinetic (compare

chapter 7): flurazepam presents its maximum concentration about 1 hour p.a. and then declines considerably whereas desalkylflurazepam has its maximum in a broad period of time between 7 and 12 hours p.a. and thereafter declines slowly. Both agents (flurazepam as well as desalkylflurazepam) influence negatively performance. Hence it was impossible to distinguish the impairment described in experimental studies between the effects of the two agents. Therefore neither a time-dependent nor a concentration-dependent analysis with respect to flurazepam was meaningful. The 15 mg dose as well as the 30 mg dose (the dose 45 mg was tested only with 8 effects) showed over a time span up to 7 hours p.a. (15 mg) and accordingly 12 hours p.a. (30 mg) considerably high performance deficits of more than 50%, the higher dose even about 70% with a "dip" probably caused by the two kinetics or the difference of frequency of impairment between morning and evening administration, compare report on nitrazepam (the following graph shows the distribution of empirical values for 30 mg dose without an approximation). That means flurazepam with its active metabolite desalkylflurazepam illustrated severe impairment over at least 12 hours p.a. and the performance deficits probably will not diminish up to more than 24 hours.

Flurazepam 30 mg, time-dependent impairment (16 studies, 84 effects)

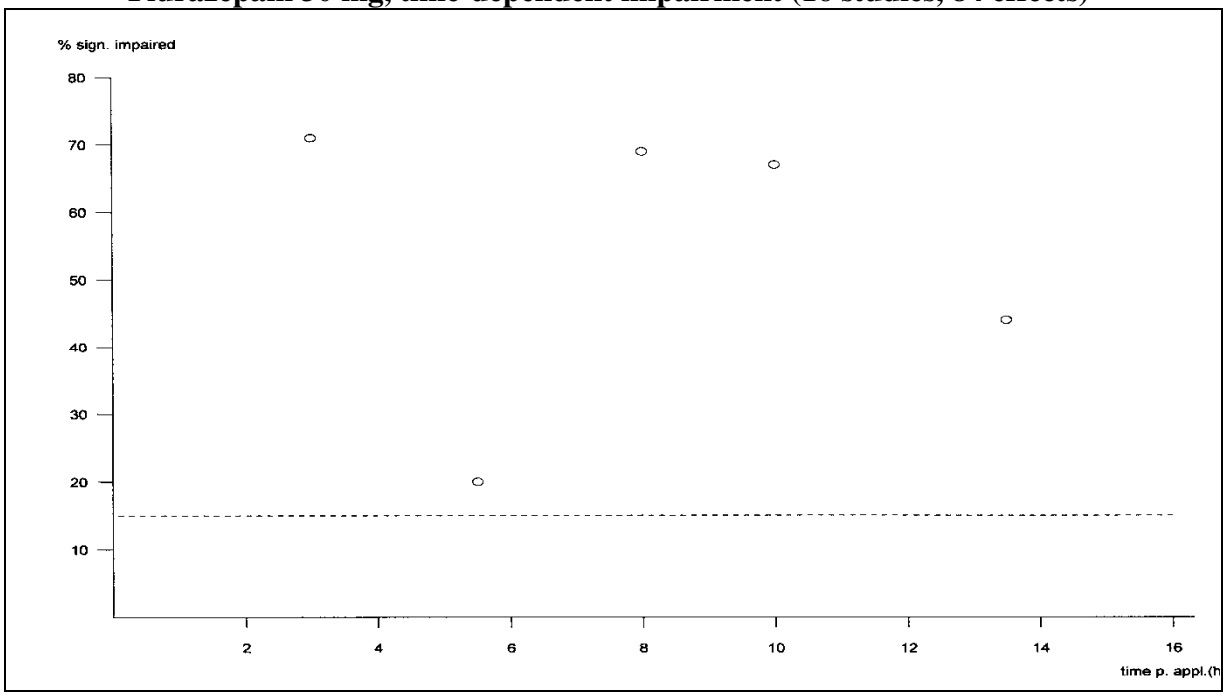

Figure 32: Flurazepam 30 mg, time-dependent impairment.

Table 29: Flurazepam, summary of results.

Summary **Single administration**	**N05CD01 Flurazepam**	
Number of studies	22	
Number of effects	203	
Checked doses (mg)	15 - 45	
Recommended dose (mg)	15 - 30	
Tabularly evaluable doses (mg)	15 *)	30 *)
No. studies / no. effects	9 / 61	16 / 84
Max. sign. impaired test results (%)	approx. 65 - 70	approx. 70 - 75
Hour p.a. of maximum impairment	approx. 2 - 4	approx. 2 - 11
Alcohol equivalence of max. imp. (%)	>0,08	>0,08
Duration p.a. until <15% impairment (h)	>24	>24
Degree of impairment	not meaningfully calculable due to active metabolite	
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not meaningfully calculable due to active metabolite	

*) no curve fitting due to active metabolite

Multiple administrations to healthy subjects

In about 12 studies published before 1983 37% of 82 effects were statistically significant impaired up to 1 week, no impairment (14 effects) was found for the time interval between 1 week and 1 month [Berghaus 1997]. Flurazepam 30 mg/day at bedtime vs. placebo over a period of 2 days statistically significant impaired driving tests (highway driving and car-following) which were conducted in healthy female volunteers in the morning of day 3, 10 hours after the last dose [Vermeeren et al. 1998].

Summary multiple administrations: Impairment for at least up to 1 week.

Administration to patients

The studies with patients illustrated that in the first week of treatment and even up to at least one month there are considerable reductions of performance [Berghaus 1997].

Summary patients: Impairment without improvement over months.

3.2.3.6 N05CD02 Nitrazepam

(N05CD Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

With respect to nitrazepam we gathered 44 publications in which 417 effects were described. Doses between 2.5 and 15 mg were tested. The research concentrated on doses 5 mg (185 effects) and 10 mg (204 effects) whereas the other doses emerged only very infrequently (≤15 effects).

In contrast to other agents and in contrast to the kinetics for nitrazepam the time-dependent analysis of performance showed an irregular distribution of statistically significant impaired effects for both doses 5 mg and 10 mg.

Concerning the 5 mg dose for the first 3 hours p.a. impairment came to 14 to 25%. Between the 4^{th} and 8^{th} hour p.a. no single effect out of 13 effects measured were impaired. Thereafter up to 15 hours p.a. the impairment fluctuated between 3% and 33%.

The same held true for 10 mg dose but, of course, with higher impairment. In the first 3 hours the impairment fluctuated between 50% and 68%. Between the 4^{th} and 8^{th} hour p.a. no single effect out of 21 effects measured were impaired. From 9 up to 15 hours p.a. the impairment moved between 12% and 60% without a transparent trend.

Of course, a time-dependent approximation as well as a concentration-dependent approximation of empirical data is not meaningful due to the described inconvenient distribution of data. (In the following two graphs only the empirical data are drawn. If necessary neighboring classes of hours are aggregated to reach a number of at least 10. Hence, for example the value 8% for point of time 7.5 is aggregated for the 3 hours between 6 and 9 p.a.).

Of course, the question emerged how to explain such an inconvenient distribution. At first, there seemed to be no outliers. Especially the results of the time span with no statistically significant impaired effects were based on 7 different research groups and 5 different performance areas so that there was no hint for a bias. Secondly, so far as we know, nitrazepam has no active metabolites that could explain the unusual run of impairment. Thirdly the kinetics of nitrazepam may explain the impairment late in time p.a. but not the missing deficits between the 4^{th} and 8^{th} hour p.a.

But there was at least one essential difference in the experimental design between those effects measured in the first 8 hours p.a. and those effects measured later: in the first group

the agent was administered at most in the morning or in the midday (89% of 179 effects with known time of administration), in the second group the agent was administered at most in the evening or in the night (96% of 211 effects). Hence the statistics confirmed the typical "hang-over". The duration of effects of nitrazepam essentially depended on the time of day when the substance was administered and consequently there exists no correlation between concentration and percentage of impaired effects.

Furthrtmore qualitative differences in test procedures may have be contributed to the "gap".

Nitrazepam 5 mg, time-dependent impairment (24 studies, 173 effects)

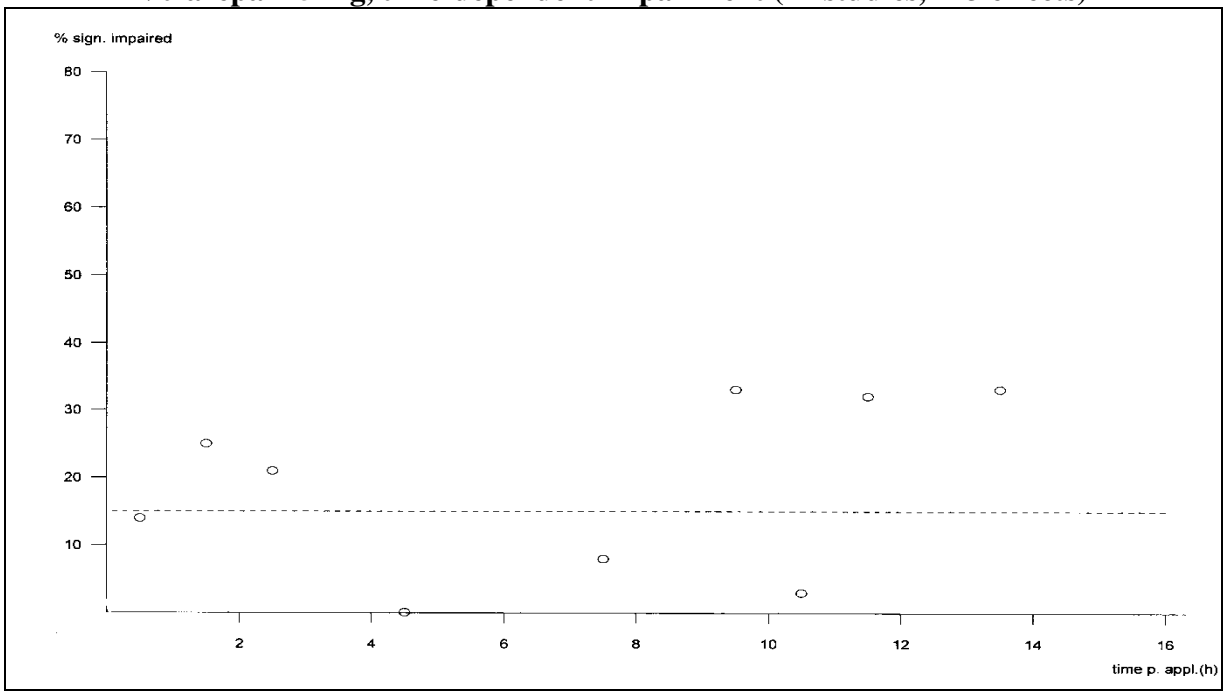

Figure 33: Nitrazepam 5 mg, time-dependent impairment.

Nitrazepam 10 mg, time-dependent impairment (17 studies, 190 effects)

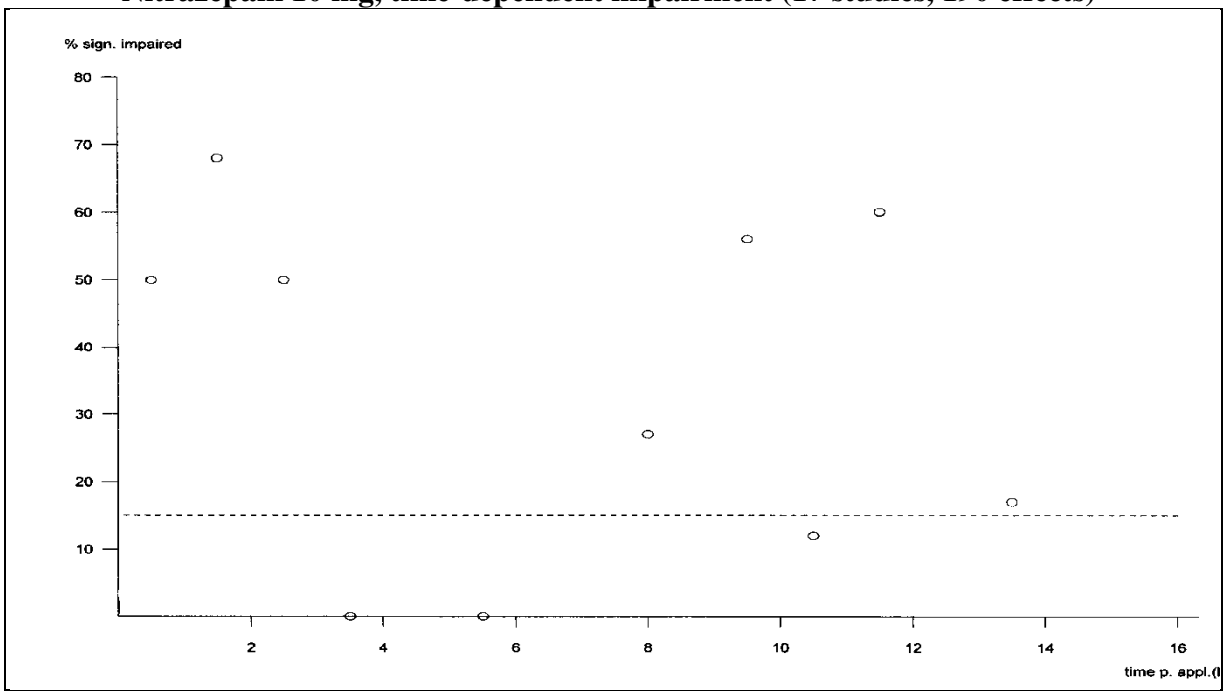

Figure 34: Nitrazepam 10 mg, time-dependent impairment.

Table 30: Nitrazepam, summary of results.

Summary **Single administration**	**N05CD02 Nitrazepam**	
Number of studies	44	
Number of effects	417	
Checked doses (mg)	2.5 - 15	
Recommended dose (mg)	2.5 - 5	
Tabularly evaluable doses (mg)	5 *)	10 *)
No. studies / no. effects	24 / 173	17 / 190
Max. sign. impaired test results (%)	15 - 35	70
Hour p.a. of maximum impairment	0 - 15	0 - 15
Alcohol equivalence of max. imp. (%)	0,03 - 0,08	>0,08
Duration p.a. until <15% impairment (h)	>15	>15
Degree of impairment	not calculable due to different impairment profiles dependent on time of administration	
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not calculable due to different impairment profiles dependent on time of administration	

*) no curve fitting due to different impairment profiles

Multiple administrations to healthy subjects

In about 8 studies approx. 10% of test results were statistically significant impaired up to 1 week, 13% impairment rate was found for the time interval between 1 week and 1 month [Berghaus 1997].

Summary multiple administrations: Possible impairment at least up to 1 month.

Administration to patients

Studies in patients revealed only minor deficits later than one week after starting a therapy [Berghaus 1997]. An interesting experiment was conducted by Peck et al 1977 in which the dose administered was varied. Because of the importance of the results even for othrt agents we will report it in the "comparison of hypnotics".

Summary patients: Minor impairment up to 1 month.

3.2.3.7 N05CD03 Flunitrazepam

(N05CD Benzodiazepine derivative, long half-life)

Single administration to healthy subjects

29 studies with 491 effects built up the basis for the meta-analytic approach to flunitrazepam. Of the doses tested (0.5 mg - 4 mg), the frequencies of effects of the 1 mg and the 2 mg doses were sufficiently high to try a curve-fitting. At first we had to eliminate 3 publications from 2 working groups because their results were completely different from all other studies that surrounded these studies with respect to dose and time.

Bearing in mind the results of nitrazepam namely that there could be different distributions between the results of effects administered in the morning or at noon in comparison to the administration in the evening or by night a corresponding analysis of this influencing factor for flunitrazepam 1 mg showed only at the 11th hour p.a. some statistically significant reduced effects whereas before and thereafter no effects were statistically significant impaired. Only one study in the 11th hour p.a. administered the agent in the morning and this study indicated no deficits. That could be a hint that even with flunitrazepam there may be a minor "hang-over". But since the percentage of statistically significant reduced effects was very low and hence would not influence the curve-fitting essentially we did not eliminate the effects for the 11th hour p.a. The curve for 1 mg climbs very quickly to its maximum of about 66%

statistically significant impaired test results in the first hour p.a. The maximum of dynamics was earlier than the maximum of the kinetics. It takes about 5 hours to the 15% level.

The same held true for the 2 mg dose. Research groups that administered the agent in the morning or at midday measured effects only up to 9 hours p.a. whereas all effects measured later than 9 hours p.a. stem from administrations in the evening or at night. But since there was no differences between the percentage of statistically significant reduced effects between the 9^{th} hour p.a. (morning, midday application) and the 10^{th}-11^{th} hour (evening, night application) and only the value for the 12^{th}-15^{th} hour was a little bit higher we did not select cases and calculated the fitting curve based on all effects measured. The fitted curve of the empirical results for 2 mg illustrated a considerably higher maximum (92%) as for the 1mg dose. Accordingly, it takes about 14 hours to the 15% level and the degree of impairment was the 4fold as for 1 mg.

Concerning the concentration-dependent analysis of the after absorption phase ≥1.5 hour p.a. there was a continuously and sufficiently numbered distribution of frequencies up to a concentration of 10 ng/mL. According to the curve-fitting (R^2 = .993) the 30% equivalent was 5.4 ng/mL. This value was in good agreement with the time-dependent curve for 1 mg as well as 2 mg bearing in mind the variability of kinetic calculations.

Flunitrazepam 1 mg, time-dependent impairment (15 studies, 155 effects)

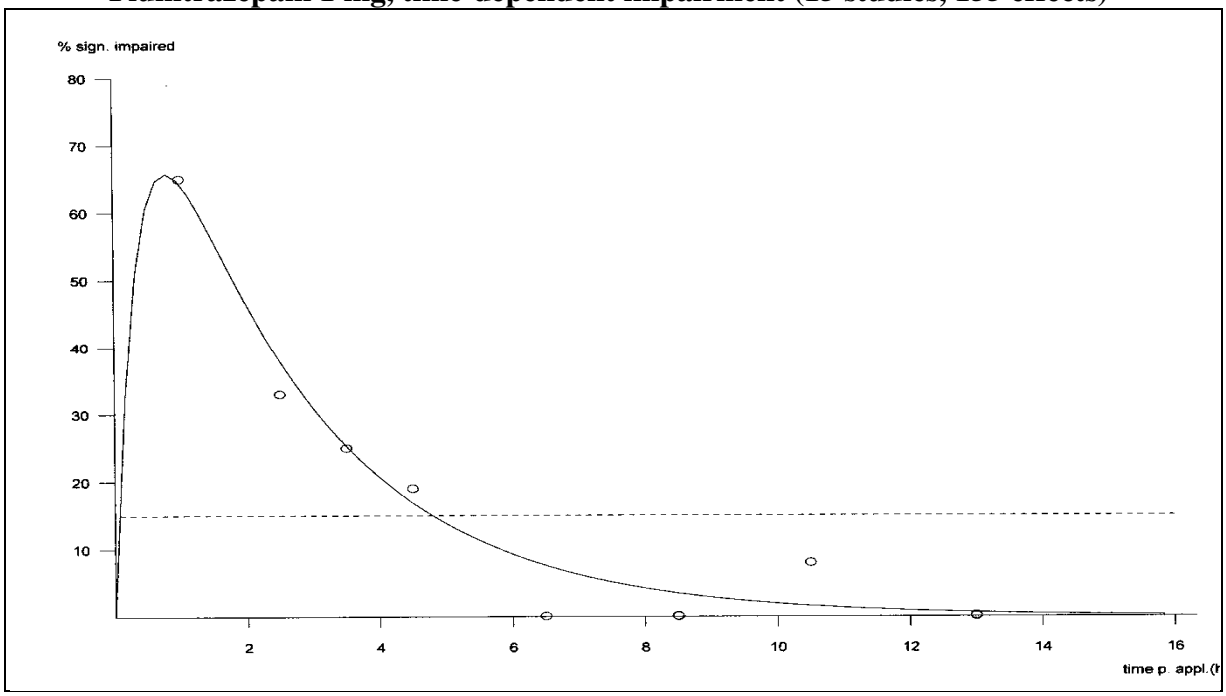

Figure 35: Flunitrazepam 1 mg, time-dependent impairment.

Flunitrazepam 2 mg, time-dependent impairment (11 studies, 176 effects)

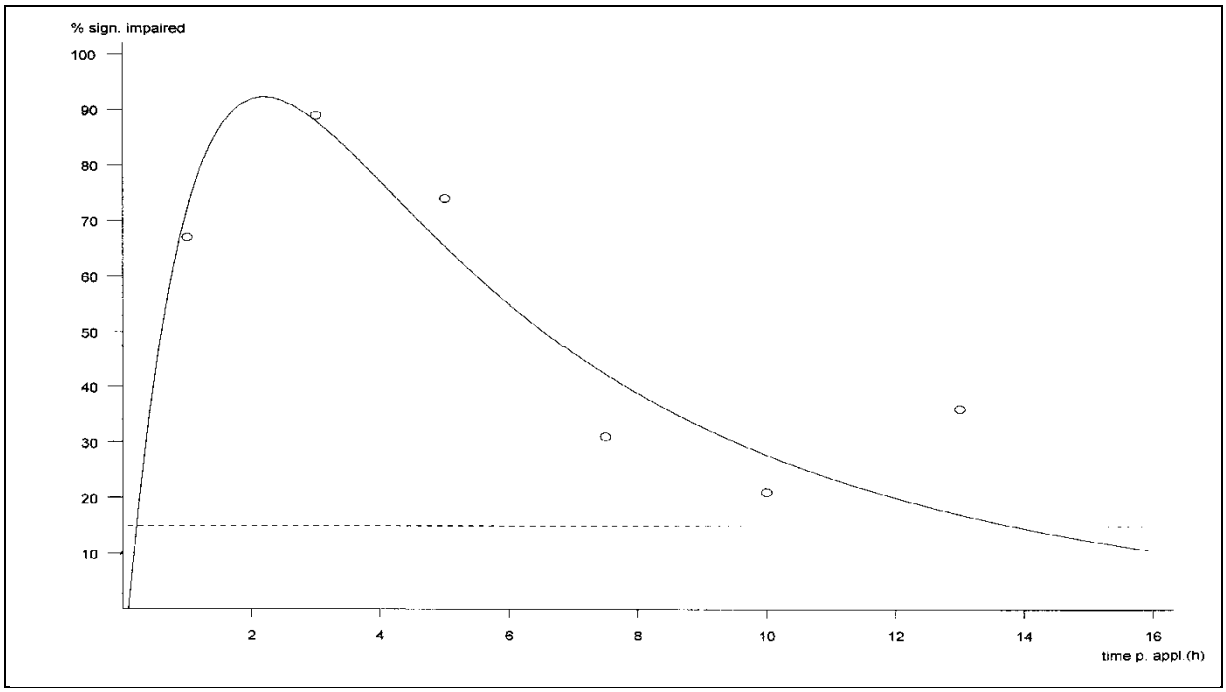

Figure 36: Flunitrazepam 2 mg, time-dependent impairment.

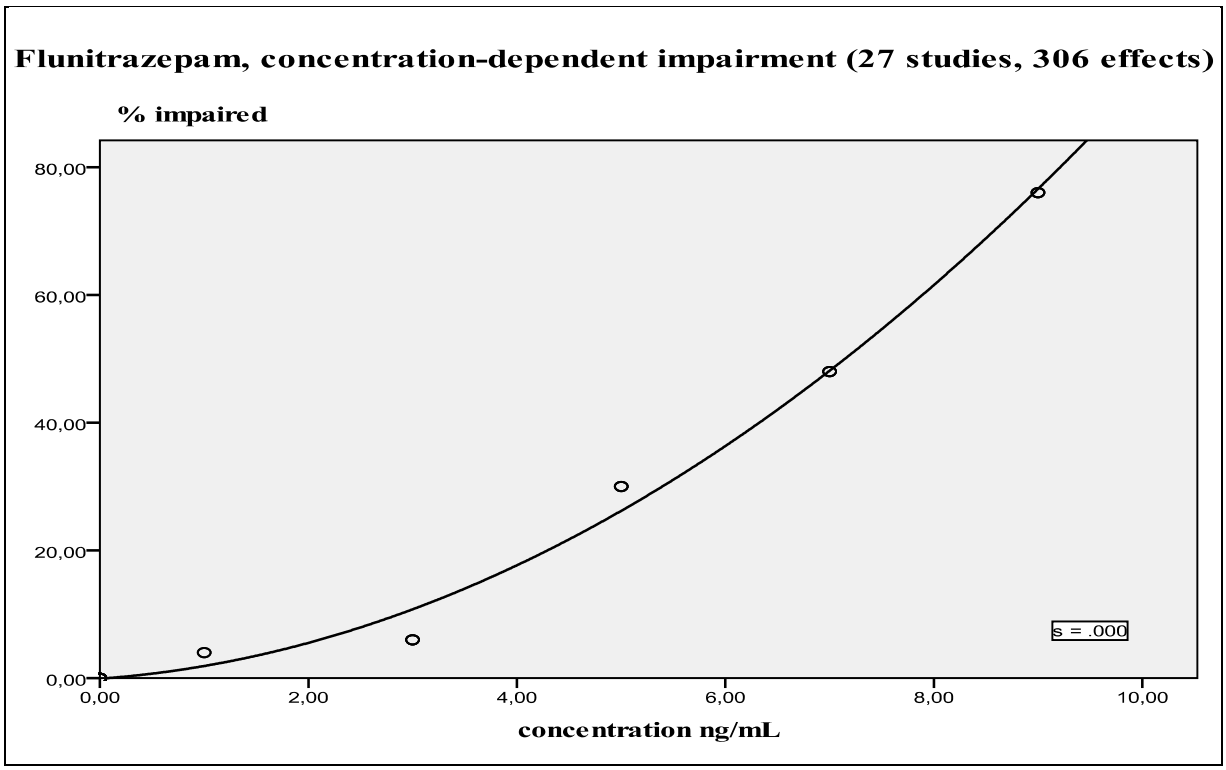

Figure 37: Flunitrazepam, concentration-dependent impairment.

Table 31: Flunitrazepam, summary of results.

Summary **Single administration**	**N05CD03 Flunitrazepam**	
Number of studies	29	
Number of effects	491	
Checked doses (mg)	0.5 - 4.0	
Recommended dose (mg)	0.5 - 1	
Tabularly evaluable doses (mg)	1	2
No. studies / no. effects	15 / 155	11 / 176
Max. sign. impaired test results (%)	66 (60 - 98)	92 (81 - 100)
Hour p.a. of maximum impairment	0.75 (0.50 - 1.0)	2.25 (2.0 - 2.25)
Alcohol equivalence of max. imp. (%)	>0,08	>0,08
Duration p.a. until <15% impairment (h)	5.0 (3.75 - 7.75)	14.0 (12.75 - 15.25)
Degree of impairment	115 (85 - 177)	461 (374 - 562)
0,05% alcohol equ. (ng/mL)	5.4 (5.0 - 5.8)	
% of max. rec. dose (mg)	70 of 1 (65 - 75)	

Multiple administrations to healthy subjects

There are only a few studies concerning the acute effect approximately 1 to 2 hours after administration. In these cases, a development of tolerance seems to be unusual, deficits of performance have to be expected. However, only multiple administration up to 8 days was investigated: Thus, the application of flunitrazepam 1 mg caused continuing impairment of reaction time, short-term and long-term memory within this time interval when repeated tests were carried out [Ingum et al. 1993, Ingum u. Bjorklund 1994]. Flunitrazepam in a dose of 2 mg for 3 nights produced memory deficits, too [Fossen et al. 1983].

In contrast to these acute findings, essential deficits need no longer to be considered in cases with a long-term therapy on the next morning after an administration in the evening before. These tests included investigations which were done about 10 to 13 hours after the administration of flunitrazepam 0,5 mg - 2 mg during time intervals of up to 8 days [Lader et al. 1982, Hindmarch 1977, Hindmarch et al. 1977, Stanley et al. 1987]. A lot of parameters such as reaction, memory, time assessment etc. were evaluated. So far as an impairment still was present (e.g. subtraction test), the performance developed to normal level from the second

to the fourth night after an intake [Stanley et al. 1987]. Following high doses of 2 mg of flunitrazepam for a period of four nights, on the next morning the feeling of sleepiness was mentioned, however, in driving simulator tests no differences were observed compared to placebo [Laurell u. Törnros 1987 u. 1991]. The development of tolerance which was documented by an improvement of saccadic eye movements [Salonen et al. 1986] or memory [Bixler et al. 1979] has already been noticed after not more than three applications of 2 mg of flunitrazepam when tested on the next morning.

Summary multiple administrations: The primary impairment by flunitrazepam can be improved after several days (up to about one week), however, in single cases some deficits may persist for longer times.

Administration to patients

Flunitrazepam at higher doses of mainly 2 mg or more was compared with placebo in patients with sleep disorders. Against the background of great interindividual variability several laboratory tests brought no statistically significant impaired results after therapy periods of up to 15 days [Linnoila et al. 1982]. Furthermore, impairments were seen on the next morning within time intervals of up to 7 days concerning the speed of special driving operations and the frequency of wrong operating procedures, which however did not differentiate from the normal spectrum of healthy individuals [Schmidt et al. 1985]. In driving experiments, hang-over effects were noticed on the second day of administration concerning the lateral deviation [Volkerts et al. 1984, Volkerts and O´Hanlon 1986]. Partially, reduced memory function and increased sleepiness were reported [Vermeeren and O´Hanlon 1991, Vermeeren et al. 1995]. A study with the administration of only 1 mg of flunitrazepam versus placebo disclosed statistically significant deficits of attention and memory on the next morning [Dujardin et al. 1998]. The plasma concentrations of flunitrazepam were mainly not correlated with the degree of performance impairment.

Summary patients: Flunitrazepam in patients with insomnia reveals deficits at least on the first mornings after the first intake (partly up to several weeks). In other studies no differences were observed compared to healthy individuals.

3.2.3.8 N05CF01 Zopiclone

(N05CF Benzodiazepine related drug)

Single administration to healthy subjects

21 studies with 331 effects and doses tested between 2.5 mg and 10 mg could be integrated in the evaluation. Research concentrated on 7.5 mg that means the recommended dose whereas doses 2.5 mg, 5 mg and 10 mg were tested only per 9 effects each.

The time-dependent impairment curve (there were no hints for outliers) for 7.5 mg demonstrated 58% statistically significant impaired effects as the maximum in the 3rd hour p.a. The impairment lasted for about 11.5 hours. There is only a marginal hint for "hang over".

The distribution of concentrations was continuously and sufficient high up to the maximum concentration of about 50 ng/mL. The linear fitted curve (effects measured ≥2.0 hours p.a., R^2 = .912) revealed the 30% level at 26 ng/mL in full agreement with the time-dependent impairment curve.

Zopiclone 7.5 mg, time-dependent impairment (21 studies, 291 effects)

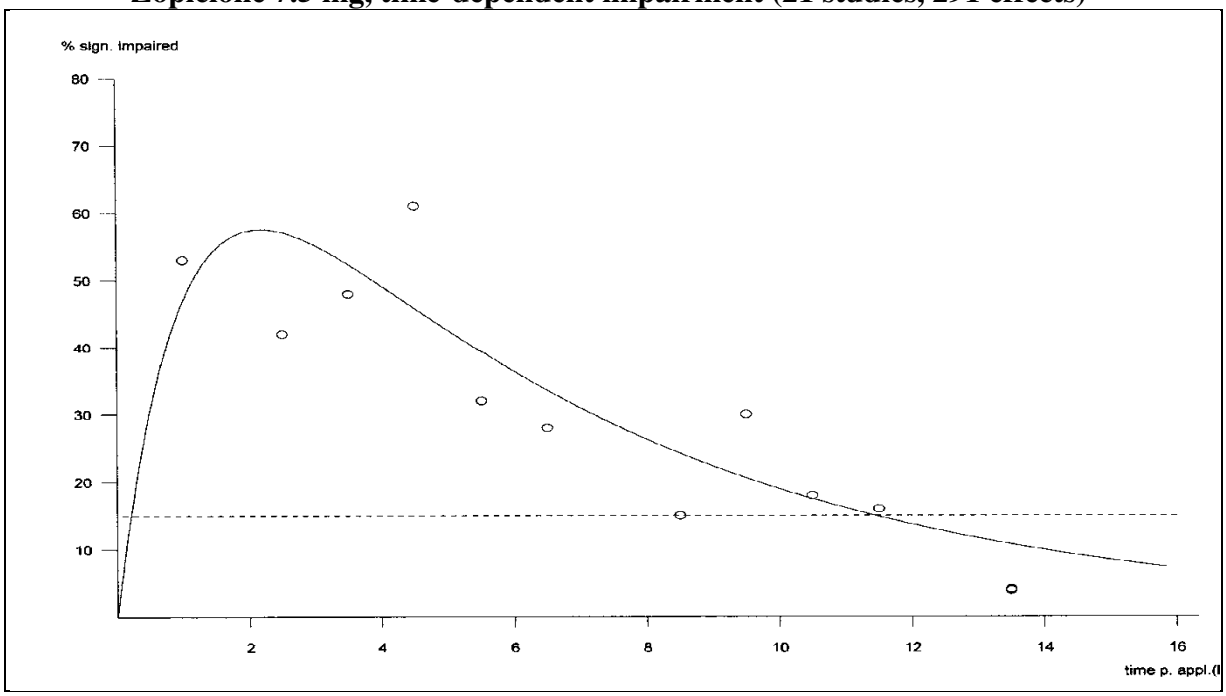

Figure 38: Zopiclone 7.5 mg, time-dependent impairment.

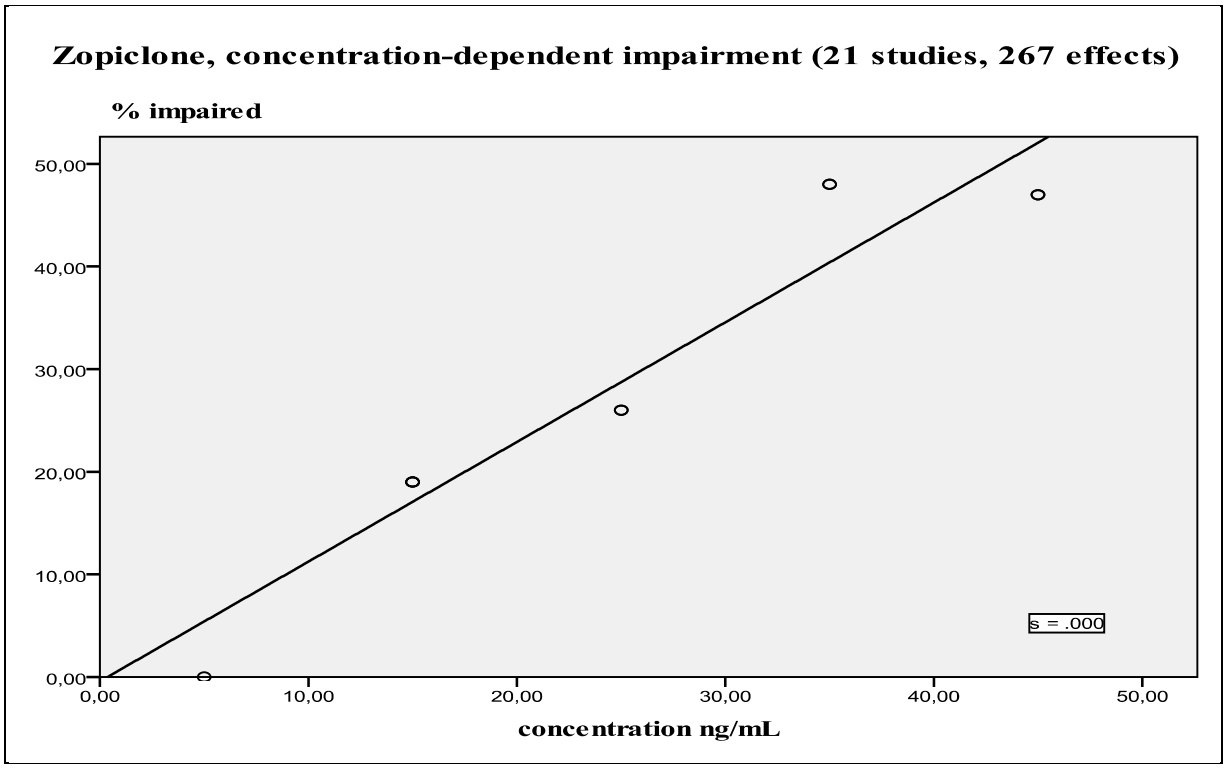

Figure 39: Zopiclone, concentration-dependent impairment.

Table 32: Zopiclone, summary of results.

Summary **Single administration**	**N05CF01 Zopiclone**
Number of studies	21
Number of effects	331
Checked doses (mg)	2.5 - 10
Recommended dose (mg)	7.5
Tabularly evaluable doses (mg)	7.5
No. studies / no. effects	21 / 291
Max. sign. impaired test results (%)	58 (51 - 68)
Hour p.a. of maximum impairment	2.25 (2.25 - 2.25)
Alcohol equivalence of max. imp. (%)	>0,08
Duration p.a. until <15% impairment (h)	11.5 (9.25 - 12.5)
Degree of impairment	240 (174 - 299)
0,05% alcohol equ. (ng/mL)	26 (23 - 30)
% of max. rec. dose (mg)	57 of 7.5 (51 - 66)

Multiple administrations to healthy subjects

Again only a few data were available. The performance deficits in the case of a single daytime dose seem to correspond to those of a single administration. Following the second night of therapy with a small dose of 3,75 mg of zopiclone the eye-hand-coordination and after the common average dose of 7,5 mg the complex reaction time in addition were impaired when testing was done only 2 hours after application [Billiard et al. 1987].

Summary multiple administrations: Zopiclone seems to impair the performance for at least several days (no further data).

Administration to patients

Corresponding to the results of experiments in healthy subjects studies dealing with patients suffering from insomnia revealed only slight evidence of hang-over effects in performance tests on the next morning after an administration in the evening for several weeks [Whitehead et al. 1994]. As a rule, in the morning no negative effects were noticeable. Patients even reported subjectively better handling of their daily work under a permanent therapy with zopiclone 7,5 mg for 6 weeks; performance tests after 2, 4 and 6 weeks disclosed in this study no impairment in e.g. tapping and reaction time [Tamminen u. Hansen 1987]. Similar results were also obtained in performance tests after a therapy with zopiclone of two or three weeks duration [Ngen u. Hassan 1990, Ponciano et al. 1990, Stip et al. 1999]. Under a standard dose of zopiclone 7,5 mg and a comparison with placebo, numerous single tests or questionnaires, respectively, on memory, attention, reaction time or coordination and others brought normal results in repeated procedures during a period of up to four weeks [Stip et al. 1999, Elie et al. 1990, Fleming et al. 1990, Mamelak et al. 1987]. In one study with a 3-week therapy interval, however, 75% of the probands complained at least once about a side effect such as sleepiness in the morning [Fleming et al. 1990]. Deficits in driving tests were detectable in the early phase of a therapy with zopiclone 7,5 mg vs. placebo, as statistically significant worse results concerning the lateral deviation were observed after the second administration in the evening, although the insomniac probands had already received hypnotic medication for longer times; the deficit was present up to 10 hours after the administration, it disappeared after 16 hours, at the same time the plasma concentrations reduced to about the half [Volkerts u. O´Hanlon 1986]. More recent study data [Staner et al. 2005] on patients with insomnia, who received zopiclone 7,5 mg either as single or repeated dose in the evening for one week and were tested in driving simulator 9-11 hours later on the next day, point to a similar direction: in contrast to zolpidem and placebo, zopiclone increased the number of collisions at the time of

testing, it further caused alterations in EEG being typical of benzodiazepine effects which could be interpreted as a prolonged dysfunction of the central activation.

Compared to placebo the therapy with zopiclone 7,5 mg – as well as with other hypnotics – improved the sleep quality statistically significant, which was documented by a reduction/normalization of alterations in polysomnography and EEG as they were typical of patients with sleep disorders and absent in healthy controls [Terzano et al. 2003].

Summary patients: The studies are heterogeneous. Zopiclone patients either demonstrated to have driving impairment in the first week(s) or no deficits at all were noticed. The results seem to depend on the time interval between intake and testing.

3.2.3.9 N05CF02 Zolpidem

(N05CF Benzodiazepine related drug)

Single administration to healthy subjects

Overall we could select 31 studies with 857 effects and doses tested between 5 mg and 20 mg (referring to zolpidemtartrat). For 3 doses (5mg, 10 mg, 20 mg) a tabular evaluation seemed possible, especially for the 10 mg dose with by far the most effects measured.

For the 5 mg dose only 3 of 124 effects showed statistically significant impaired. All 3 effects were measured in the 2nd hour p.a. 7 publications with 41 effects contributed to this result, and in 3 publications in each case 1 negative effect could be found. That means on the one hand that there is no outlier and on the other hand that this time period is the only category with negative effects (7.3% of 41). It is clear that a curve-fitting was not meaningful.

The 10 mg dose (1 study was selected because it was an outlier in another agent) showed its maximum impairment (50%) in the 2nd hour p.a. too. It lasted 7 hours till the decrease reached 15%.

Expectedly, the 20 mg dose revealed a higher maximum (64%) at the same time. Even the time period till the 15% line lasted longer (17 hours) and the degree of impairment was about the 2fold in comparison to the 10 mg dose.

The concentration-dependent evaluation could be based on 656 effects (up to 160 ng/mL) measured ≥1.5 h p.a. The linear fitted curve (R^2 = .939) showed the 30% level at 71 ng/mL. This could be a hint that the time-dependent approximation for 10 mg should show a steeper decline and for 20 mg a smoother decline.

Zolpidem 10 mg, time-dependent impairment (27 studies, 379 effects)

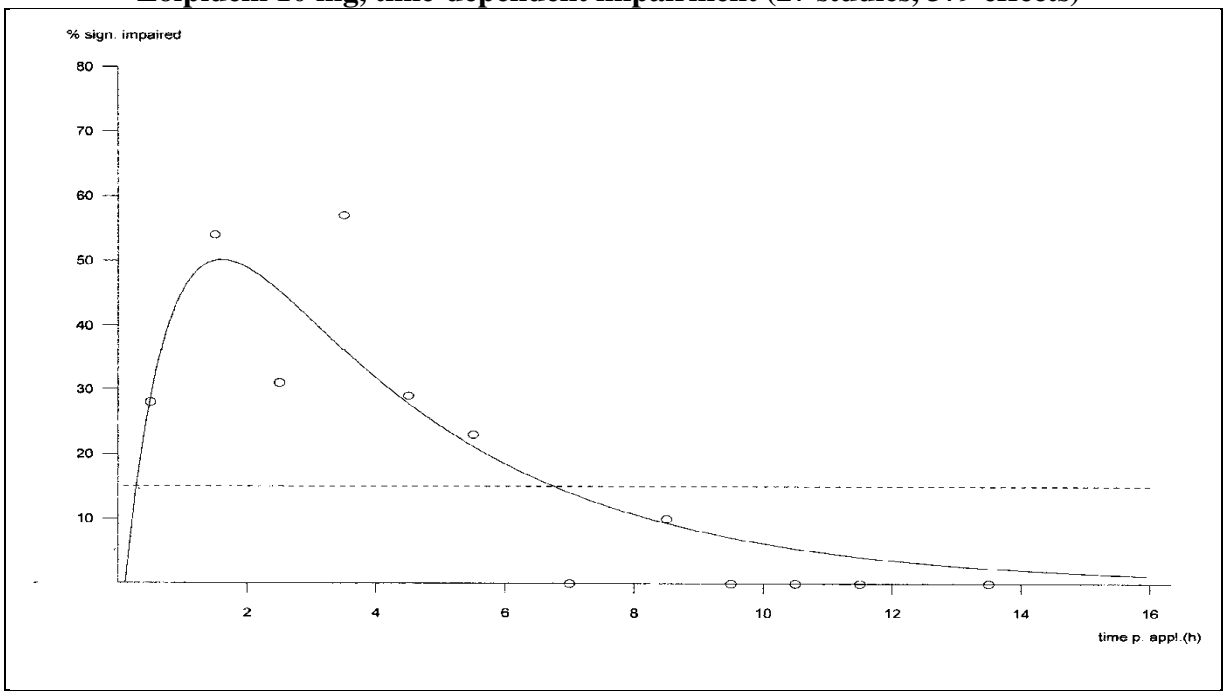

Figure 40: Zolpidem 10 mg, time-dependent impairment.

Zolpidem 20 mg, time-dependent impairment (13 studies, 172 effects)

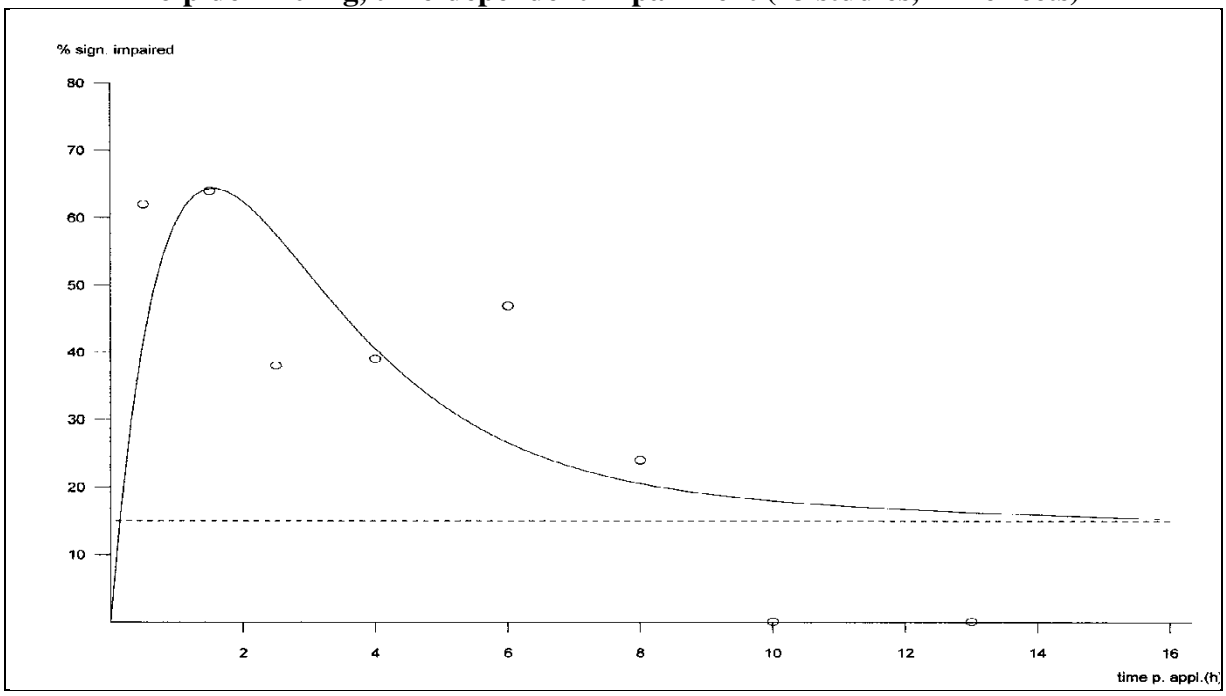

Figure 41: Zolpidem 20 mg, time-dependent impairment.

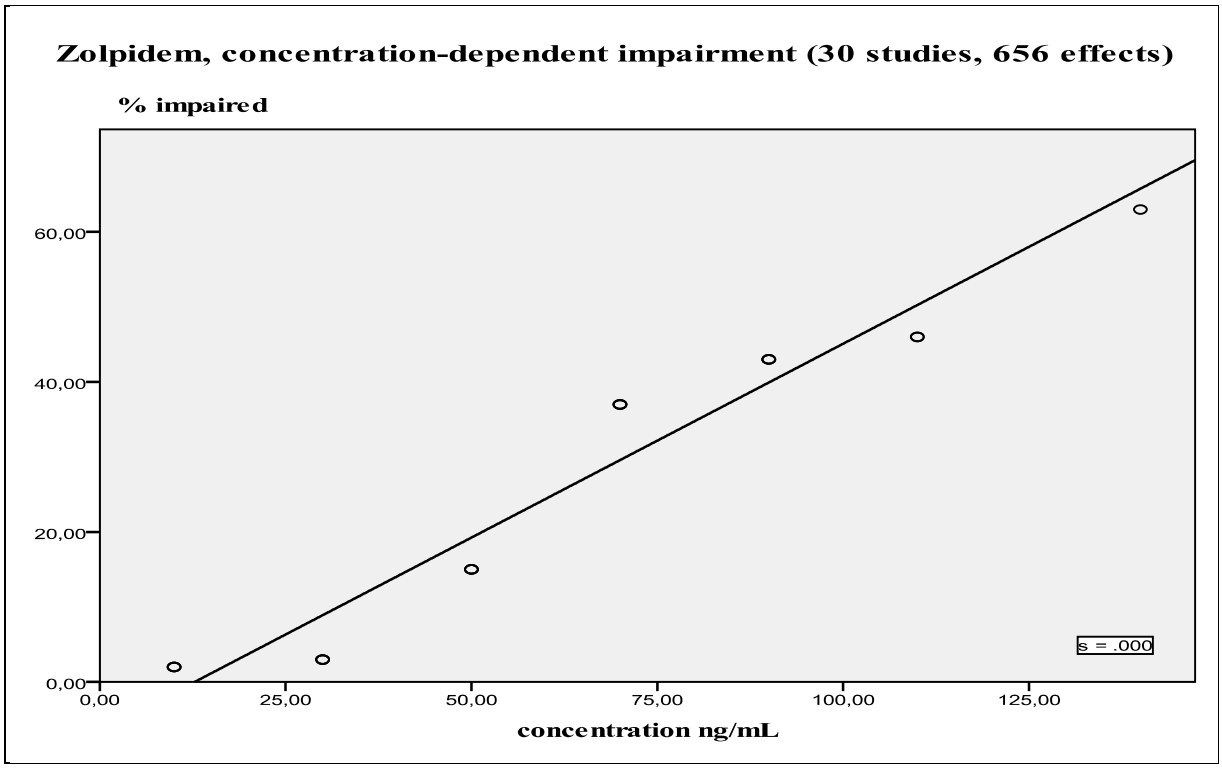

Figure 42: Zolpidem, concentration-dependent impairment.

Table 33: Zolpidem, summary of results.

Summary **Single administration**	**N05CF02 Zolpidem**		
Number of studies	31		
Number of effects	857		
Checked doses (mg)	5 - 20		
Recommended dose (mg)		10	
Tabularly evaluable doses (mg)	5 *)	10	20
No. studies / no. effects	7 / 124	27 / 376	13 / 172
Max. sign. impaired test results (%)	0 - 10	50 (43 - 57)	64 (59 - 75)
Hour p.a. of maximum impairment	1-2	1.5 (1.5 - 1.5)	1.5 (1.0 - 1.5)
Alcohol equivalence of max. imp. (%)	<0,03	approx. 0,08	>0,08
Duration p.a. until <15% impairment (h)	0	7.0 (6.5 - 8.25)	17.0 (10.5 - 17.0)
Degree of impairment	0	119 (81 - 159)	214 (183 - 258)
0,05% alcohol equ. (ng/mL)		71 (65 - 78)	
% of max. rec. dose (mg)		73 of 10 (67 - 80)	

*): no curve fitting due to minimal impairment

Multiple administrations to healthy subjects

There are only a few data. Whereas an impairment of saccadic eye movements was detected after each dose of zolpidem (5 mg, 10 mg or 20 mg) 1.5 hours after the first nocturnal administration, it was only present after the highest dose at a time 7 days later; independent of the dosage, there were no deficits at all on the next morning (9-11 hours later) [Richens et al. 1993]. Similarly, no impairment, among others of the reaction time, was noticed 10.5 hours after administration of zolpidem for 2 nights (doses of 2.5 mg up to 20 mg) [Merlotti et al. 1989].

Summary multiple administrations: Zolpidem shows only little impairment, even after short time intervals of a few days. Other studies stated that zolpidem at regular doses did not affect driving performance at all.

Administration to patients

No reduced performance was obtained during a two-week therapy and a following test of coordination, attention, memory etc. approximately 8.5 hours after the intake [Monti 1989]. As well the application of zolpidem 10 mg for 7 nights was not associated with a reduced performance in the morning in persons with sleep disorders [Kryger et al. 1991]. The testing of attention in patients with chronic insomnia showed no slump even during an observation time of 35 days and application of 10 mg or 15 mg of zolpidem [Scharf et al. 1994]. In laboratory testing, zolpidem did not cause so called hang-over effects on the following morning, neither in usual doses of 10 mg nor in higher doses up to 20 mg, while multiple applications were done for 3 or 5 days, respectively, in studies with patients suffering from insomnia [Frattola et al. 1990, Fleming et al. 1995]. The positive effects concerning reaction time, attention and vigilance could also be observed in patients, who had received zolpidem 10 mg and placebo: In driving experiments in the morning, they obtained good results with regard to lateral deviation and memory function [Vermeeren et al. 1995]. In a placebo-controlled study with patients (n=136), where short-term sleep disorders (duration of 3-9 nights) were treated with zolpidem 10 mg for 7-10 nights, neither sleepiness nor concentration deficits were registered on the next day over the complete treatment period using subjective questionnaires; side effects had equal frequencies in both groups; the extent of sleepiness decreased in both groups with increasing study time [Dockhorn and Dockhorn 1996]. Compared to placebo the single application of zolpidem 10 mg in the morning showed no effects on memory and attention, sleep structure and cognitive functions were not disturbed [Dujardin et al. 1998]. In the case of an intake of 10-20 mg of zolpidem in the evening,

generally no performance deficits were observed on the next morning. Patients with insomnia (both without medication and with zolpidem 10 mg) and healthy individuals did not differ statistically significant on the following morning with regard to numerous parameters such as concentration, attention, memory and reaction time [Saletu-Zyhlarz et al. 2000]. Compared to placebo the therapy with zolpidem 10 mg – as well as with other hypnotics – improved the sleep quality statistically significant, which was documented by a reduction/normalization of alterations in polysomnography and EEG as they were typical of patients with sleep disorders and absent in healthy controls [Terzano et al. 2003]. In a placebo-controlled study with women suffering from insomnia, an intentional late (2 am) administration of a single dose of zolpidem 10 mg exhibited no statistically significant deficits of psychomotor performance (memory) or the majority of parameters of driving simulation (speed, reaction time), whereas deviations of the lane position occurred statistically significant more frequently when tested 5.5 hours after medication. Essential residual effects on the following day were excluded, however, there was a minority of patients with an increased number of collisions in driving simulation which made a late medication not recommendable [Partinen et al. 2003]. New study data [Staner et al. 2005] confirmed the older findings for patients with sleep disorders who received zolpidem 10 mg in the evening for one week either as a single or multiple dose and were tested in driving simulator approximately 9-11 hours later on the next day. Whereas the administration of zopiclone and lormetazepam produced conspicuous findings (see respective chapter), zolpidem did not differ from placebo effects (number of collisions, deviation from speed or speed limit, lateral deviation). The missing hang-over effects of zolpidem were associated with normal activity in EEG. On the other hand, despite an improved subjective sleep quality, recent Japanese investigations pointed out, that mild sleepiness on the next morning was present as the most frequent side effect of zolpidem 10 mg in some patients (3 out of 14, 3-day administration, placebo before and after study) [Uchimura et al. 2006]. The residual effects were regarded as being less severe as with a dose of 0.25 mg of brotizolam supposed to have a comparable potential.

Zolpidem-MR (modified release):

In order to achieve a sufficient effect of zolpidem with its short half-life (2-3 hours) during the whole night, a preparation with delayed release (modified release, MR) was developed. In a study with young healthy persons (n=18), a single dose of 12,5 mg produced a good sedating effect during sleep phase and caused no essential impairment of psychomotor or cognitive functions except tracking when tested in comparison to placebo 8 hours later on the next day [Blin et al. 2006]. Sedating side effects were only present occasionally in both

groups (n=2/18). For an evaluation among others tests for reaction time, memory function and compensatory tracking were used. A similar study design was applied to elderly healthy test persons over 65 years of age (n=24): zolpidem-MR doses of 6,25 mg and 12,5 mg did not cause statistically significant residual effects on the next morning [Hindmarch et al. 2006]. Complaints on side effects were much more frequent than in young test persons (up to 65%), however, associated problems were not severe and appeared with comparable frequencies in the three groups with either zolpidem or placebo.

Summary patients: Due to its short half-life, zolpidem did not exhibit any residual effects in most of the studies. The results of patients were comparable to the placebo group and the healthy controls. Only a minority of patients and studies showed slighter degrees of sleepiness as a side effect.

3.2.3.10 N05CF03 Zaleplon

(N05CF Benzodiazepine related drug)

Single administration to healthy subjects

12 publications with 350 effects described built up the basis for the evaluation of zaleplon. Doses 10 mg (262 effects) and 20 mg (88 effects) were administered.

The curve-fitting of the 10 mg dose (260 effects measured up to 15 hours p.a.) demonstrated deficits in essence only for the first 3 hours p.a. This result was in line with the 20 mg dose where the deficits concentrated in the 2nd hour p.a. and corresponded to the kinetic curve. The concentration curve climbed up in the first hour to its maximum and than rapidly decreased within the next two hours to a concentration of ca. 10 ng/mL.

For that reason a concentration-dependent approximation of the empirical points was not meaningful. By far most of the effects were measured during a concentration range up to about 10 ng/mL (76% of the 336 effects of the after maximum concentration) and indicated only marginal deficits (0 to 6% within the 2 ng/mL concentration classes). Starting with about 10 ng/mL even deficits increased. But because there remained only 82 effects on which an approximation-curve could be based a valid interpretation was impossible. The 0,05% alcohol equivalent seemed to be located between 15 and 19 ng/mL, a good agreement to the 10 mg time-dependent approximation.

Zaleplon 10 mg, time-dependent impairment (12 studies, 260 effects)

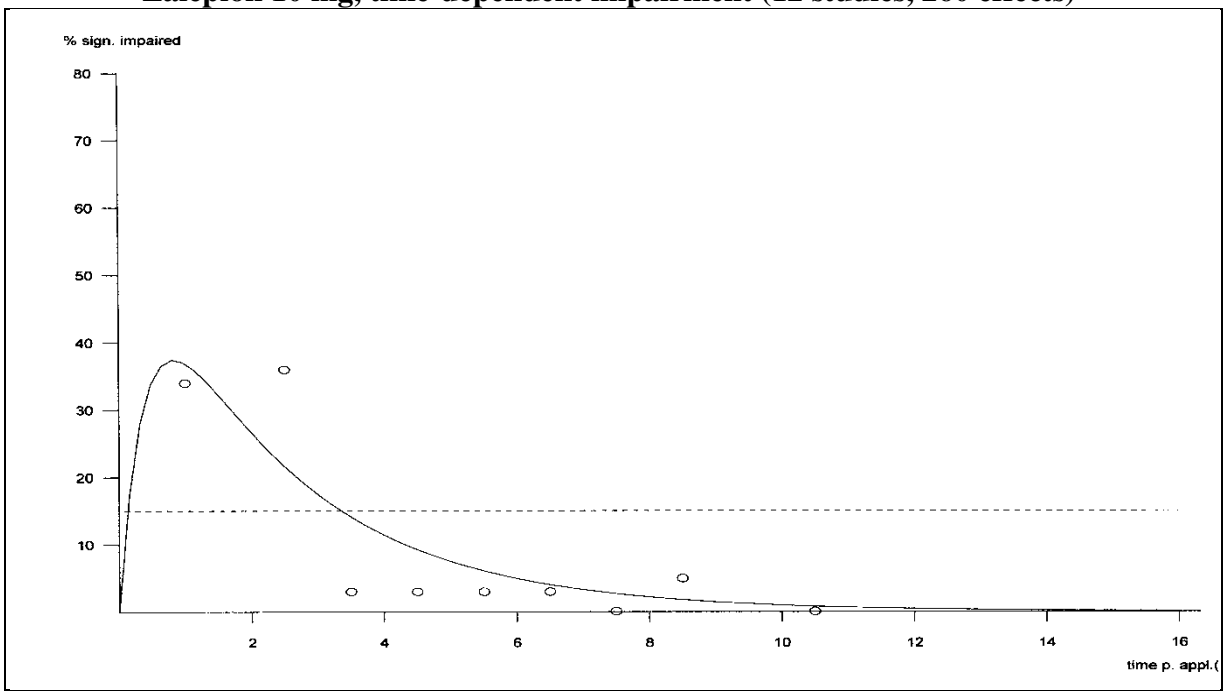

Figure 43: Zaleplon 10 mg, time-dependent impairment.

Table 34: Zaleplon, summary of results.

Summary **Single administration**	**N05CF03 Zaleplon**
Number of studies	12
Number of effects	350
Checked doses (mg)	10 and 20
Recommended dose (mg)	10
Tabularly evaluable doses (mg)	10
No. studies / no. effects	12 / 260
Max. sign. impaired test results (%)	37 (34 - 44)
Hour p.a. of maximum impairment	0.75 (0.75 - 1.0)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08
Duration p.a. until <15% impairment (h)	3.5 (3.0 - 4.25)
Degree of impairment	40 (28 - 60)
0,05% alcohol equ. (ng/mL)	probably 15 - 19
% of max. rec. dose (mg)	probably 75 - 100 of 10

Multiple administrations to healthy subjects

There are no data on hand. Due to the short half-life of approximately 1 hour, the effect is supposed to be similar to a single administration.

Summary multiple administrations: No data on hand. Similar effect as single administration.

Administration to patients

In only a few studies with patients suffering from sleep disorders, neither performance deficits nor sleepiness were noticed on the next morning after 5 mg or 10 mg of zaleplon versus placebo; longer therapy periods of up to 2 weeks were also considered [Walsh et al. 1998 and 2000].

Summary patients: No deficits were obtained with patients taking zaleplon.

3.2.3.11 Comparison of agents of Hypnotics and Sedatives

Single administration to healthy subjects

Analogous to the antipsychotics and anxiolytics the characteristics of the different agents of the hypnotics/sedatives were summarized in the following tables with the help of which one can inform on the parameters of an interesting substance. The agents are classified according to benzodiazepine derivates with short, medium and long half-life and the Z-substances.

We would like to compare results of the different agents with regard to the degree of performance impairment.

Table 35: Comparison of profiles: N05C Hypnotics and sedatives (N05CD Benzodiazepine derivatives).

Agent	short half-life N05CD05 Triazolam	short half-life N05CD09 Brotizolam	intermediate half-life N05CD06 Lormetazepam	intermediate half-life N05CD07 Temazepam
Number of studies	46	6	13	30
Number of effects	1305	78	161	695
Checked doses (mg)	0.125 - 3.0	0.1 - 0.5	0.5 - 2.0	5 - 60
Recommended dose (mg)	0.125 - 0.25	0.125 - 0.25	0.5 - 2.0	10 - 20
Tabularly evaluable doses (mg)	0.25 0.50	no *)	1	10 20
No. studies / no. effects	34 / 528 21 / 389		11 / 95	9 / 152 12 / 251
Max. sign. impaired test results (%)	41 (37 - 47) 71 (67 - 80)	too few data	27 (22 - 30)	12 (7 - 14) probably approx. 30
Hour p.a. of maximum impairment	2.0 (2.0 - 2.0) 1.75 (1.75 - 1.75)	too few data	0.5 (0.5 - 1.25)	1.25 (.75 - 1.25) probably approx. 2
Alcohol equivalence of max. imp. (%)	0,05 - 0,08 >0,08	too few data	0,03 - 0,05	<0,03 probably approx. 0,05
Duration p.a. until <15% impairment (h)	6.5 (5.75 - 8.25) 10.0 (7.5 - 11.75)	probably 9 for 0.25 mg dose	4.25 (2.0 - 7.75)	0 (0 - 0) probably approx. 4
Degree of impairment	89 (65 - 122) 247 (197 - 323)	too few data	22 (7 - 48)	0 (0 - 0) probably approx. 40
0,05% alcohol equ. (ng/mL)	1.6 (1.5 - 1.8)	(2.8) ((2.3 - 4.5))	(9.2) ((7.5 - 10.6))	450 (390 - 510)
% of max. rec. dose (mg)	80 of 0.25 (75 - 90)	(100) of 0.25 ((82 - 161))	(125) of 1 ((102 - 144))	106 of 20 (92 - 121)
Adaption	In higher dose strong impairment up to 1 week, sometimes up to 1 month	No negative effects	Possible impairment up to 1 week, then full recovery	Impaired test results possible up to 1 month
Results in patients	Improvement of performance but deficits remained	Slight sleepiness for at least several days	Impairment up to several weeks, then normal status possible	Heterogeneous results, slight impairment

*): no curve fitting due to too few data

Table 36: Comparison of profiles: N05C Hypnotics and sedatives (N05CD Benzodiazepine derivatives, long half-life).

Agent	N05CD01 Flurazepam		N05CD02 Nitrazepam		N05CD03 Flunitrazepam	
Number of studies	22		44		29	
Number of effects	203		417		491	
Checked doses (mg)	15 - 45		2.5 - 15		0.5 - 4.0	
Recommended dose (mg)	15 - 30		2.5 - 5		0.5 - 1	
Tabularly evaluable doses (mg)	15 *)	30 *)	5	10	1	2
No. studies / no. effects	9 / 61	16 / 84	24 / 173	17 / 190	15 / 155	11 / 176
Max. sign. impaired test results (%)	approx. 65 - 70	approx. 70 - 75	15 - 35	70	66 (60 - 98)	92 (81 - 100)
Hour p.a. of maximum impairment	approx. 2 - 4	approx. 2 - 11	0 - 15	0 - 15	0.75 (0.50 - 1.0)	2.25 (2.0 - 2.25)
Alcohol equivalence of max. imp. (%)	>0,08	>0,08	0,03 - 0,08	>0,08	>0,08	>0,08
Duration p.a. until <15% impairment (h)	>24	>24	>15	>15	5.0 (3.75 - 7.75)	14.0 (12.75 - 15.25)
Degree of impairment	not meaningfully calculable due to active metabolite		not calculable due to different impairment profiles dependent on time of administration		115 (85 - 177)	461 (374 - 562)
0,05% alcohol equ. (ng/mL)	not meaningfully calculable due to active metabolite		not calculable due to different impairment profiles dependent on time of administration		5.4 (5.0 - 5.8)	
% of max. rec. dose (mg)					70 of 1 (65 - 75)	
Adaption	Impairment for at least up to 1 week		Possible impairment at least up to 1 month		Impairment up to 1 week, sometimes persistence of impairment	
Results in patients	No improvements over months		Minor impairment up to 1 month		Impairment for up to several weeks, other studies without deficits	

*): no curve fitting due to active metabolite or different impairment profiles

Table 37: Comparison of profiles: N05C Hypnotics and sedatives (Z-substances).

Agent	N05CF01 Zopiclone	N05CF02 Zolpidem			N05CF03 Zaleplon
Number of studies	21	31			12
Number of effects	331	857			350
Checked doses (mg)	2.5 - 10	5 - 20			10 and 20
Recommended dose (mg)	7.5		10		10
Tabularly evaluable doses (mg)	7.5	5 *)	10	20	10
No. studies / no. effects	21 / 291	7 / 124	27 / 376	13 / 172	12 / 260
Max. sign. impaired test results (%)	58 (51 - 68)	0-10	50 (43 - 57)	64 (59 - 75)	37 (34 - 44)
Hour p.a. of maximum impairment	2.25 (2.25 - 2.25)	1-2	1.5 (1.5 - 1.5)	1.5 (1.0 - 1.5)	0.75 (0.75 - 1.0)
Alcohol equivalence of max. imp. (‰)	>0,08	<0,03	approx. 0,08	>0,08	0,05 - 0,08
Duration p.a. until <15% impairment (h)	11.5 (9.25 - 12.5)	0	7.0 (6.5 - 8.25)	17.0 (10.5 - 17.0)	3.5 (3.0 - 4.25)
Degree of impairment	240 (174 - 299)	0	119 (81 - 159)	214 (183 - 258)	40 (28 - 60)
0,05% alcohol equ. (ng/mL)	26 (23 - 30)	71 (65 - 78)			probably 15 - 19
% of max. rec. dose (mg)	57 of 7.5 (51 - 66)	73 of 10 (67 - 80)			probably 75 - 100 of 10
Adaption	At least several days	Impairment for several days (or no deficits)			No data on hand. Impairment comparable to single administration
Results in patients	Heterogeneous data, impairment several weeks or not at all	Slighter degrees of sleepiness, nearly status of healthy controls			No deficits

*): no curve fitting due to minimal impairment

Single administration to healthy subjects: comparison within an agent

Within all groups of hypnotics there was at least one agent that was meta-analytically analyzable for more than one dose. All these agents (triazolam; temazepam; flurazepam, nitrazepam, flunitrazepam; zolpidem) showed increasing performance impairment with increasing doses. As for anxiolytics, this increase could be realized with regard to all parameters calculated. Hence the statements formulated for anxiolytics hold true even for hypnotics/sedatives.

The comparison within agents clearly demonstrated that after single administration of a medicament to healthy subjects the dose was the essential influencing factor that determines the degree of performance impairment for a special agent.

Single administration to healthy subjects: comparison between agents

Apart from Z-substances for which the manufacturers indicated a precise dose as recommendation, for benzodiazepines only mg-areas were given. Since, as indicated before, the degree of impairment essentially depends on the dose we had to decide which doses we would like to assume as “single” dose before comparing different agents. We took the two-fold minimum recommended dose as references. That meant for most of the agents the maximum recommended dose, only for lormetazepam the assumed “single” dose (1 mg) was lower than the maximum of the recommended area (2 mg).

The results for short half-life benzodiazepines as well as for intermediate half-life benzodiazepines seemed to be homogeneous within the corresponding group concerning the duration of impairment, the alcohol equivalent and the% of maximum recommended dose. Even if, within the long half-life benzodiazepines, the interpretation had to be very cautious with regard to flurazepam and nitrazepam, flunitrazepam seemed to have advantages concerning the duration of impairment whereas nitrazepam revealed the lowest alcohol equivalence of the agents and the lowest% of statistically significant impaired effects. The Z-substances showed a clear distinction from zaleplon with the lowest extent of impairment up to zopiclone with the highest degree. Concerning all parameters calculated there was an increase from zaleplon to zopiclone.

Table 38: N05C Hypnotics and sedatives: Comparison of "single" dose profiles.

parameter	short half-life		intermediate half-life		long half-life			Z-substances		
	N05CD05 Triazolam 0.25 mg	**N05CD09 Brotizolam 0.25 mg**	**N05CD06 Lormetazepam 1 mg**	**N05CD07 Temazepam 20 mg**	**N05CD01 Flurazepam 30 mg**	**N05CD02 Nitrazepam 5 mg**	**N05CD03 Flunitrazepam 1 mg**	**N05CF01 Zopiclone 7.5 mg**	**N05CF02 Zolpidem 10 mg**	**N05CF03 Zaleplon 10 mg**
Max. sign. impaired test results (%)	41	/	27	prob. 30	70-75	15-35	66	58	50	37
Hour p.a. of maximum impairment	2.0	/	0.5	prob. ca. 2	2-11	0-15	.75	2.25	1.5	.75
Alcohol equivalence of max. imp. (‰)	0,05-0,08	/	0,03-0,05	prob. ca. 0,05	>0,08	0,03-0,08	>0,08	>0,08	ca. 0,08	0,05-0,08
Duration p.a. until <15% impairment (h)	6.5 (5.75-8.25)	prob. 9 (-)	4.25 (2.0-7.75)	prob. ca. 4 (-)	>24 (-)	>15 (-)	5.0 (3.75-7.75)	11.5 (9.25-12.5)	7.0 (6.5-8.25)	3.5 (3.0-4.25)
Degree of impairment	89 (65-122)	/ (-)	22 (7-48)	prob. ca. 40 (-)	/ (-)	/ (-)	115 (85-177)	240 (174-299)	119 (81-159)	40 (28-60)
% of max. single dose (mg)	80 (75-90)	(100) ((82-101))	(125) ((102-144))	106 (92-121)	/	/	70 (65-75)	57 (51-66)	73 (67-80)	prob. 75-100 (-)

Comparing all the agents analysed there seemed to be a 3-tier grouping, especially according to the parameters "% area of 0,05% alcohol equivalence" and the "degree of impairment". But even the "duration of impairment" supported the grouping. Hence the agent flurazepam and nitrazepam were estimated according to this parameter.

Table 39: Percentage of doses necessary to reach the 0.05% alcohol equivalent and degree of impairment for different hypnotics and sedatives.

Agent	**"Single" dose (mg)**	**%-area of 0,05% alcohol equivalence**	**Degree of impairment**
zopiclone	10	51 - 66	174 - 299
flunitrazepam	1	65 - 75	85 - 177
zolpidem	10	67 - 80	81 - 159
flurazepam	30	-	-
nitrazepam	5	-	-
triazolam	0.25	75 - 90	65 - 122
zaleplon	10	75 - 100	28 - 60
brotizolam	0.25	-	-
temazepam	20	92 - 121	Prob. 40
lormetazepam	1	102 - 144	7 - 48

Expectedly the long half-life benzodiazepines showed the highest degree of impairment. But even zopiclone and zolpidem of the Z-substances were comparable to these benzodiazepines concerning the extent of impairment. Only about 50% to 80% of a single dose were sufficient to create impairment like 0,05% alcohol.

The next group with a lower impairment consisted of the short half-life benzodiazepines triazolam and brotizolam and the Z-substance zaleplon.

The intermediate benzodiazepines temazepam and lormetazepam showed the lowest impairment in comparison to the other agents. At least the administration of at least one whole single dose was necessary to reach the 0,05% alcohol equivalence.

Apart from flurazepam, nitrazepam and zopiclone for all other agents the duration p.a. until the impairment declined below 15% was below about 8 to 9 hours. That means that in general according to the experimental studies (healthy subjects of age <60) after the approved evening application of a hypnotic and after sufficient time of sleep there will be only minor impairment the next morning. Bearing in mind that the degree of impairment essentially depended on the dose of an agent the results give hints to physicians to eventually prescribe at the beginning of a therapy a dose lower than the above mentioned "single" dose thus excluding a danger for his patient (dose gradually increasing).

Multiple administrations to healthy subjects and patients

The potential side effects of hypnotics and sedatives under multiple administrations are essentially dependent on the half-life of the single substances. Whereas benzodiazepines with short and intermediate half-lives show no major impairment, benzodiazepines with longer half-lives are associated with a more or less severe extent of residual daytime sleepiness which is reduced with longer times of treatment (weeks). The z-drug zaleplon, seemed to be one of the best candidate for the treatment of insomnia, as there are (nearly) no impairments when usual doses are used and the patients are tested on the next morning.

3.3 N06 Psychoanaleptics

3.3.1 N06A Antidepressants

Since their discovery in the end of the 1950s, antidepressant drugs gained in importance and nowadays belong to the most frequently prescribed medications at all. Due to their wide-spread use, the traffic relevance is high, in particular because many out-patients are among the users who – similarly to neuroleptics – frequently need this treatment to reach a (nearly) "normal" status which allows them the participation in regular life. Antidepressant drugs are not only used in major or minor forms of depression, but also in anxiety disorders, panic attacks, long-term pain treatment, phobia, and obsessive-compulsive disorders. Patients suffering from severe depression are unable to drive a motor-car, patients with the other disorders mainly have lesser limitations with regard to their psychophysical and traffic-relevant capability. In general, in contrast to patients who are administered antipsychotics, patients under antidepressants are more heterogeneous and it depends on the type and severity of disease whether they are fit to drive and how they profit by a medical treatment. Against this background the possible administration of antidpressants has to be weighted carefully.

In the meantime, there are several classes of antidepressants with different traffic-relevant side effects. The most important agents can be summarized in the following groups [Volz and Sturm 1995]:

- Tricyclic antidepressants, e.g. amitrityline, imipramine
- Tetracyclic antidepressants, e.g. mianserin
- Monoamine oxidase inhibitors (MAO-I), non-selective and selective
- Atypical/other antidepressants, e.g. trazodone
- Selective serotonin reuptake inhibitors (SSRI), e.g. fluoxetine, paroxetine, sertraline

3.3.1.1 N06AA02 Imipramine

(N06AA Non-selective monoamine reuptake inhibitor)

Single administration to healthy subjects

13 publications with 210 effects and doses between 17 and 100 mg could be integrated in the analysis. At first glance, a sufficient number of effects to build up a time-dependent impairment curve were given for the 75 mg dose. But selecting the appropriate effects it became obvious that these effects were based on only 3 publications. Hence the results should be interpreted with caution.

The temporal development after using a 75 mg dose demonstrates only a slight exceed of the 15% level but over a relatively long period of time (10 hours). May be, even the metabolites (nortryptiline, desipramine) made a contribution to this time span. But imipramine itself has a half-life period of about 15 hours. The maximum of impairment (about 20%) is low in comparison to other antidepressants, it emerges over a relatively long period of time according to the kinetics of the agent.

A concentration-dependent analysis was not meaningful since during the elimination phase too few effects were measured to be the basis for a calculation.

Imipramine 75 mg, time-dependent impairment (3 studies, 116 effects)

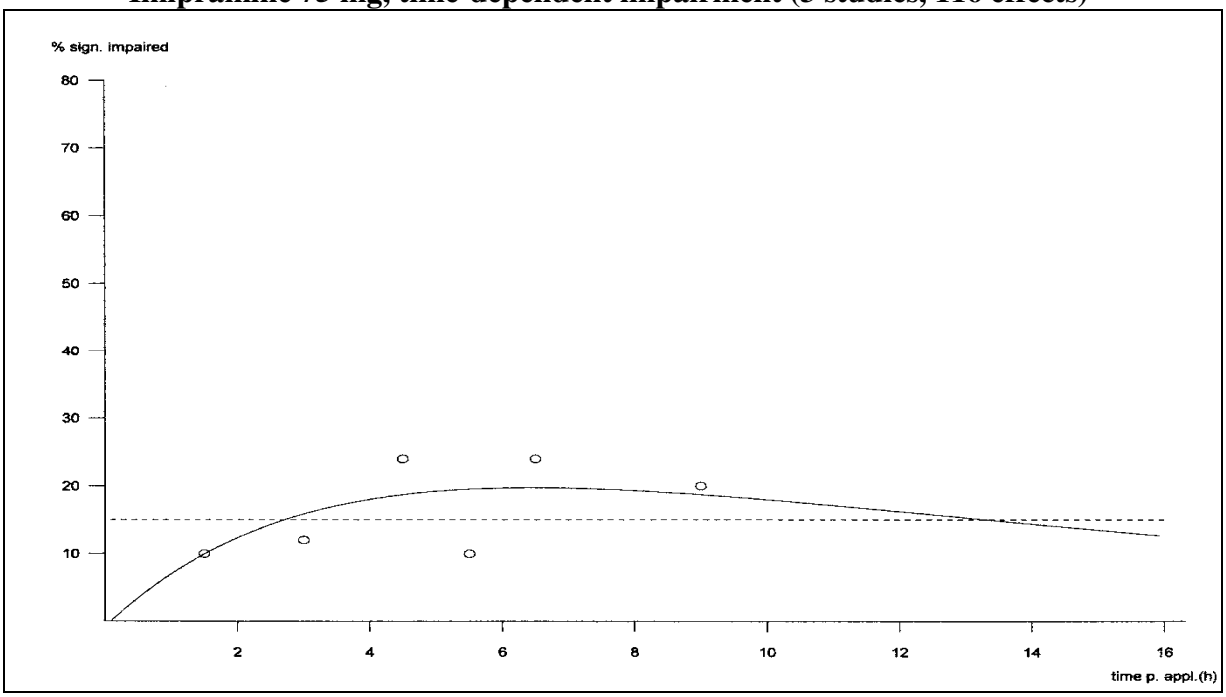

Figure 44: Imipramine 75 mg, time-dependent impairment.

Table 40: Imipramine, summary of results.

Summary Single administration	N06AA02 Imipramine
Number of studies	13
Number of effects	210
Checked doses (mg)	17 - 100
Recommended dose (mg) **Tabularly evaluable doses (mg)** **No. studies / no. effects**	50 - 150 /day 75 3 / 116
Max. sign. impaired test results (%)	20 (15 - 25)
Hour p.a. of maximum impairment	6.25 (5.75 - 7.5)
Alcohol equivalence of max. imp. (%)	0,03 - 0,05
Duration p.a. until <15% impairment (h)	13.5 (0 - 17)
Degree of impairment	32 (0 - 94)
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	too few effects

Multiple administrations to healthy subjects

In a study review of Volz and Sturm [1995], comprising the literature on psychomotor performance from 1970-1995, multiple administration of imipramine (75-100 mg) mainly led to no statistically significant changes. In a review of Amado-Boccara et al. [1995], the long-term administration of imipramine caused impairment of attention compared to baseline in the beginning, but progressive return to baseline performance after 7 days of treatment. Motor activity recovered after 14 days. Deficits were mainly found up to 1 week, in some cases up to 1 month. Driving performance of healthy subjects returned to placebo levels after 1 week of treatment (50 mg/day) due to development of tolerance [Ramaekers 2003].

Summary multiple administrations: Imipramine mainly caused deficits up to 1 week, in several cases impairment up to 1 month seemed to be possible.

Administration to patients

In the above mentioned review of Amado-Boccara et al. [1995], the long-term administration of imipramine to depressed patients led to progressive return to baseline attention performance after more than 21 days of treatment. In an older study of Karp and Pollack [1963], no statistically significant impairment was found in comparison to placebo.

Summary patients: Patients under imipramine seem to reach their baseline capacity after about 3 weeks of treatment.

3.3.1.2 N06AA09 Amitriptylin

(N06AA Non-selective monoamine reuptake inhibitor)

Amitriptyline is regarded as the typical representative of being one of the most sedative antidepressants. Hence it did not astonish that we could find most publications of all antidepressants for this agent.

Single administration to healthy subjects

32 publications with 475 effects could be encoded. Doses between 10 and 75 mg were tested in experiments. A sufficient number of effects to try to construct time-dependent performance curves were given for 25 mg, 50 mg and 75 mg.

In contrast to other agents there were considerable difficulties to construct time- and concentration-dependent approximations. On the one hand this was due to the variability of the percentages of impaired effects at the different time classes within the selected mg-groups as well as between the mg-groups (effects are included into the analysis only quantitatively and not qualitatively; due to too few data it was impossible to account even for the kind of performance tests). On the other hand it was due to the fact that experiments measured performance only up to 10 hours p.a. and that in the last hour of every mg-group the percentage of impaired effects was very high so that the duration of impairment could hardly be estimated.

Already within the first hour p.a. of 25 mg amitriptylin the impairment was about 46% and even at the 10^{th} hour, the latest time-period in which effects were measured, 2 of 5 effects were statistically significant impaired. The approximation of the empirical data indicated the maximum about .75 hour p.a. with 47% statistically significant reduced effects. But probably, in comparison to the kinetic curve and to the time-dependent approximations of higher doses, the maximum should be later between the 2^{nd} and 4^{th} hour p.a. The maximum equals 0,05-0,08% alcohol. It took about 24 hours till the deficits crossed the 15% line.

The approximation of the empirical data for the 50 mg dose was much more difficult. The earliest measurements were done in the 2^{nd} hour p.a. with 39% effects impaired, the latest in the 9^{th} hour p.a. with 67%. Moreover in the 6^{th} hour there was a relatively low impairment frequency of 9%. Since there was no hint for an outlier in this time-class (3 studies of

different working groups, 11 effects, 6 performance areas) we could not eliminate these empirical data. Even there was no hint that the interruption could be caused by active metabolites. All in all, due to these shortcomings the fitting was problematic. Surely the 50 mg curve rises above the 25 mg curve. Due to the empirical data points one would have assumed that the curve should be even higher but the very low percentage for the 6th hour p.a. drops the curve. The maximum impairment probably should be higher than the 51% indicated by the fitting curve (fitting without the value for the 6th hour: 59%). The assumption holds true for another reason: with a higher maximum even the elimination part of the curve would run higher and hence the 15% impairment line would be crossed essentially later in relation to the value for the 25 mg dose (without the 6Th hour value: essentially longer than 24 hours).

Concerning the 75 mg dose we had to eliminate one study. It attracted attention because it was the only study in the 2nd hour p.a. and in strong contradiction to the results of the 25 mg and the 50 mg doses no single effect of 8 effects measured was impaired. Since this study covered effects in other time-classes too (overall 40 effects) the number of effects for the 75 mg dose was reduced to 62, a frequency too small to establish a time-dependent curve. Measuring started in the 3rd hour p.a. (57% of 21 effects impaired) and lasted till the 9th hour p.a. (57% of 7 effects impaired). But between these periods of time the percentage of deficits was lower. Hence results resembled results of the other doses.

With respect to the concentration-dependent impairment we had, of course, to exclude the above mentioned study so that the number of effects after the concentration maximum (≥4.5 hours) reduced to 97. Unfortunately these remaining data were not continuously distributed over the concentration classes. Only one class (21 to 24 ng/mL) showed a sufficient number of effects (42) the other classes presented population numbers ≤14. Moreover no effect was measured between 12 and 18 ng/mL. Hence by aggregating classes to reach sufficient high frequencies we would have established only two combined classes of which it would be meaningless to calculate a fitting curve.

Amitriptyline 25 mg, time-dependent impairment (10 studies, 108 effects)

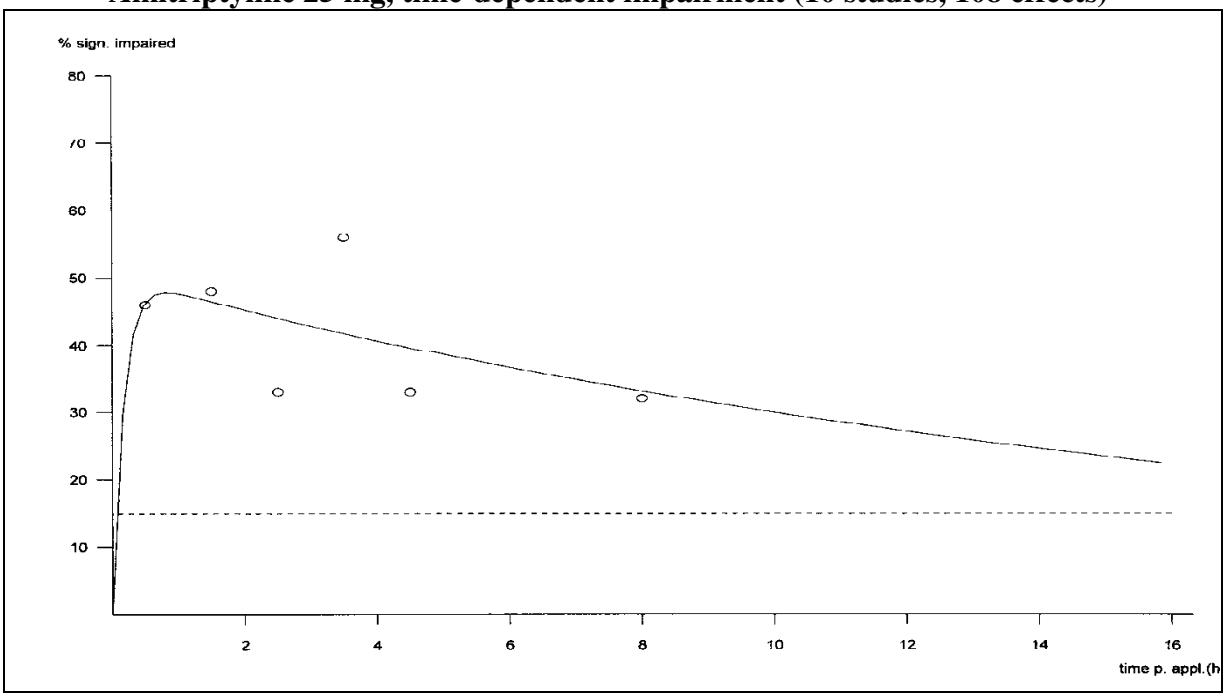

Figure 45: Amitriptyline 25 mg, time-dependent impairment.

Amitriptyline 50 mg, time-dependent impairment (16 studies, 209 effects)

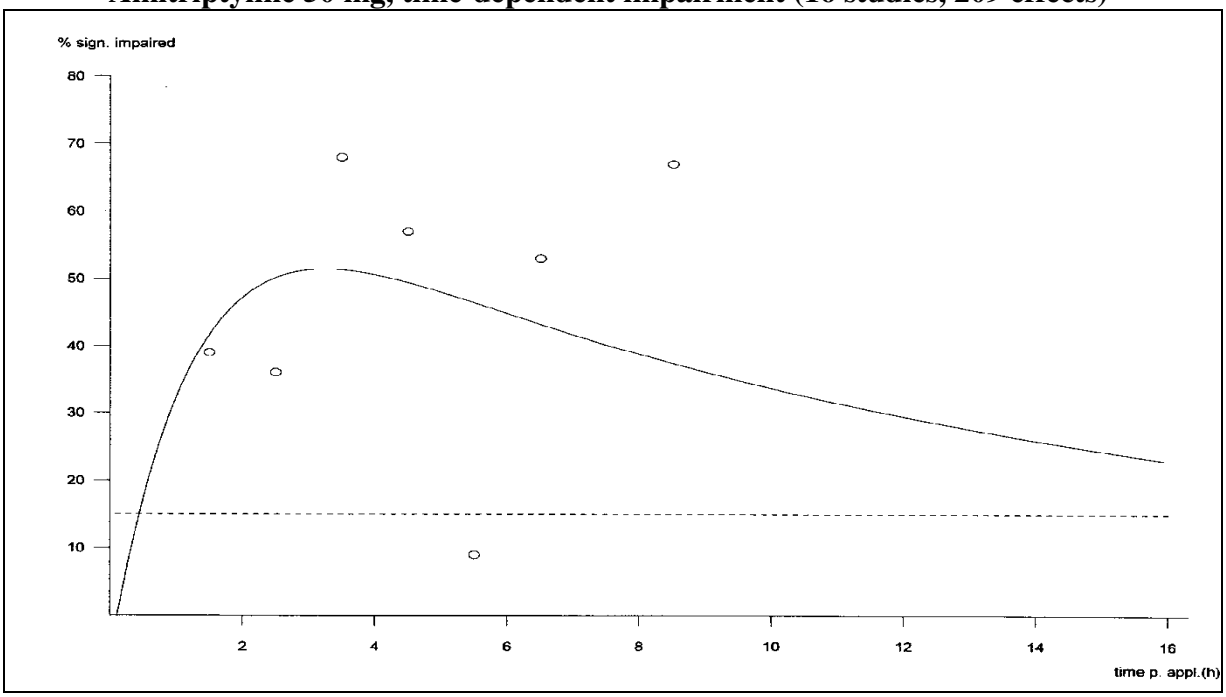

Figure 46: Amitriptyline 50 mg, time-dependent impairment.

Table 41: Amitriptyline, summary of results.

Summary **Single administration**	**N06AA09 Amitriptyline**	
Number of studies	32	
Number of effects	475	
Checked doses (mg)	10 - 75	
Recommended dose (mg)	50 - 75 /day	
Tabularly evaluable doses (mg)	25	50
No. studies / no. effects	10 / 108	16 / 209
Max. sign. impaired test results (%)	47 (41 - 55)	(51) prob. higher ((45 - 58))
Hour p.a. of maximum impairment	(0.75) prob. later ((0.5 - 1.25))	3 .25 (3.25 - 3.75)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08	>0,08
Duration p.a. until <15% impairment (h)	24.25 (17.5 - >24)	(23.0) prob. longer ((16.75 - >24))
Degree of impairment	327 (196 - 437)	(380) prob. higher ((248 - 621))
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	too few and not continuously distributed effects	

Multiple administrations to healthy subjects

In a study review of Volz and Sturm [1995], comprising the literature on psychomotor performance from 1970-1995, multiple administration of amitriptyline (30-100 mg) was without changes in the majority of investigations, but in approximately 40% of studies statistically significant decreases were observed concerning in particular the critical flicker fusion frequency and the complex reaction time. In a review of Amado-Boccara et al. [1995], the long-term administration of amitriptyline caused impairment of attention performance compared to baseline after 7 days, but progressive return to baseline performance after 21 days of treatment. In a study over 9 days, with administration of amitriptyline 75 mg/day, there was initial sedation, but no negative result of psychometric assessment after 9 days (no memory and learning tests). The maximal plasma levels of amitriptyline were approximately 47 ng/ml for males and 56 ng/ml for females, respectively [Sennef et al. 2003]. Driving performance of healthy subjects returned to placebo levels after 1 week of treatment (75 mg/day) due to development of tolerance [Ramaekers 2003].

Summary multiple administrations: In the first week of a treatment with amitriptyline marked impairment (sedation) is probable. The return to baseline (placebo) is described heterogeneously, deficits up to 1 month or longer cannot be excluded.

Administration to patients

In the review of Amado-Boccara et al. [1995], the long-term administration of amitriptyline to depressed patients caused impairment of memory performance compared to baseline after 7 days, but progressive return to baseline performance after 21 days of treatment with individual variations of results. In a newer study [Veldhuijzen et al. 2006] after two weeks of treatment, performance deficits were no longer observed.

Summary patients: Impairment in the first week, return to baseline after 3 weeks.

3.3.1.3 N06AB03 Fluoxetine

(N06AB Selective serotonin reuptake inhibitor)

Single administration to healthy subjects

In contrast to amitriptyline we only could gather 5 studies with 150 effects for fluoxetine of which one publication aggregates 108 effects. Hence the interpretation had to be very cautious. The most frequent examined dose of 60 mg totaled only 52 effects. No single effect was statistically significant impaired. Summarizing all effects ≥40 mg (88) only 3.4% were reduced. With respect to these results the time-dependent curve fitting as well as a concentration-dependent analysis had to be omitted.

Table 42: Fluoxetine, summary of results.

Summary **Single administration**	**N06AB03 Fluoxetine**
Number of studies	5
Number of effects	150
Checked doses (mg)	20 - 75
Recommended dose (mg)	20 - 60 / day
Tabularly evaluable doses (mg)	60 *)
No. studies / no. effects	3 / 52
Max. sign. impaired test results (%)	0
Hour p.a. of maximum impairment	no
Alcohol equivalence of max. imp. (%)	0
Duration p.a. until <15% impairment (h)	0

Degree of impairment	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached

*): no curve fitting due to minor impairment and too few effects

Multiple administrations to healthy subjects

In the study review of Volz and Sturm [1995], comprising the literature on psychomotor performance from 1970-1995, multiple administration of fluoxetine (20 mg) caused statistically significant decreases, but also no changes of the critical flicker fusion frequency and the complex reaction time.

Summary multiple administrations: Statistically significant deficits are not to be expected.

Administration to patients

Summary patients: No study at hand but statistically significant deficits are not to be expected.

3.3.1.4 N06AB05 Paroxetine

(N06AB Selective serotonin reuptake inhibitor)

Single administration to healthy subjects

The same as for fluoxetine holds true for paroxetine. We only could gather 6 publications with 118 effects of which one publication aggregates 60 effects. The 30 mg dose, highest frequent, showed 69 effects of which only 2 effects (1 of 13 in the 3rd, 1 of 16 in the 5th hour p.a.) were statistically significant impaired. It may be that higher impairment is associated only with higher doses. But due to the fact that only one study of our selection examined 40 mg (4 effects in the 2nd hour without any effect reduced and 7 effects in the 4th hour with 4 effects reduced) a reasonably valid conclusion is impossible. Neither a time-dependent nor a concentration-dependent analysis was meaningful.

Table 43: Paroxetine, summary of results.

Summary **Single administration**	**N06AB05 Paroxetine**
Number of studies	6
Number of effects	118

Checked doses (mg)	10 - 40
Recommended dose (mg) **Tabularly evaluable doses (mg)** **No. studies / no. effects**	20 /once a day 30 *) 3 / 69
Max. sign. impaired test results (%) **Hour p.a. of maximum impairment** **Alcohol equivalence of max. imp. (%)** **Duration p.a. until <15% impairment (h)**	<10 (3 - 5) (<0,03) 0
Degree of impairment	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached too few effects

*): no curve fitting due to minor impairment and too few effects

Multiple administrations to healthy subjects

In the above mentioned study review of Volz and Sturm [1995], comprising the literature on psychomotor performance from 1970-1995, multiple administration of paroxetine (20 mg) caused no statistically significant changes and even the review of Amado-Boccara et al. [1995] did not report impairments of attention, motor activity and memory performance compared to baseline under administration of paroxetine for 7 days.

Summary multiple administrations: No impairment

Administration to patients

Summary patients: No study at hand but statistically significant deficits are not to be expected.

3.3.1.5 N06AX03 Mianserin

(N06AX Other antidepressant)

Single administration to healthy subjects

8 studies with 145 effects and doses 10 mg and 20 mg could be integrated in the analysis. Even if a sufficient number of effects were given neither for 10 mg nor for 20 mg we tried to fit the data for the effects of 10 mg.

Analysing the 10 mg dose only 4 studies with 63 effects were at hand but the results up to 7 hours p.a. (the period of time with continuous registration of effects) were clear: considerable deficits emerge in contrast to fluoxetine and paroxetine. The maximum impairment is to be

seen in the first hour p.a. with just below 50% statistically significant impaired effects. Hence impairment that equals about 0.08% alcohol. Since the 15% line is crossed not until a time span of at least 24 hours the degree of impairment even is comparatively high.

Even if the concentration-dependent quadratic curve fitting is not a good one (R^2 = .919) because of the few data and the fact that an essential impairment is associated already with low concentrations the 0.05% equivalent (8.9 ng/mL) agrees very well with the according value of the time-dependent curve fitting.

Mianserin 10 mg, time-dependent impairment (4 studies, 63 effects)

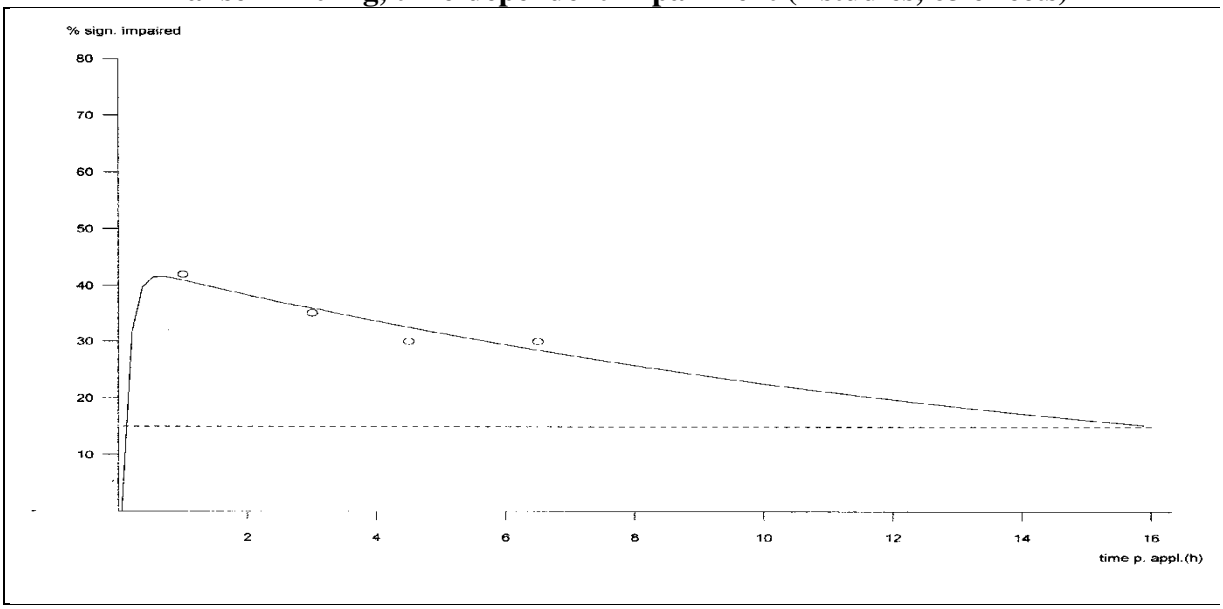

Figure 47: Mianserin 10 mg, time-dependent impairment.

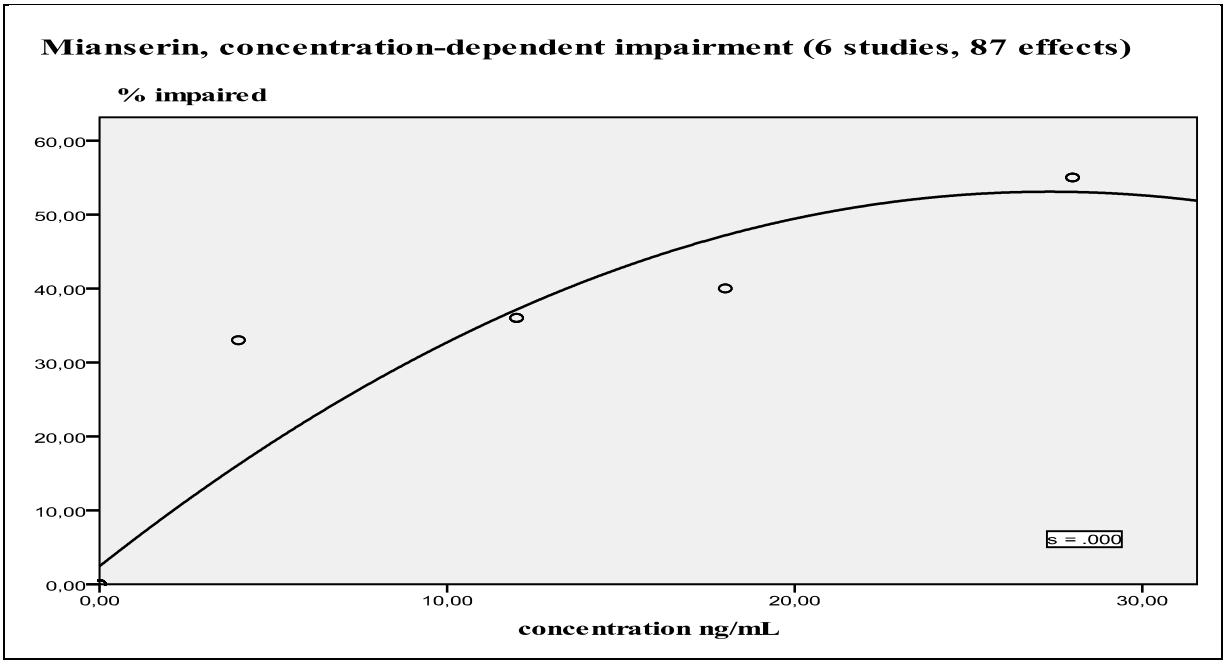

Figure 48: Mianserin, concentration-dependent impairment.

Table 44: Mianserin, summary of results.

Summary **Single administration**	**N06AX03 Mianserin**
Number of studies	8
Number of effects	145
Checked doses (mg)	10 - 20
Recommended dose (mg)	30 / day
Tabularly evaluable doses (mg)	10
No. studies / no. effects	4 / 63
Max. sign. impaired test results (%)	42 (35 - 48)
Hour p.a. of maximum impairment	0.75 (0.75 - 0.75)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08
Duration p.a. until <15% impairment (h)	16.25 (8.5 - >24)
Degree of impairment	185 (79 - 397)
0,05% alcohol equ. (ng/mL)	8.9 (7.4 - 11.9)
% of max. rec. dose (mg)	21 of 30 (17 - 28)

Multiple administrations to healthy subjects

In the above mentioned study review of Volz and Sturm [1995] multiple administrations of mianserin (20-100 mg) mainly led to statistically significant decreases, in particular with respect to the critical flicker fusion frequency and the complex reaction time. According to the review of Amado-Boccara et al. [1995], the long-term administration of mianserin caused impairment of attention, motor activity and memory performance compared to baseline in the beginning, but progressive return to baseline performance after 7 days of treatment. Mianserin showed profoundly and consistently impaired driving (parameter: standard deviation of lateral position) and statistically significant decreased psychomotor performance when administered to healthy volunteers at doses of 30-60 mg/day for a 15-day period with tests on days 1 and 7, and after dose increments on days 8 and 15. In addition, mianserin statistically significant impaired vigilance performance with maximal effects on day 1 [O'Hanlon et al. 1998]. Driving performance of healthy subjects did not return to placebo levels after 1 week of treatment (30 mg/day), there was no development of tolerance, only a slight improvement

[Ramaekers 2003]. Similar results are mentioned in a study review by Verster and Ramaekers [2009].

Summary multiple administrations: Mianserin causes marked impairments of driving and psychomotor performance up to at least 1 week, several deficits were found even after 1 month.

Administration to patients

According to the review of Amado-Boccara et al. [1995], the long-term administration of mianserin to depressed patients caused impairment of attention, motor activity and memory performance compared to baseline in the beginning, but progressive return to baseline performance after 7 days of treatment.

Summary patients: Strong impairment in the beginning, improvement after 1 week.

3.3.1.6 N06AX05 Trazodone

(N06AX Other antidepressant)

Single administration to healthy subjects

8 studies with 146 effects could be gathered for trazodone. Doses between 25 and 200 mg were tested of which the 100 mg dose comprising 86 effects was most frequently examined.

The curve fitted the empirical data relatively good. The start of the approximation curve about half an hour p.a. was, of course, a virtual one that exclusively was determined by the technique of curve fitting and must not reflect any physiological reality. As explained in the discussion, the approximation-curve could have been started even earlier but since the first effects were measured not until the second hour p.a. the approximation technique determines the starting point as it is shown in the figure. The maximum impairment is to be seen, comparable to mianserin, with about 44% effects impaired but essentially later (2.75 hour p.a.). It takes more than 6 hours till the impairment crosses the 15% line.

The concentration-dependent analysis (quadratic, $R^2 = .954$) revealed the 30% impairment with 1240 ng/mL which corresponds to the time-dependent curve for 100 mg.

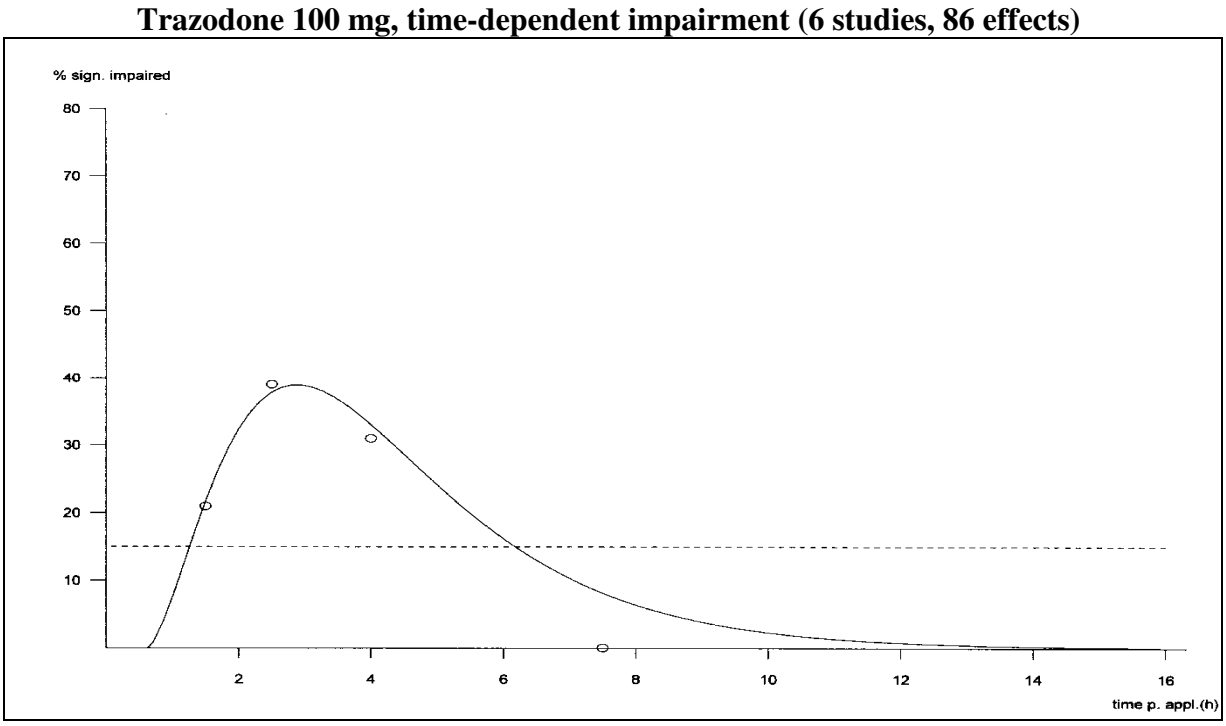

Figure 49: Trazodone 100 mg, time-dependent impairment.

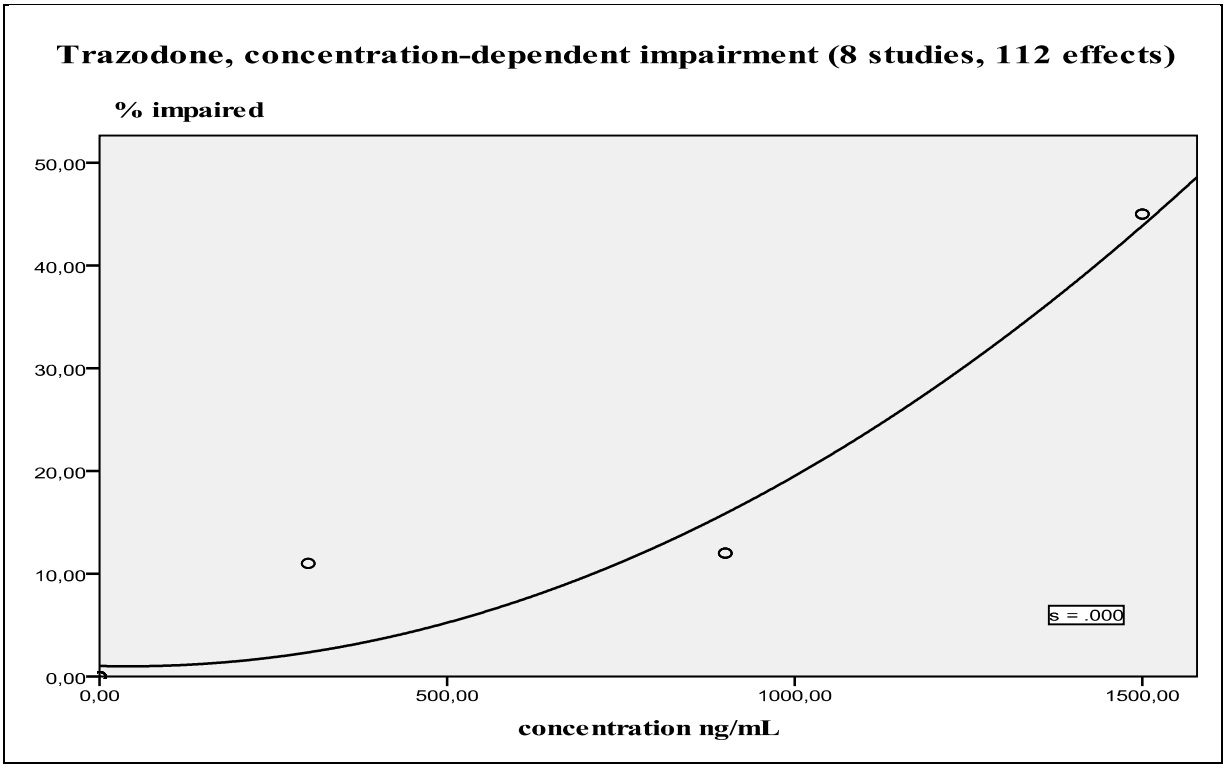

Figure 50: Trazodone, concentration-dependent impairment.

Table 45: Trazodone, summary of results.

Summary **Single administration**	**N06AX05 Trazodone**
Number of studies	8
Number of effects	146
Checked doses (mg)	25 - 200
Recommended dose (mg)	50 - 100 / day
Tabularly evaluable doses (mg)	100
No. studies / no. effects	6 / 86
Max. sign. impaired test results (%)	44 (31 - 44)
Hour p.a. of maximum impairment	2.75 (2.75 - 3.0)
Alcohol equivalence of max. imp. (%)	0,05 - 0,08
Duration p.a. until <15% impairment (h)	6.5 (6.0 - 9.0)
Degree of impairment	87 (42 - 135)
0,05% alcohol equ. (ng/mL)	1240 (1160 - 1330)
% of max. rec. dose (mg)	81 of 100 (76 - 87)

Multiple administrations to healthy subjects

According to the study review of Volz and Sturm [1995] multiple administration of trazodone (100-200 mg) led to statistically significant decreases, in particular with respect to the critical flicker fusion frequency and the complex reaction time.

Summary multiple administrations: Trazodone leads to performance deficits, the temporal duration is questionable.

Administration to patients

No studies at hand.

Summary patients: No studies on hand

3.3.1.7 Comparison of Antidepressants

Single administration to healthy subjects

Table 46 shows the comparison of the profiles of antidepressants.

Single administration to healthy subjects: comparison within an agent

Unfortunately only for amitriptyline two different doses could be analyzed meta-analytically. Expectedly, even for this agent the impairment increased with the higher dose which could be seen best by the parameters “alcohol equivalence of maximal impairment” and “degree of impairment”.

Single administration to healthy subjects: comparison between agents

Apart from amitriptyline for the other antidepressants the number of effects was very low. In addition the distribution of effects for amitriptyline was not continuously and only for mianserin and trazodone the parameter “0,05% alcohol equivalence” could be calculated meaningfully with taking as “single” dose the maximum of the daily recommended doses. Hence the interpretation had to be very cautious.

If we assumed for all agents the recommended daily maximum dose as “single” dose the following statements were possible. At first it seemed to be clear that the selective serotonin reuptake inhibitors fluoxetine and paroxetine did not produce impairment. Fluoxetine was tested with its daily maximum (60 mg) and showed no essential impairment. The same held true for paroxetine. Since the meta-analytic results were based on the 30 mg dose it could be concluded that for the daily recommended maximum dose (20 mg) the impairment even would be marginal. It followed trazodone and, probably, imipramine. Since imipramine was not tested meta-analytically with its maximum recommended daily dose (150 mg) but only with 75 mg the “degree of impairment” and the other parameters probably will be higher. But the effects of trazodone were by far more compact that ment especially that the duration p.a. until the impairment decreased below 15% was for trazodone by far shorter than for imipramine. Concerning the degree of impairment mianserin of dose 10 mg followed in the next position. The “degree of impairment” (185) was by far higher than for the other mentioned antidepressants and only 21% of the “single” dose were necessary to reach the 0,05% alcohol equivalence. Finally amitriptyline presented the highest extent of performance impairment. Already with the 50 mg dose the “degree of impairment” and the other parameters were higher than for the other antidepressants so that for the recommended maximum daily dose (75 mg) the impairment probably would be more intensive.

Hence, psychomotor performance seemed to be independent of chemical structure, anticholinergic functions or specific reuptake inhibiting properties, but the sedative features of a compound appear to be rather important [Volz and Sturm 1995]. According to Amado-Boccara et al. [1995] antidepressants can be classified in correspondence to their effect on cognitive functions and sedative potency:

- antidepressants with sedative effect: amitriptyline, imipramine, mianserin, nortriptyline, desipramine, trimipramine, doxepin, maprotiline, trazodone, dothiepin
- antidepressants with no sedative effect: cericlamine, fluvoxamine, bupropion, viloxazine, fluoxetine, moclobemide
- antidepressants with positive cognitive effect: nomifensine, midalcipran, zimeldine, lofepramine, paroxetine, sertraline

The results of our meta-analytic approach, as far as the agents could be analyzed meta-analytically, coincided in essence with this order. Even Ramaekers [2003] summarized the major results of published studies from 1983 to 2000 that have determined the effects of antidepressants on actual driving performance using a standard test (mainly in healthy volunteers) with essentially the same results.

Multiple administrations to healthy subjects and patients

Correspondent to the results of the single administration fluoxetine and paroxetin revealed no performance deficits during multiple administrations. The duration of adaption of the other antidepressants depended on the dose applied and took at least up to one month (imipramine, mianserin, trazodone) or even longer (amittriptyline).

Table 46: Comparison of profiles: N06A Antidepressants.

Agent	*N06AA Non-selective monoamine reuptake inhibitors*		*N06AB Selective serotonin reuptake inhibitors*		*N06AX Other antidepressants*	
	N06AA02 Imipramine	**N06AA09 Amitriptyline**	**N06AB03 Fluoxetine**	**N06AB05 Paroxetine**	**N06AX03 Mianserin**	**N06AX05 Trazodone**
Number of studies	13	32	5	6	8	8
Number of effects	210	475	150	118	145	146
Checked doses (mg)	17 - 100	10 - 75	20 - 75	10 - 40	10 - 20	25 - 200
Recommended dose	50 - 150 / day	50 - 75 / day	20 - 60 / day	20 /once a day	30 / day	50 - 100 / day
Tabularly evaluable doses (mg)	75	25 50	60 *)	30 *)	10	100
No. studies / no. effects	3 / 116	10 / 108 16 / 209	3 / 52	3 / 69	4 / 63	6 / 86
Max. sign. impaired test results (%)	20 (15 - 25)	47 (51) prob. higher (41 - 55) ((45 - 58))	0	<10	42 (35 - 48)	44 (31 - 44)
Hour p.a. of maximum impairment	6.25 (5.75 - 7.5)	(0.75) prob. later 3.25 ((0.5 - 1.25)) (3.25 - 3.75)	no	(3 - 5)	0.75 (0.75 - 0.75)	2.75 (2.75 - 3.0)
Alcohol equivalence of max. imp. (%)	0,03-0,05	0,05-0,08 >0,08	0	(<0,03)	0,05-0,08	0,05-0,08
Duration p.a. until <15% impairment (h)	13.5 (0 - 17)	24.25 (23.0) prob. longer (17.5 - >24) ((16.75 - >24))	0	0	16.25 (8.5 - >24)	6.5 (6.0 - 9.0)
Degree of impairment	32 (0 - 94)	327 (380) prob. higher (196 - 437) ((248 - 621))	0	0	185 (79 - 397)	87 (42 - 135)
0,05% alcohol equ. (ng/mL)	too few effects	too few and not continuously distributed effects	not reached	not reached too few effects	8.9 (7.4 - 11.9)	1240 (1160 - 1330)
% of max. rec. dose (mg)					21 of 30 (17 - 28)	81 of 100 (76 - 87)
Adaption	Impairment up to 1 week, sometimes 1 month	Impairment at least 1 week, 1 month or longer possible	Stat. significant deficits are not to be expected	No impairment	Impairment at least 1 week, possibly up to 1 month	Performance deficits, temporal duration questionable
Results in patients	Impairment for 3 weeks	Impairment in the first week, return to baseline after 3 weeks	Stat. significant deficits are not to be expected	Stat. significant deficits are not to be expected	Strong impairment in the beginning, improvem. after 1 week	No studies on hand

*): no curve fitting due to minor impairment and too few effects

3.4 R06 Antihistamines

3.4.1 R06A Antihistamines for systemic use

Antihistamines are substances which block the effects of the transmitter histamine in the human body. At present, there are mainly drugs against H1- and H2-receptors. Whereas H2-receptors are located in heart and stomach, H1-receptors are responsible for the allergic effects of histamine. Substances against these H1-receptors, so-called H1-antagonists, are generally meant when the term “antihistamines” is used. In this sense, antihistamines play an essential role in the treatment of wide-spread allergic diseases such as allergic rhinitis, asthma and sinusitis. In most of the cases, the treatment period is short (days or weeks) and is recommended for the duration of allergic symptoms. There are antihistamines of the first generation (e.g. diphenhydramine, triprolidine, promethazine), which were associated with severe side-effects, in particular with marked sedation.

By contrast, second-generation antihistamines (e.g. cetirizine, loratadine, terfenadine) are more lipophobic and therefore far less likely to cross the blood-brain barrier. These newer substances should cause little if any sedation at therapeutic concentrations (effect below that of a BAC of 0.5 g/kg) and are recommended for patients whose occupation requires vigilance and attention [Kay 2000]. Only at higher doses, second-generation anithistamines penetrate into the brain and may cause sedation and affect performance [Rosenzweig and Patat 1999].

Sometimes even a third generation of antihistamines is separated (e.g. levocetirizine, desloratadine, fexofenadine) and it is stated that these substances are free from sedative effects.

General side effects of a treatment with antihistamines can include gastro-intestinal complaints, dry mouth and drowsiness.

With regard to driver fitness, the severity of all side effects must be considered against the background of relatively slight or missing driving impairment by the underlying allergic diseases.

A sufficient amount of studies could be gained for the first generation antihistamines diphenhydramine, triprolidine and promethazine, for the second generation agents loratadine and terfenadine and for the third generation substance fexofenadine. Results for promethazine are integrated in the chapter on antipsychotics (3.2).

3.4.1.1 R06AA02 Diphenhydramine

(R06AA Aminoalkyl ether)

As a typical representative of first-generation antihistamines, diphenhydramine is an effective antagonist of H_1-receptors and useful in the treatment of allergic symptoms.

Single administration to healthy subjects

28 studies with 481 effects and doses tested between 25 and 100 mg could be integrated in the analysis. A sufficient number of effects to build up a time-dependent impairment curve were given for the 25 mg and 50 mg doses whereas for doses 75 and 100 mg only 17 and 60 effects could be gathered.

The time dependent impairment curve for 25 mg shows a very good adaption of the fitting curve to the empirical data. The maximum impairment is located about 1.25 hour p.a. with about a range of 39 to 53 percent impairment equalling 0,05% to 0,08% alcohol. In comparison to the time-dependent impairment of the 50 mg dose and in comparison to the concentration-dependent 30% impairment level that corresponds excellently with the 30% level of the time-dependent 50 mg fitting curve the time-dependent impairment-curve for 25 mg seems to be too high. It should not reach the 30% line. Hence the results of the 25 mg curve should be handled very carefully (we use brackets in the table). The 15% impairment line is crossed in the fourth hour. In all 43 effects measured 4 hours and later p.a. there was no single statistically significant impaired effect.

In contrast to the 25 mg dose the empirical data for the 50 mg dose are more irregularly distributed. But there is no hint for an outlier. While the maximum impairment range is about 34 to 45% the duration up to the hour of maximum impairment is a little bit longer as for the 25 mg dose and even the duration of impairment is up to eight hours. Consequently the degree of impairment is essentially higher for the 25 mg dose. As mentioned above the 30% levels of the time-dependent curve and the concentration dependent curve agree very well.

Concerning the concentration-dependent impairment we analysed the data after the concentration maximum 2.5 hours p.a. A somewhat continuous and high enough population number was to be seen up to 70 ng/mL. For this area the quadratic approximation curve excellently fitted the empirical data ($R^2 = 1.000$). The 30% impairment was equivalent 60 ng/mL, that means 95% of the maximum concentration of the normal dose of 50 mg.

Diphenhydramine 25 mg, time-dependent impairment (9 studies, 102 effects)

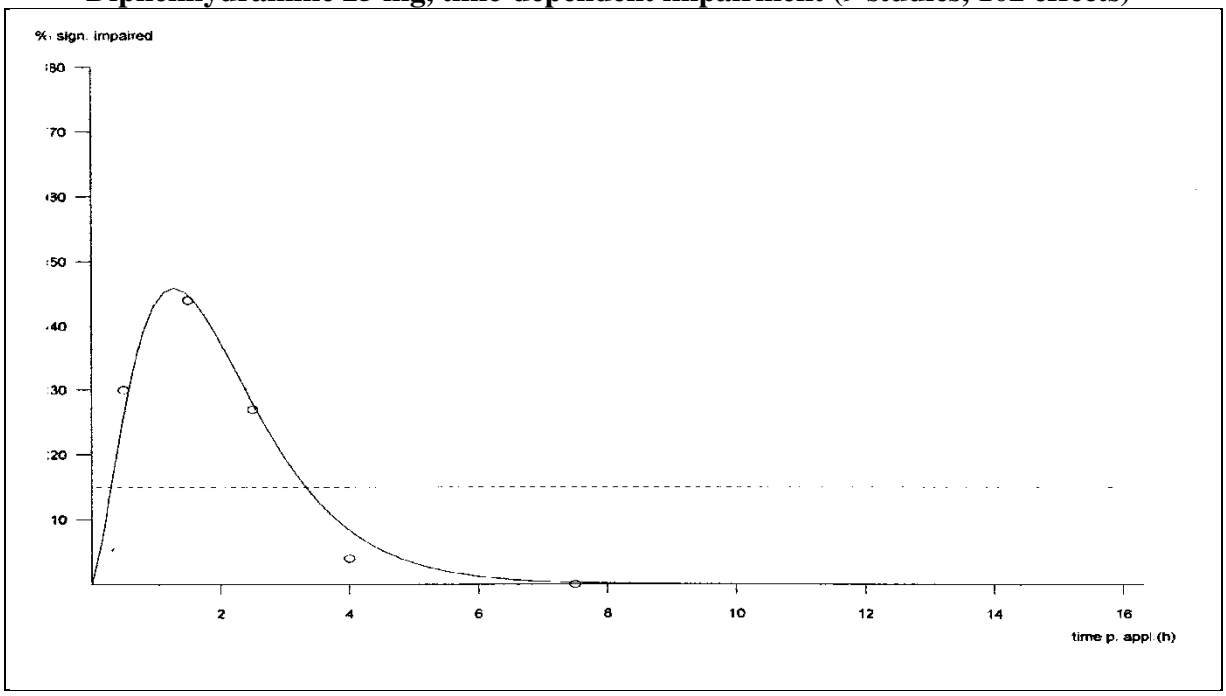

Figure 51: Diphenhydramine 25 mg, time-dependent impairment.

Diphenhydramine 50 mg, time-dependent impairment (22 studies, 284 effects)

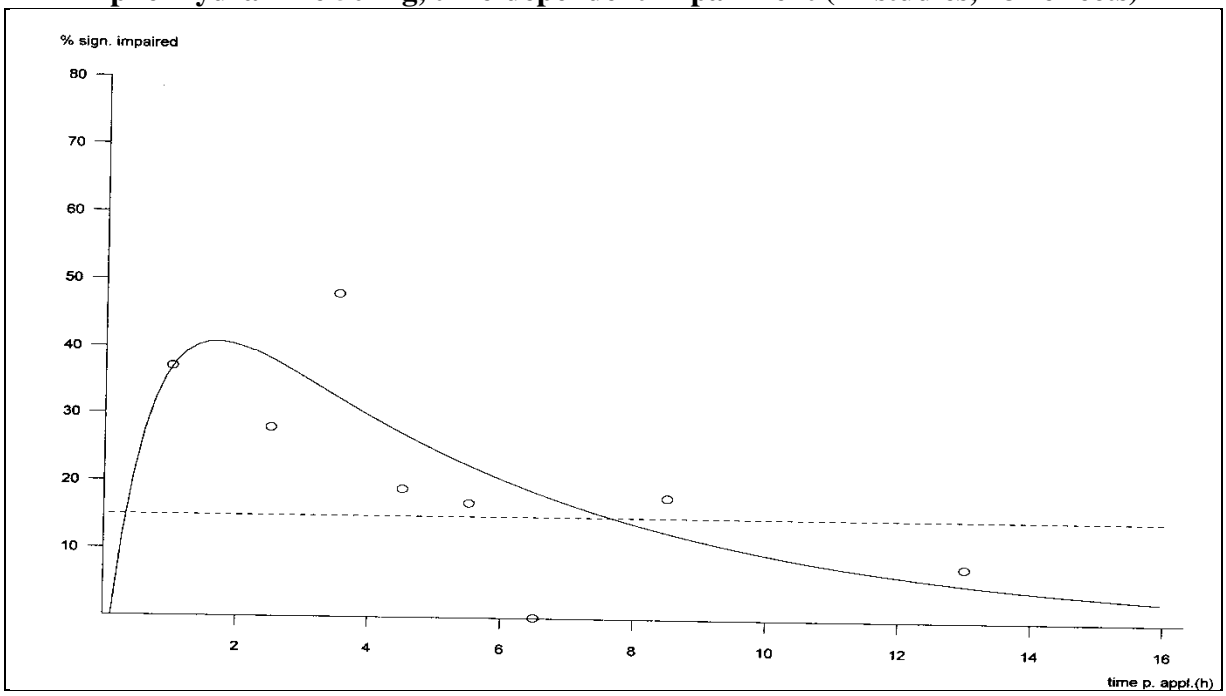

Figure 52: Diphenhydramine 50 mg, time-dependent impairment.

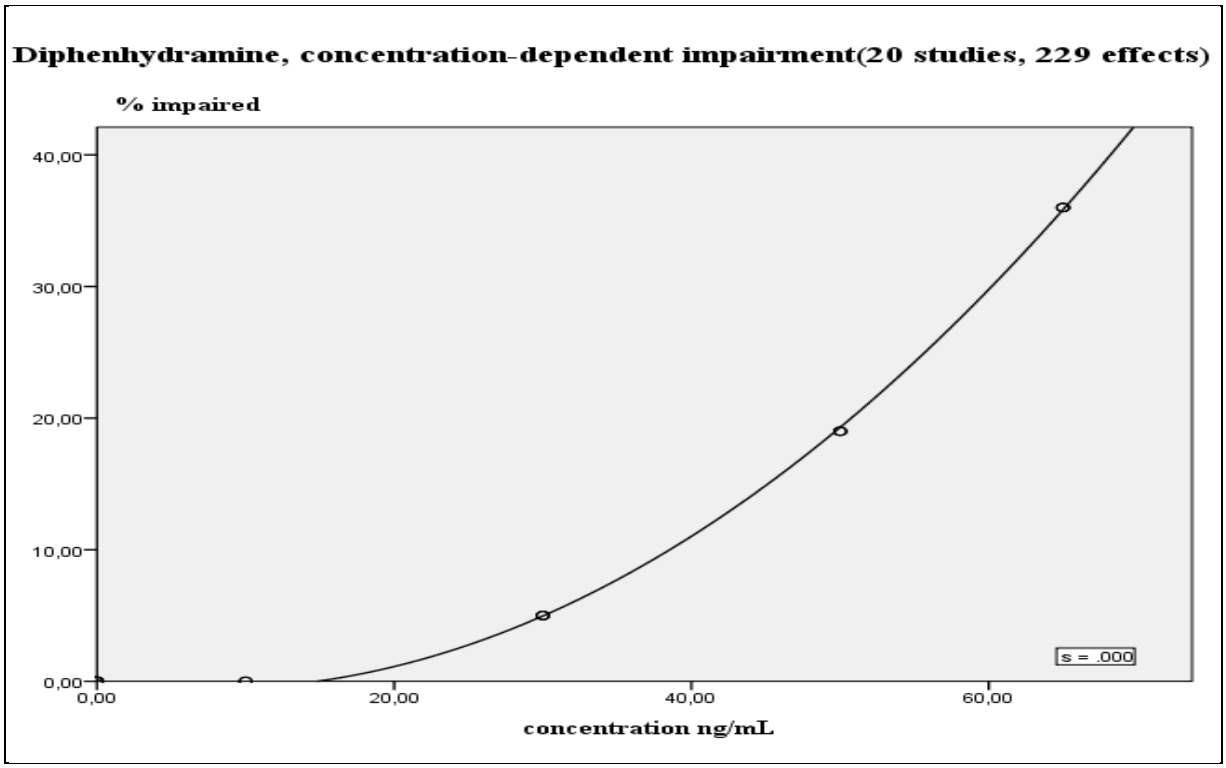

Figure 53: Diphenhydramine, concentration-dependent impairment.

Table 47: Diphenhydramine, summary of results.

Summary **Single administration**	***R06AA Aminoalkyl ethers*** **R06AA02 Diphenhydramine**	
Number of studies	28	
Number of effects	481	
Checked doses (mg)	25 - 100	
Recommended dose (mg)	50	
Tabularly evaluable doses (mg)	25	50
No. studies / no.effects	9 / 102	22 / 284
Max. sign. impaired test results (%)	(46) ((39 - 53))	41 (34 - 45)
Hour p.a. of maximum impairment	(1.25) ((1.0 - 1.25))	1.75 (1.25 - 1.75)
Alcohol equivalence of max. imp. (%)	(0,05 - 0,08)	0,05 - 0,08
Duration p.a. until <15% impairment (h)	(3.5) ((3.25 - 4.25))	7.75 (7.0 - 11.25)
Degree of impairment	(54) ((39 - 79))	92 (61 - 149)
0,05% alcohol equ. (ng/mL)	60 (57 - 65)	
% of max. rec. dose (mg)	95 of 50 (91 - 103)	

Multiple administrations to healthy subjects

Healthy volunteers received a 5-day treatment with diphenhydramine (day 1: 100 mg in 3 units, day 2-5: 25 mg) and were tested on days 1, 3, and 5, 1.5 hours after the drug intake: After the initial dose, subjects under diphenhydramine showed poorer cognitive performance than under (loratadine or) placebo on tasks of divided attention, working memory, speed, and vigilance. The test subjects also reported greater fatigue and sleepiness and lower levels of motivation. The cognitive and psychomotor performance improved on days 3 and 5, there were no statistically significant group differences (compared to (loratadine and) placebo). However, on day 3, volunteers taking diphenhydramine still presented with more fatigue and lower motivation [Kay et al. 1997, Kay 2000]. In a study [Gandon and Allain 2002] healthy volunteers received diphenhydramine 50 mg/day (therapeutic dose) for a 5-day interval and were tested on days 1 and 5 for critical flicker fusion, choice reaction time, body sway, learning memory, subjective assessment of alertness, and mood. Compared with placebo (and levocetirizine), the subjects demonstrated statistically significant impairments concerning the critical flicker fusion, body sway and subjective assessment of alertness on day 1, in particular when tested 1 to 3 hours after dosing. All effects were less marked on day 5 and no longer statistically significant. In this sense, the administration of diphenhydramine 50 mg/day for 4 days statistically significant impaired the standard deviation of lateral position in driving tests of healthy volunteers which were conducted 1.5 hours after drug intake on day 1 and 4; the performance on day 4 was better than on day 1 which reflected a development of tolerance [Verster et al. 2003]. Moreover, in the same study, on day 1, diphenhydramine statistically significant impaired tracking performance and divided attention. Results on word-learning tests and memory scanning tests were not statistically significant impaired. On day 4, the effects of diphenhydramine did not reach statistical significance [Verster et al. 2003 (2)].

Even older studies (Hughes and Forney 1964, Mattila et al. 1986 and Burns and Moskowitz 1993) revealed similar results.

If one assumes that the subjects tested under multiple application reached the therapeutic range of 50-100 ng/mL [Schulz & Schmoldt 2003] after the 5 day treatment, the results of multiple administration are an excellent demonstration of the role of adaption: whereas with a concentration of about 60 ng/mL there was in single administration an impairment exceeding 30% of the effects the results of multiple users of diphenhydramine did not reach the statistical significance level. Of course, this demonstrates too that the concentration limits derived from the single administration does not hold for multiple application or for patients.

Summary multiple administrations: Diphenhydramine shows strong impairment in the beginning of a treatment. It takes at least 4 days to reach normal levels comparable to placebo and so-called non-sedating antihistamines.

Administration to patients

Patients with chronic allergic rhinitis (n=24) received either placebo or diphenhydramine 50 mg as a single dose and were investigated in a battery of skilled performance tests (divided attention, visual backward masking, stimulus response conflict, and vigilance) when they suffered from rhinitis and when they were free of symptoms. Diphenhydramine impaired vigilance performance and results of divided attention and stimulus response conflict tests. Symptoms alone did not affect performance. The largest performance changes were observed when the subjects were free of symptoms [Burns et al. 1994]. Atopic patients (n=12) who received diphenhydramine 150 mg/day for 3 days suffered from marked impairment on the first day of drug administration (sleepiness and performance tests). By the third day, this impairment was no longer present, the results were not different from a treatment with (cetirizine and) placebo, apparently because of development of tolerance to the sedative effects of diphenhydramine [Schweitzer et al. 1994]. Patients with seasonal allergic rhinitis (n=40) who received diphenhydramine 50 mg at weekly intervals demonstrated statistically significant impairment in driving simulator tests (coherence, lane keeping, response time), 2.5 hours after medication at supposed peak plasma levels, when compared with placebo (or fexofenadine 60 mg). The performance was even worse than under the influence of alcohol (approximately 0.1%) [Weiler et al. 2000]. Similarly, patients with ragweed-induced allergic rhinitis who received a single dose of diphenhydramin 50 mg demonstrated statistically significant decrements on all vigilance parameters, elevated subjective sleepiness, and impairments on all cognitive domains evaluated (working memory, psychomotor speed, reasoning, divided attention) when tested 1.5 hours after medication and compared with placebo (and desloratadine 5 mg) [Wilken et al. 2003].

Summary patients: The performance of patients without a treatment was comparable to that one of healthy persons (no negative effects of disease). Patients with a treatment showed severe impairment in the beginning, after a period of several days (at least 3 days) they showed increasing improvement and adaptation, they reached the level of patients without a treatment (who had similar results as healthy persons in other studies).

3.4.1.2 R06AD02 Promethazine

(R06AD Phenothiazine derivative)

Due to the RED LIST ® the agent promethazine predominantly is used as neuroleptic. Hence we integrated the report on this substance in the chapter on psycholeptics (3.2).

3.4.1.3 R06AX07 Triprolidine

(R06AX Other histamines for systemic use)

Single administration to healthy subjects

For triprolidine we gathered 14 studies with 233 effects and doses applied between 1.25 mg and 10 mg. At first glance the dose 10 mg with 92 effects seems to be analysable. But of the 7 studies describing results on this dose one study dominates with 50 effects measured and all effects were not statistically significant impaired. Since this result is a strong contradiction to the results of the other studies we abstained from evaluating a time dependent impairment by curve fitting. The maximum impairment seems to be about 1.5 to 2.5 hours p.a. with about 60% to 70% statistically significant reduced effects at the time of the maximum concentration. About 5 hours p.a. the percentage of impaired effects drops under 15%. The degree of impairment is not measurable. But, interpreting these data, one should point out that the recommended dose is only a quarter of the 10 mg dose.

For the concentration dependent impairment (quadratic curve fitting) we analysed the data in the post absorption phase (≥2.25 h) for the continuous part of concentrations (up to 18 ng/mL) without the above mentioned outlier. The fitting is quite a good one ($R^2 = .979$) and the 0,05% alcohol equivalence is about 5.7 ng/mL.

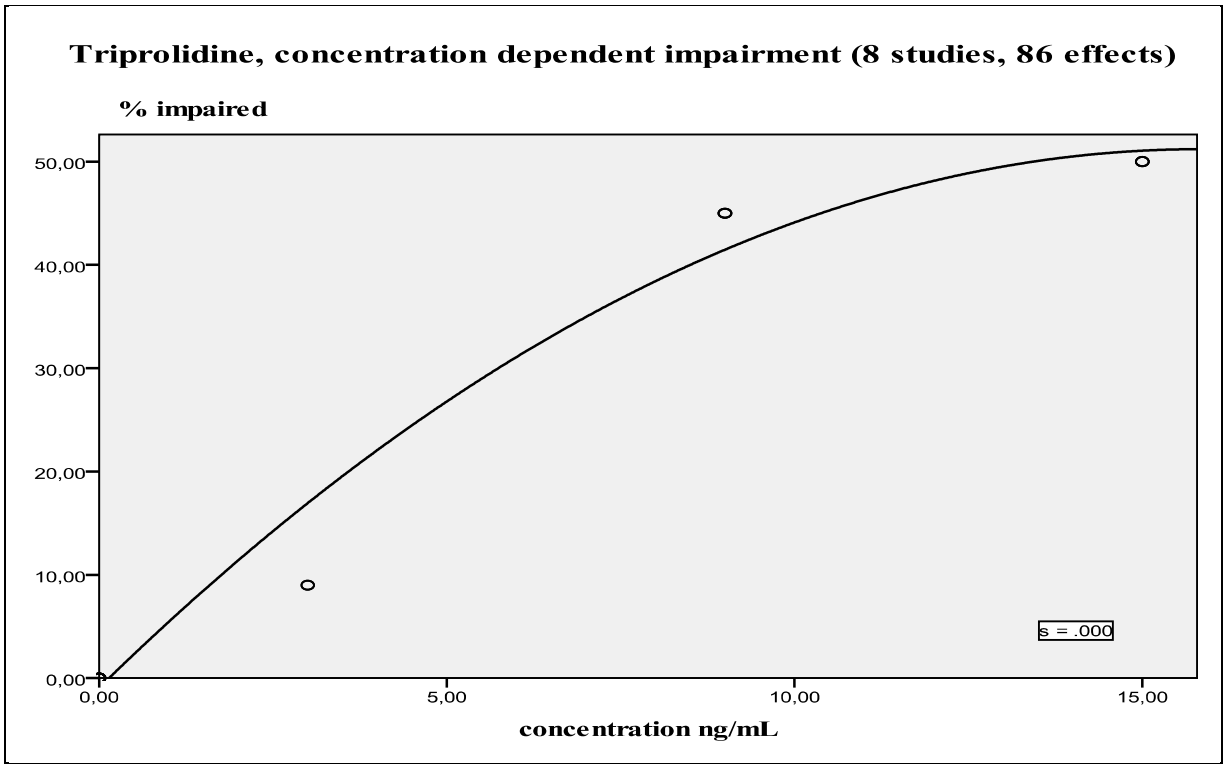

Figure 54: Tripolidine, concentration-dependent impairment.

Table 48: Tripolidine, summary of results.

Summary **Single administration**	**R06AX07 Triprolidine**
Number of studies	14
Number of effects	233
Checked doses (mg)	1.25 - 10
Recommended dose (mg)	2.5
Tabularly evaluable doses (mg)	10 *)
No. studies / no.effects	7 / 92
Max. sign. impaired test results (%)	(60 - 70)
Hour p.a. of maximum impairment	(1.5 - 2.5)
Alcohol equivalence of max. imp. (%)	(>0,08)
Duration p.a. until <15% impairment (h)	(5)
Degree of impairment	not calculable
0,05% alcohol equ. (ng/mL)	5.7 (4.8 - 7.0)
% of max. rec. dose (mg)	90 of 2.5 (75 - 110)

*): no curve fitting due to too few effects

Multiple administrations to healthy subjects

In studies that tested triprolidine up to one week in doses of 5 mg or 10 mg one dose daily to 3 doses daily [Betts et al. 1984, Brookhuis et al. 1989, 1993, Robbe et al. 1990, Volkerts et al 1990, 1992] impairments outlasted. Overall 15 of 27 effects measured showed a statistically significant decrease especially with the 10 mg doses.

Summary multiple administrations: Triprolidine shows strong impairment in the beginning of a treatment. It seems to takes at least more than a week to reach normal levels.

Administration to patients

Summary patients: no studies being on hand

3.4.1.4 R06AX12 Terfenadine

(R06AX other histamines for systemic use)

Single administration to healthy subjects

Overall we encoded 16 studies with 259 effects at doses from 60 mg to 240 mg. At most the 60 mg dose was tested. Only one effect of 197 measured was statistically significant reduced. Even in 4 studies (52 effects) with doses of more than 60 mg no single effect was impaired. Hence there was no performance decrease associated with terfenadine.

Table 49: Terfanadine, summary of results.

Summary **Single administration**	**R06AX12 Terfenadine**
Number of studies	16
Number of effects	259
Checked doses (mg)	60 - 240
Recommended dose (mg)	60
Tabularly evaluable doses (mg)	60 *)
No. studies / no.effects	16 / 197
Max. sign. impaired test results (%)	1 effect of 197
Hour p.a. of maximum impairment	no
Alcohol equivalence of max. imp. (%)	0
Duration p.a. until <15% impairment (h)	0
Degree of impairment	0

0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached

*): no curve fitting due to missing impairment

Multiple administrations to healthy subjects

In line with the results of the oral single application to healthy subjects multiple administrations seemed to create no performance deficits. Terfenadine 60 mg/day in the morning was combined with an evening administration of chlorpheniramine 8 mg or 12 mg over a period of 3 days and tested versus placebo administration. Both combinations did not impair driving tests (highway driving and car-following) which were conducted in healthy female volunteers 30 minutes after the last morning dose of terfenadine on day 3 [Vermeeren et al. 1998]. Even in the older studies [Kulshrestha et al. 1978, Betts et al. 1984, Riedel et al. 1989, 1990, Volkerts et al. 1990, 1992, Burns et al. 1993] that tested 60 and 120 mg up to 1 week or up to 1 month with single or double dose per day only 3 effects of 55 were statistically significant reduced. Only at higher doses (from 240 mg/day upwards), terfenadine should be able to cause sedative effects like other second-generation antihistamines [Rosenzweig and Patat 1999].

Summary multiple administrations: Terfenadine shows no impairment under recommended doses. However, it has severe cardio-toxic side effect, therefore it nearly disappeared from the German market.

Administration to patients

Patients (n=28) with hay fever were treated with terfenadine 120 mg/day for 2 weeks. The effects on central nervous system were assessed at baseline and at the end of the treatment by neuropsychological tests (attention, visuomotor abilities and anxiety). No statistically significant impairment of psychomotor performance occurred and no difference was seen in comparison with cetirizine 10 mg [Bonifazi et al. 1995].

Summary patients: No statistically significant impairment

3.4.1.5 R06AX13 Loratadine

(R06AX Other histamines for systemic use)

Single administration to healthy subjects

Loratadine reveals similar results as terfenadine. Of 213 effects measured in 13 studies at doses between 10 and 40 mg only 2 effects were statistically significant impaired. Hence there is no performance decrease.

Table 50: Loratadine, summary of results.

Summary **Single administration**	**R06AX13 Loratadine**
Number of studies	13
Number of effects	213
Checked doses (mg)	10 - 40
Recommended dose (mg) Tabularly evaluable doses (mg)	10 10 *)
No. studies / no.effects	13 / 166
Max. sign. impaired test results (%)	2 effects of 166
Hour p.a. of maximum impairment	no
Alcohol equivalence of max. imp. (%)	0
Duration p.a. until <15% impairment (h)	0
Degree of impairment	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached

*): no curve fitting due to missing impairment

Multiple administrations to healthy subjects

Persons who were treated with this typical second-generation antihistamine performed as well as subjects who received placebo. In detail, these healthy volunteers received a 5-day treatment with loratadine 10 mg/day and were tested on days 1, 3, and 5, 1.5 hours after drug intake: there were no differences between loratadine and placebo after the initial dose or steady-state (day 5) dosing for any measure of cognitive or psychomotor test performance (divided attention, working memory, speed), mood, or sedation [Kay et al. 1997, Kay 2000]. Similar results revealed the older studies [Roth et al 1987, Riedel et al 1989, Herberg 1990].

Only at higher doses (from 40 mg/day upwards), loratadine seems to be able to cause sedative effects like other second-generation antihistamines [Riedel et al. 1990, Rosenzweig and Patat 1999].

Summary multiple administrations: Loratadine shows no impairment under recommended doses.

Administration to patients

Patients under permanent therapy with loratadine (n=13) showed normal daytime sleepiness and no statistically significant deficits in psychophysical tests [Grellner et al 1993].

Summary patients: no impairment

3.4.1.6 R06AX26 Fexofenadine

(R06AX Other histamines for systemic use)

Single administration to healthy subjects

5 studies with 170 effects were analysed. Since there was no single statistically significant impairment we interrupted the information extraction for fexofenadine. There was no performance deficits associated with a single administration of fexofenadine.

Table 51: Fexofenadine, summary of results.

Summary **Single administration**	**R06AX26 Fexofenadine**
Number of studies **Number of effects**	5, then interrupted 170
Checked doses (mg)	30 - 180
Recommended dose (mg) **Tabularly evaluable doses (mg)** **No. studies / no.effects**	120 - 180 HCl all doses *) 5 / 170
Max. sign. impaired test results (%) **Hour p.a. of maximum impairment** **Alcohol equivalence of max. imp. (%)** **Duration p.a. until <15% impairment (h)**	0 effects of 170 No 0 0
Degree of impairment	0
0,05% alcohol equ. (ng/mL) **% of max. rec. dose (mg)**	not reached

*): no curve fitting due to minor or missing impairment

Multiple administrations to healthy subjects

In a study on healthy volunteers [Vermeeren and O'Hanlon 1998] with daily doses of 120 or 240 mg, given over 5 days, fexofenadine did not impair driving performance (psychomotor tests and driving test 1.5 to 4 hours after administration of the morning dose on days 1, 4, and 5). On the contrary, driving performance was consistently better during twice daily treatment with 120 mg fexofenadine than with placebo, even statistically significant on day 4. Only the first dose (120 and 240 mg) of fexofenadine had statistically significant impairing effects on the critical tracking test, the other psychomotor tests were without impairment. It was concluded that fexofenadine has no effect on performance under recommended doses of 60 mg twice daily.

Summary multiple administrations: Fexofenadine, the active metabolite of terfenadine, shows no impairment under recommended doses.

Administration to patients

Patients with seasonal allergic rhinitis (n=40) who received fexofenadine 60 mg at weekly intervals demonstrated no impairment in driving simulator tests (coherence, lane keeping, response time), 2.5 hours after medication at supposed peak plasma levels, when compared with placebo [Weiler et al. 2000].

Summary patients: Patients with a medication showed the same performance as patients without a treatment.

3.4.1.7 Comparison of Antihistamines

Single administration to healthy subjects

Table 52 shows the comparison profiles of the antihistamines.

Single administration to healthy subjects: comparison within an agent

Only diphenhydramine could be analyzed for two doses in which the higher dose showed a higher extent of impairment especially demonstrated by the "degree of impairment" and the duration p.a. until <15% impairment.

Single administration to healthy subjects: comparison between agents

The comparison table clearly demonstrated the marked separation between the different groups of agents of the antihistamines: the first generation antihistamines we analysed

(diphenhydramine, triprolidine) impaired driving by the sedation they produce. After the first dose the degree of impairment reached about 1 to 2 hours p.a. an alcohol equivalent of more than 0,05%. According to the concentration-dependent impairment curve, both agents were comparable in terms of reaching the 0,05% alcohol equivalent with about 90% of the recommended dose. The second and third generation agents (terfenadine, loratadine, fexofenadine) revealed no negative side effects on driving performance when used at recommended doses.

Multiple administrations to healthy subjects and patients

Antihistamines of the first generation needed a time of adaptation of at least 4 days (or longer) whereas the second and third generation substances in general showed no negative side effects when administered therapeutically for some days. Only under higher doses, a possible impairment could not be excluded. These results confirm in essence a review of Verster et al. 2004. A comprehensive review on antihistamines and driving-related behaviour can be found in an excellent survey by Moskowitz and Wilkinson [2004] which includes many details of papers having been published up to 1998.

Table 52: Comparison of profiles: R06 Antihistamines for systemic use.

Agent	*R06AA Aminoalkyl ethers*		*R06AX Other antihistamines for systemic use*			
	R06AA02 Diphenhydramine		**R06AX07 Triprolidine**	**R06AX12 Terfenadine**	**R06AX13 Loratadine**	**R06AX26 Fexofenadine**
Number of studies	28		14	16	13	5, then interrupted
Number of effects	481		233	259	213	170
Checked doses (mg)	25 - 100		1.25 - 10	60 - 240	10 - 40	30 - 180
Recommended doses (mg)	50		2.5	60	10	120 - 180 HCl
Tabularly evaluable doses (mg)	25	50	10 *)	60 *)	10 *)	all doses *)
No. studies / no.effects	9 / 102	22 / 284	7 / 92	16 / 197	13 / 166	5 / 170
Max. sign. impaired test results (%)	(46) ((39 - 53))	41 (34 - 45)	(60 - 70)	1 effect of 197	2 effects of 166	0 effects of 170
Hour p.a. of maximum impairment	(1.25) ((1.0 - 1.25))	1.75 (1.25 - 1.75)	(1.5 - 2.5)	no	no	no
Alcohol equivalence of max. imp. (%)	(0,05 - 0,08)	0,05 - 0,08	(>0,08)	0	0	0
Duration p.a. until <15% impairment (h)	(3.5) ((3.25 - 4.25))	7.75 (7.0 - 11.25)	(5)	0	0	0
Degree of impairment	(54) ((39 - 79))	92 (61 - 149)	not calculable	0	0	0
0,05% alcohol equ. (ng/mL)	60 (57 - 65)		5.7 (4.8 - 7.0)	not reached	not reached	not reached
% of max. rec. dose (mg)	95 of 50 (91 - 103)		90 of 2.5 (75 - 110)			
Adaption (weeks)	Impairment for 1 week		Impairment for at least 1 week	No impairment	No impairment	No impairment
Results in patients	Strong initial impairment, improvement from day 3, full recovery possible		No studies being on hand	No impairment	No impairment	No impairment

*): no curve fitting due to too few effects or minor or missing impairment

3.5 Illegal Drugs: Amphetamines, Cocaine, Cannabis

Before starting to report on illegal drugs it is very important to point out to some basic differences between medicines and illegal drugs, differences that are important primarily not from a scientific point of view (only the problem of the effects of the different agents is of interest) but from an ethic and legal point of view.

At first, medicines have to be used by patients to cure or alleviate indispositions or diseases, partly indispositions or diseases that themselves may impair driving related performance. Secondly, the medicine is prescribed by a physician and the patient can not buy such a medicine without a prescription of a doctor (apart from over-the-counter medicines that in general are not as dangerous as prescribed medicines). Thirdly the physician determines the dose of a medicament and he should check, as far as possible, the correct use by a medical exploration or a blood screening with respect to the therapeutic range of the agent.

In contrast: an illegal drug must not be used, the dose is not regulated (in part the user himself does not know the dose accurately) and the effects are not controlled by a physician.

The following evaluations pick out as central theme the single administration to healthy subjects who use drugs for recreational purposes and who are no poly-drug users or dependents on drugs.

3.5.1 N06BA01 Amphetamine, amphetamine-like drugs and psychostimulants

For medicinal purposes amphetamines rank among psychostimulants, agents used for ADHD and nootropics (N06B), especially among centrally acting sympathicomimetics (N06BA). But in general amphetamine is used as an illegal drug with performance-enhancing effects. It produces euphoria, strong stimulation and increased wakefulness.

Besides amphetamine and methamphetamine the so-called designer amphetamines belong to the same class and have similar effects as amphetamines [Iten 1994] and include among others the following substances:

- MDMA (3,4-methylenedioxymethamphetamine, also known as ecstasy)
- MDA (3,4-methylenedioxyamphetamine)
- MDEA, MDE (3,4-methylenedioxy-N-ethylamphetamine)

To a very limited degree, amphetamine-like substances are used in medicaments:

- Stimulants: e.g. amfepramone, methylphenidate, cathine; they are used in states of exhaustion, reduced motivation, impairments of performance or concentration and as anoretics.
- Methylphenidate: standard treatment of attention-deficit hyperactivity disorder (ADHD)
- Atomoxetine: treatment of ADHD
- Modafinil: analeptic drug for the treatment of narcolepsy
- Selegiline: treatment of Parkinson's disease

Concerning the meta-analytic approach to the published studies on amphetamines there are two basic publications on the topic: Schulz et al. [1997] as well as Berghaus [1997] analysed – independently of each other – the literature up to 1995.

The comprehensive analysis of Schulz et al. [1997], based on an assessment of experimental literature data, can still be used to obtain a fundamental survey on the topic. According to their data collection on amphetamines, including 85 experimental studies with 2775 effects, a negative influence on the driver fitness cannot be stated. On the contrary, statistically significant positive effects were markedly more frequent than statistically significant negative effects when all substances, all doses and all results (after different time intervals) were summarized. Especially, if one restricts the analysis to the results on driving related performance tests as we had done for medicines, that means if one selects the 'physiological' and the 'state of health' parameters, the remaining results are clear without ambiguity: only 2% of the 751 effects were statistically significant impaired whereas 14% were improved. Methylphenidat, d-amphetamine, l-amphetamine, methamphetamine, and phentermine were included in the analysis. **D-amphetamine** was the most frequent analysed substance with doses applied between 1 and 34 mg and effects measured between 5 minutes and 34 hours. Only 1% of 515 effects were statistically significant impaired. Besides the oral administration even other administration forms (intravenously, subcutaneously) were integrated.

Table 53: Summary of changes of performance due to amphetamine effects [Schulz et al. 1997].

	Stat. significant impaired effects		Not stat. significant changed		Stat. significant improved effects		All effects	
Performance area	**n**	**Line%**	**n**	**Line%**	**n**	**Line%**	**n**	**Line%**
Tracking			13	87	2	13	15	100
Psychomotor function	1	1	61	84	11	15	73	100
Reaction	2	3	57	85	8	12	67	100
Visual function	1	1	69	76	21	23	91	100
Driving behaviour			1	100			1	100
Attention	5	2	264	83	51	16	320	100
Divided attention			27	90	3	10	30	100
Encoding/Decoding	8	5	137	89	9	6	154	100
Total	**17**	**2**	**629**	**84**	**105**	**14**	**751**	**100**

Comparable results were reported by Berghaus [1997], who too studied the effects of stimulants by means of a meta-analytic approach. Based on data of 565 effects from 20 publications dealing with (d-, dl-, meth-)amphetamines, coffein, methylphenidate, ephedrine, phenylpropranolamine and pseudoephedrine only 4% of the test results were statistically significant impaired, but 14% were statistically significant improved.

D-amphetamine was by far the most tested agent with doses administered between 1 mg and 36 mg. To report results according to the results of medicaments, studies with oral single application to healthy subjects aged <60 years and with a cross-over design were selected.

Overall 10 studies with doses between 1 mg and 36 mg were available. We divided the data pool into two groups dependent on the dose administered. There were 5 studies with 105 effects up to ≤7.5 mg and 10 studies with 103 effects >7.5 mg. All effects were measured up to 9 hours p.a. No single effect in the two groups was statistically significant impaired whereas 14% for the lower doses and 19% for the higher doses were statistically significant improved. Hence for the interval of doses used for recreational use (5 to 20 mg according to Iten [1994]) there was no impairment. It is clear that there was no basis to construct curve fittings or to calculate concentration-dependent impairment.

Table 54: D-amphetamine, summary of results.

Agent	d-amphetamine	
Number of studies	10	
Number of effects	208	
Checked doses (mg)	1 - 36	
Dose recreational use (mg)	5 - 20	
Tabularly evaluable doses (mg)	≥1 - ≤7.5	>7.5 - ≤36
No.studies / no.effects	5 / 105	9 / 103
Max. sign. impaired test results (%)	0	0
Hour p.a. of maximum impairment	no	no
Alcohol equivalence of max. imp. (%)	<0,03	<0,03
Duration p.a. until <15% impairment (h)	0	0
Degree of impairment	0	0
0,05% alcohol equ. (ng/mL)	Not reached	
% of max. rec. dose (mg)		

Concerning the same selection for non-d-amphetamine agents combined (14 studies, 149 effects) only 3% of effects were statistically significant impaired with an accidental distribution of impaired effects over time classes.

Overall both studies [Schulz et al. 1997, Berghaus 1997] came to the conclusion that at least with respect to driving related performance there seem to be no statistically significant impaired effects that exceed the 15% threshold.

Of course, to be on the safe side, we screened published studies after 1995 in order to realize if change happens. But the more recent studies seem to confirm the well-known effects of amphetamines and stimulant drugs on driver fitness.

Makris et al. [2007] showed that d-amphetamine and modafinil had similar effects in healthy non-sleep-deprived adults: several experiments with different doses and different test intervals after administration led to comparable increases of alerting effects and performance.

In a study with healthy test persons, 20 mg d-amphetamine decreased lapses in attention and speeded sensory motor processing time, it increased the risk taking in women and the ratings of arousal when tests were performed 1.5 hours after intake [Acheson and de Wit 2008].

In the last years attention especially was directed to designer amphetamine MDMA (ecstasy). But since there were too few studies to include in a meta-analysis we only will give some reviews.

Cami et al. [2000] came to the result that MDMA (75 mg or 125 mg) produced marked euphoria, a slight impairment in the performance of psychomotor tasks and mild changes of body perceptions in healthy male volunteers. Amphetamine 40 mg induced similar effects.

An extensive and very typical example of a MDMA study is that of Lamers et al. [2003]. In healthy recreational MDMA users, a single dose of MDMA 75 mg improved psychomotor performance, such as movement speed and tracking, also in a divided attention task, however, it impaired particular performance skills (ability to predict object movement under divided attention). There was no effect on visual search, planning or retrieval from semantic memory. Overall 11 tests were applied of which only one test showed statistically significant impairment.

MDMA 75 mg (and methylphenidate 20 mg) statistically significant decreased the standard deviation of lateral position in driving tests conducted 3-5 hours after drug administration in recreational MDMA users, but it also decreased the performance in car following tests. The authors of this study [Ramaekers et al. 2006] drew the conclusion that MDMA as a stimulant drug may improve certain aspects of driving, such as road tracking performance, but may reduce performance in other aspects, such as accuracy of speed adaptation.

MDMA in different doses exhibited increased impulse control in psychological tests conducted in recreational users approximately 2 hours after administration. However, there was no interaction between MDMA and alcohol (0.06 g/dl), so that the stimulant effects of MDMA were never sufficient to overcome the alcohol-induced impairment of impulse control and risk-taking behaviour [Ramaekers and Kuypers 2006].

Kuypers et al. [2009] reviewed positive performance effects of MDMA concerning reaction time, tracking and weaving when optimal conditions were present (daytime, moderate dose). These effects were lost when MDMA was combined with alcohol or sleep deprivation what is close to reality in motor traffic. At normal doses of 75 mg, MDMA could impair driving behaviour by reckless features.

All in all the newer publication give no reason to a fundamental revalidation of the results summarized by the meta-analyses of 1997 concerning amphetamines. Even for ecstasy the experiments seemed to indicate similar results as for other amphetamines showing by far more improvements than impairments (especially Lamers et al. [2003]). **Hence, concerning**

driver fitness as tested with "normal" doses (40 mg - 125 mg) in experimental studies, the risk potential of ecstasy comprised during the time of action primarily not the impairment of performance.

On the other hand non-experimental studies and case reports revealed negative effects of amphetamines in terms of driving safety in the effective phase such as euphoria, agitation and confusion, increased risky behaviour, overestimation of one's own possibilities, restricted critical thinking and inner restlessness. Furthermore, the effects after an acute intoxication with amphetamines are frequently characterized by sleepiness and exhaustion which are, of course, of special relevance for traffic safety. These circumstances seemed to comprise at least a certain risk for a safe participation in motor traffic. But on the one hand there was no information about the frequency of such effects and on the other hand one has to ask why these deficits did not lead to severe impairments in performance tested in experimental studies.

It seemed that the experimental research as done in the moment is at the frontier of its possibilities in this situation. May be it would be of interest to compare in an experimental approach the point of time and the concentration of amphetamine in blood when the increased performance not further overlaps the increased risky behaviour or the overestimation of one's own capacity.

But, may be, the epidemiological approach within the DRUID project will elucidate the role of amphetamine concerning traffic safety.

3.5.2 Cocaine

Cocaine has similar acute effects as the amphetamines. After the acute effects a depressive phase with exhaustion and sleepiness can follow. It is an illegal drug and not present in regular medicaments (historically used as a topical anaesthetic). It appears mainly as cocaine-hydrochloride, and furthermore as crack and free base.

Concerning driver fitness as examined by experimental studies in recreational or occasional cocaine users the situation is comparable to amphetamines.

The above mentioned analysis of Schulz et al. [1997] also comprised information on cocaine. The data collection included 17 experimental studies with 771 observations of effects. A negative influence on the driver fitness could not be stated. If one restricts the analysis to the results on driving related performance tests the remaining results are clear too without ambiguity: nary effect of the 66 performance tests was statistically significant impaired

whereas 21% were improved. Doses between 8 mg and 210 mg were tested 15 minutes up to 3 hours p.a. According to Iten [1994] a single dose concerning the oral administration would be about 100 to 300 mg. **That means that even for cocaine the doses for recreational use were tested**.

Table 55: Summary of changes of performance due to cocaine effects [Schulz et al. 1997].

	Stat.significant impaired effects		**Not stat. significant changed**		**Stat. significant improved effects**		**All effects**	
Performance area	**n**	**Line%**	**n**	**Line%**	**n**	**Line%**	**n**	**Line%**
Reaction			7	88	1	12	8	100
Visual function			5	100			5	100
Attention			7	37	12	63	19	100
Encoding/Decoding			33	97	1	3	34	100
Total	**0**	**0**	**52**	**79**	**14**	**21**	**66**	**100**

Even for cocaine we screened the newer literature. A publication on an experimental study with occasional cocaine users [Lukas et al. 1996] covers only subjective effects. All other studies we gathered did not deal with the oral single application to healthy subjects and hence did not fulfil the inclusion criteria. These publications concentrate in essence on experimental studies with poly-drug users (for example Jenkins et al [2002]), on studies with chronic cocaine users or abusers (for example Morgan et al [2006]; Aharonovich et al. [2003]; Bolla et al. [2000]; Epstein et al. [1999]), on experiments with dependents (for example McCance-Katz et al. [2005]; Hopper et al. [2004]), or on subjects with a history of cocaine or stimulant use (for example Fillmore et al. [2005, 2002]; Haga et al. [2003]; Rush et al. [2002]).

Overall, for cocaine the same held true as for amphetamines: non-experimental publications and case reports revealed negative effects in terms of driving safety of cocaine (euphoria, aggressive behaviour, agitation and confusion, in addition increased risky behaviour, overestimation of one's own possibilities and a restriction of critical thinking). Furthermore, the effects after an acute intoxication with cocaine are frequently characterized by sleepiness and exhaustion which are of special relevance for traffic safety. Even Müller et al. [2004] stated on the basis of a review of the literature that there exist no hints on neuro-psychological impairment of functions in the acute effect phase. But they point out that there are no experimental studies available focusing on the post acute cocaine phase and/or studies with high doses.

Hence, as mentioned for amphetamines, even with respect to cocaine a new experimental approach seems to be necessary to elucidate the role of the drug for driver fitness.

3.5.3 Cannabis

3.5.3.1 Cannabis, oral administration

Overall 21 studies with 482 effects and doses between 7.5 and 39 mg could be integrated in the analysis of effects under oral administration of THC. Expectedly, contrary to medicines, all the single doses did not show frequencies sufficient high to try a curve-fitting of the empirical data. Therefore we unfortunately had to classify the continuous concentration range. We decided to build up 3 classes with approximated equal frequencies: <9 mg, ≤9 mg - <18 mg, ≥18 mg - 39 mg. One study had to be selected as an outlier.

The first class, which was a relatively homogeneous one since the concentration range (7.5 mg - <9 mg) was very narrow, showed statistically significant negative results in essence only up to 4 hours p.a. Thereafter from 47 effects measured till 17 hours p.a. only 1 effect was statistically significant impaired. This one effect may be by chance and was situated outside the range till 7 h p.a. with sufficient high numbers of effects. The third hour p.a. showed the maximum of impairment of about 10%. The 15% line never was exceeded and hence the degree of impairment was zero. The start of the approximation curve about one hour p.a. was, of course, a virtual one that exclusively was determined by the technique of curve fitting and did not reflect any physiological reality. As explained in the discussion, the approximation-curve could have been started even earlier but since the first effects were measured not until the second hour p.a. the approximation technique determines about one hour as starting point.

The next class between 9 mg and 18 mg illustrated a by far more intensive impairment. The deficits concentrated in the 2nd and 3rd hour with a maximum of 51% at the end of the second hour. Later than 4 hours p.a. only 2 out of 65 effects were statistically significant impaired. Since the impairment diminished quickly till the 5th hour the degree of impairment was considerably lower than that for orally administered doses of 18 mg and more.

Unfortunately the experimental research on doses ≥18 mg focused on the first 5 hours p.a. thereafter only 3 effects were measured in the 19th hour p.a. (3 effects 0 statistically significant impaired). Since in the 5th hour there was an impairment of 45 % and thereafter no experimental information at hand a meaningful curve-fitting was impossible concerning the further elimination phase and hence concerning the point of time when the curve crosses the 15% line. The maximum of impairment emerged in the second hour with over 50%.

A comparison revealed a clear-cut trend of the degree of impairment of the 3 dose-classes: with increasing doses the performance deficits increased too. All parameters calculated illustrated the rise, especially the maximum percentage of effects impaired and herewith the comparable %-alcohol classes, which started with <0,03% from the lowest dose-class and increased up to >0,08% for the highest dose-class. In contrary, the points of time of the maximum impairment showed earlier.

Even for THC we restricted the concentration-dependent evaluation on the time after the maximum of the kinetic curve (≥1 hour), which was based on the kinetics published in one study (compare chapter 7). After selecting the above mentioned study, 18 studies with 441 effects were at hand to use for curve fitting. We summarized the concentrations calculated in 2 ng/mL classes up to 10 ng/mL. The frequency of data in the groups was sufficient to use all classes to establish an approximation curve. The empirical values seemed to be best approximated by a linear curve (R^2 = 0,934). The 0,05%-alcohol equivalent could be calculated with 3.7 ng/mL (3.1-4.5). In contrast to medicines with a concrete dose administered, it was impossible to compare results of the concentration-dependent analysis with the results of the time-dependent evaluation, because for THC there was only a range of doses.

THC oral, 7.5 mg - 9 mg, time-dependent impairment (5 studies, 110 effects)

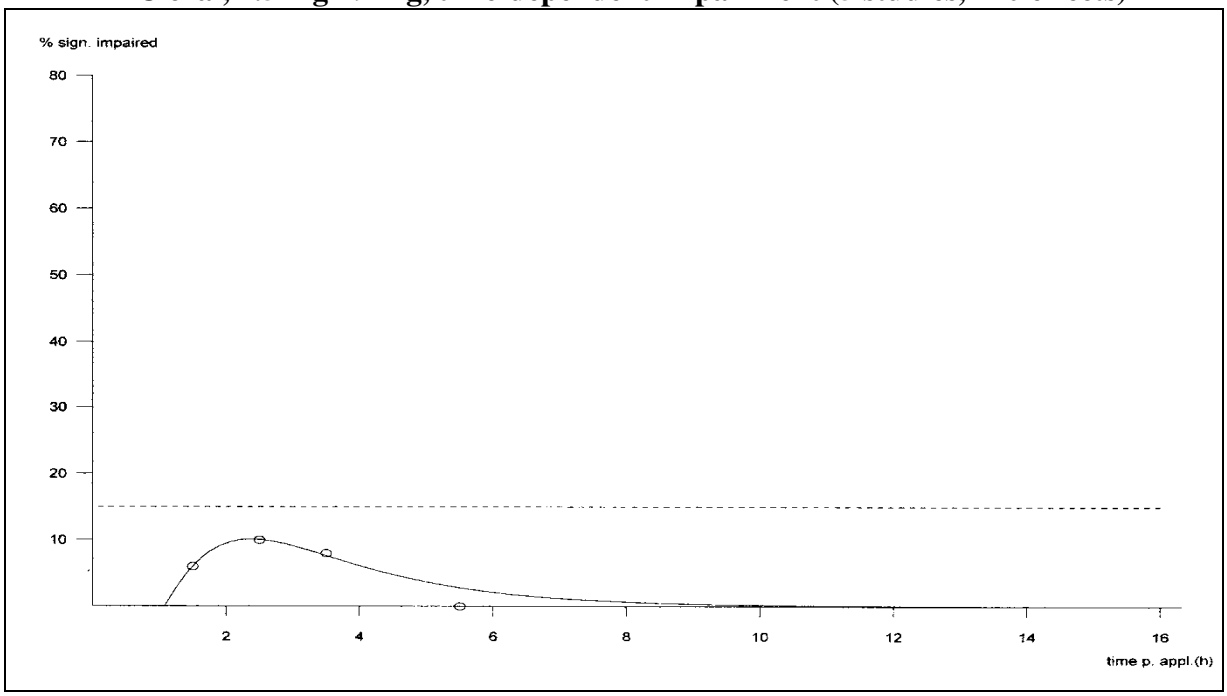

Figure 55: THC oral, 7.5 mg - 9 mg, time-dependent impairment.

THC oral, ≥9 mg - <18 mg, time-dependent impairment (9 studies, 159 effects)

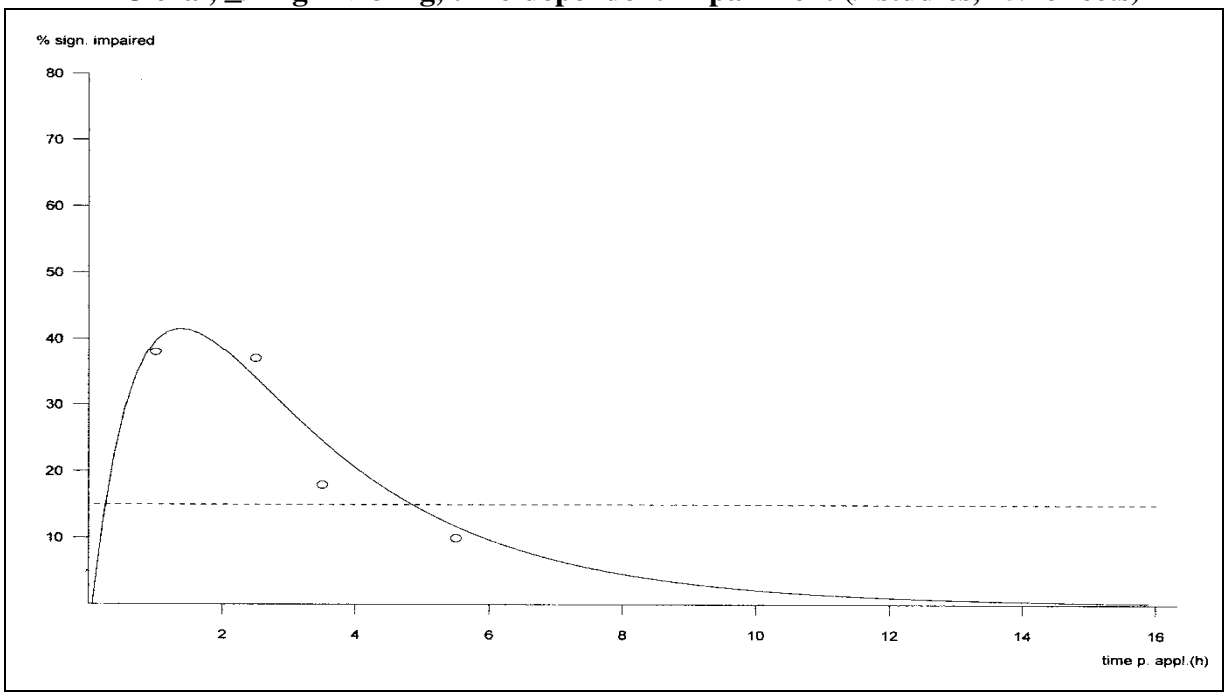

Figure 56: THC oral, ≥9 mg - <18 mg, time-dependent impairment.

THC oral ≥18 mg, time-dependent impairment (11 studies, 106 effects)

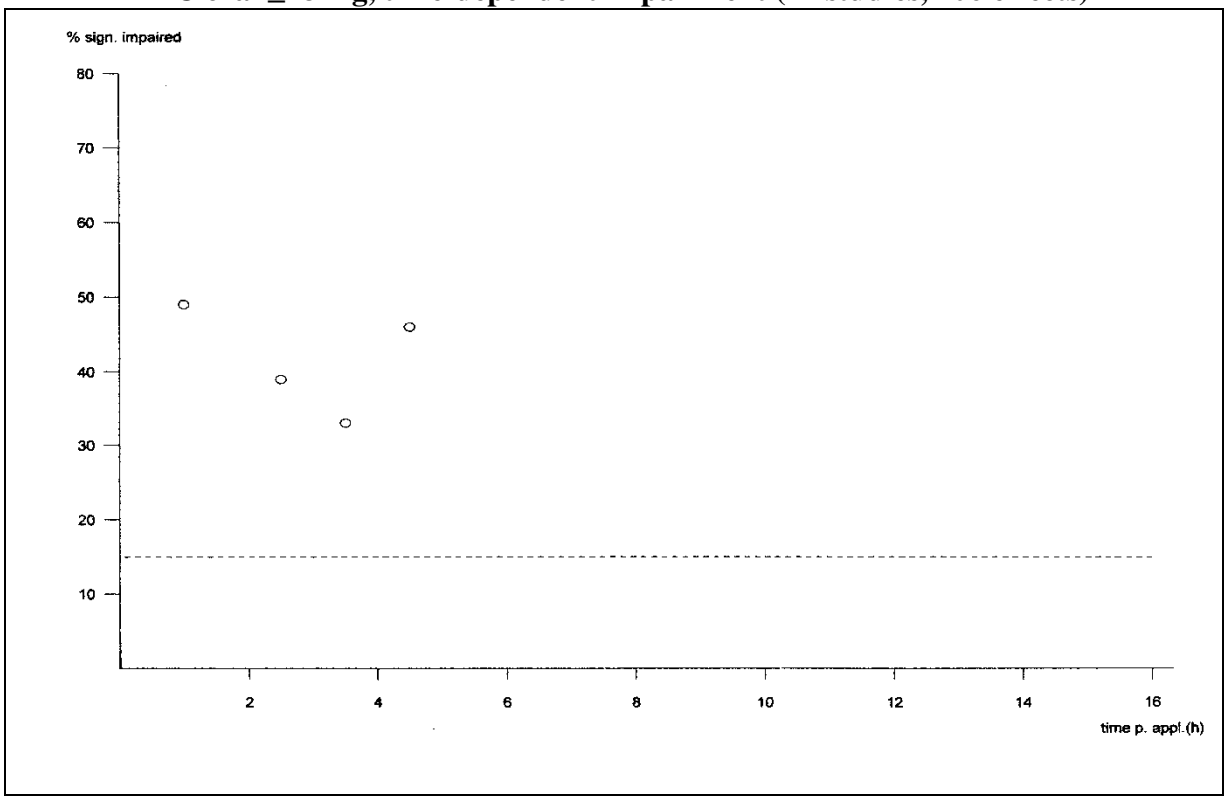

Figure 57: THC oral ≥18 mg, time-dependent impairment.

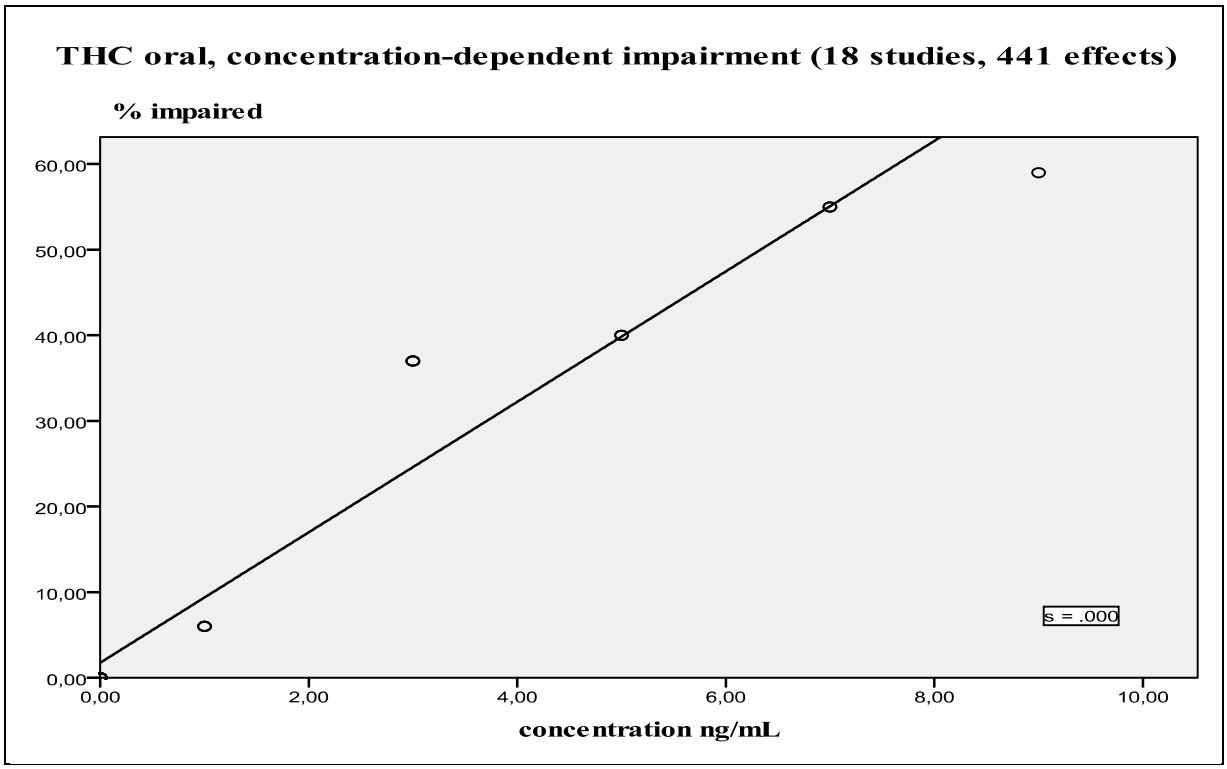

Figure 58: THC oral, concentration-dependent impairment.

Table 56: THC oral, summary of results.

Summary	**THC Oral administration**		
Number of studies	21		
Number of effects	482		
Checked doses (mg)	7.5 - 39		
Tabularly evaluable doses (mg)	7.5 - <9	≥9 - <18	≥18 – 39 *)
No. Studies/no. effects	5 / 110	9 / 159	11 / 106
Max. sign. impaired test results (%)	10 (7 - 15)	41 (37 - 46)	55
Hour p.a. of maximum impairment	2.25 (2.25 - 3.25)	1.25 (1.25 - 1.50)	1
Alcohol equivalence of max. imp. (%)	<0.03	0,05 - 0.08	>0.08
Duration p.a. until <15% impairment (h)	0	5.0 (4.25 - 5.75)	
Degree of impairment	0	68 (50 - 92)	
0,05% alcohol equ. (ng/mL)	3.7 (3.1 - 4.5)		

*): no curve fitting due to too few data

3.5.3.2 Cannabis, smoking

78 studies with 888 effects measured built up the basis for the meta-analytic approach to the smoking of THC. Concerning doses smoked we classified the effects in 3 groups analogous to the procedure for oral THC, even if we were aware of the fact that a defined dose will have different impacts dependent on the way of administration (oral, smoking; see later). A basic analysis of all effects indicated that by far most of the effects were measured within the first hour (69% of 888 effects) followed by the second hour with 15% whereas only a few studies tested later. Therefore we classified the time p.a. in 0.5 hour classes instrad of 1 hour classes to be able to construct at least for the starting time p.a. somewhat appropriate approximation curves.

The first dose-class included 40 studies with 350 effects. Statistically significant impaired effects could only be found till the third hour p.a. The maximum impairment with about 69% was located about 0.75 hour p.a. Already for the lowest dose-class the effects at the maximum impairment are comparable to those of an alcohol concentration of more than 0,08%. The duration till the 15% limit was crossed 2.5 hours p.a.

The dose-class ≥9 mg - <18 mg comprised 46 studies with 350 effects. A sufficient number of effects for the curve fitting could be detected up to the fourth hour. Of the 33 effects measured later only 3 were statistically significant impaired. The curve fitting illustrated a homogeneous distribution of the empirical values. The maximum was about 50%, the 15% limit was reached about 5 hours p.a.

Only considerably fewer studies (22) and effects (154) could be analysed for higher doses. Even for these doses at most measurements were done till the fourth hour. Continuous distributions of effects within time-classes could not be found later than 4 hours p.a., but contrary to lower doses a lot of irregularly distributed statistically significant impaired effects were to be seen even more than 5 hours p.a. (overall 41% of 34 effects). Up to the fourth hour the percentage of statistically significant impaired effects ranged in a narrow area between 44% and 56%. A meaningful curve-fitting was impossible. The maximum impairment (55%) was about the same as for the lower dose-classes. The duration of impairment could, of course, not be fixed.

A comparison between the three dose-classes indicated no essential differences, especially no correlation between doses and percentages of statistically significant impaired effects. That may be, at the first glance, exceptionally in comparison to the oral administration of THC. But one has to realize that the dose of THC that is really inhaled by smoking can be essentially

different between two users that smoke the same THC-cigarette. The absorbed dose depends on several influencing factors like for example the number and depth of inhalations during the time span the cigarette is smoked. Even if, in good studies, researchers try to standardize the inhalation technique (time of inhalation, holding, exhaling, break) it will be difficult to control the really inhaled dose (depth of inhalation). Hence a smoker who smokes a cigarette with dose >20 mg THC may really inhale a smaller dose as a user with a cigarette of a dose <9 mg. In contrary it is realizable that a smoker of a low dose cigarette will try to catch much THC by inhaling quickly and deeply. For this reason the missing correlation between dose and degree of effects does not wonder.

Concerning the concentration-dependent analysis similar considerations were necessary. Since we calculated the concentrations for the starting time of the test battery and since in the absorption and in the early elimination phase the concentrations of THC change very quickly, the concentration calculated will not represent the concentration during the test procedure itself. To avoid this shortcoming for the concentration-dependent analysis we used effects that were measured ≥1 hour p.a., that means effects that were measured during the more smooth course of the kinetics. On the other hand, as mentioned above, for high doses results measured ≥10 hours p.a. were extremely different in that some studies showed no impairment whereas other studies presented a very high percentages of impaired effects. In part these differences were caused by studies that tested performance in a flying simulator. But this test procedure seemed to create essentially more negative effects than normal laboratory tests. In addition it often is difficult to control subjects adequately during such long waiting periods. Therefore we even eliminated effects that were measured 10 hours and later p.a.

Using these prerequisites the quadratic curve fitting approximated the empirical values quite good ($R^2 = .935$) at least during the most relevant part of the curve that means up to 5 ng/mL. The late decline of the curve probably will be caused by the fact that the percentages of impaired effects range in a small area for concentrations ≥5 ng/mL. The 0,05%-alcohol equivalent was calculated with 3.7 ng/mL.

Even if the data for THC smoking are, due to the restrictions mentioned above, not so convincing as the results of the oral administration, the 0,05%-alcohol equivalents for THC smoking and THC oral administration were in agreement. Hence, merging the results of oral and smoking use, one will be able to state that the 0,05%-alcohol equivalent will be, considering the mean value, around 3.7 ng/mL - 3.8 ng/mL. The variation is, of course, considerably.

For further aspects of THC compare Grotenhermen et al. [2007] and Ramaekers et al. [2009].

THC smoking <9 mg, time-dependent impairment (40 studies, 350 effects)

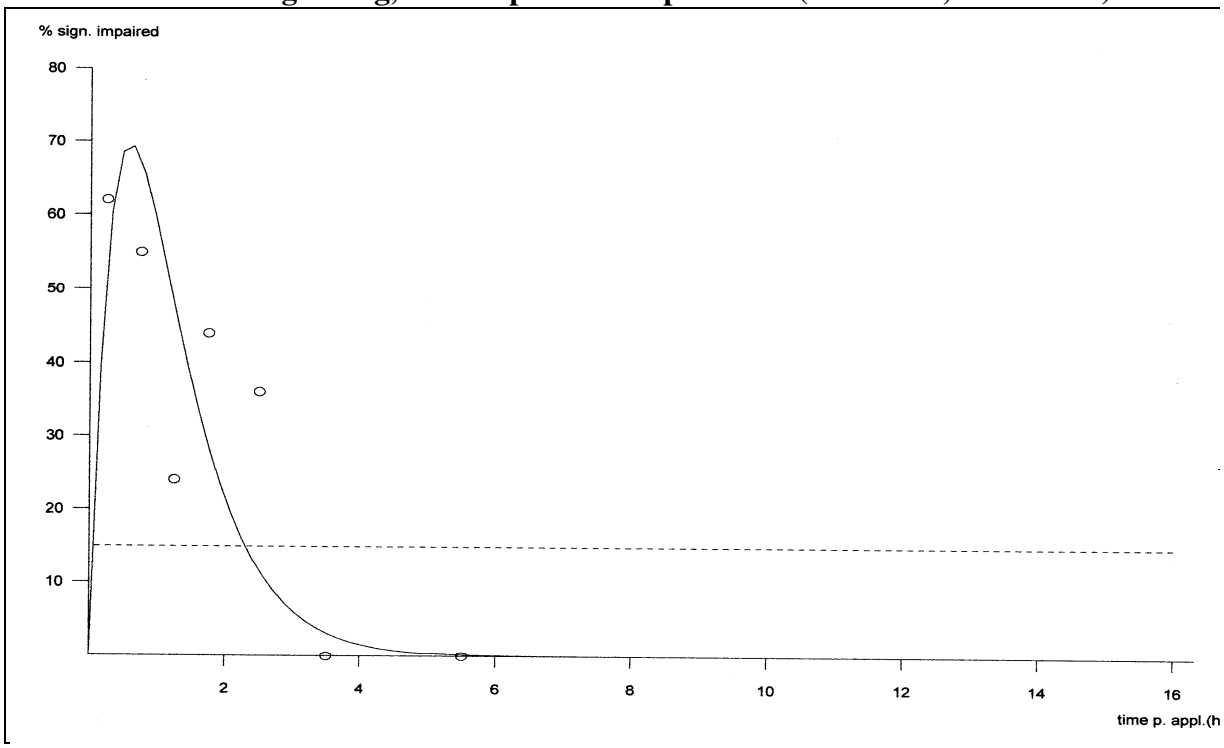

Figure 59: THC smoking <9 mg, time-dependent impairment.

THC smoking ≥9 - <18 mg, time-dependent impairment (44 studies, 317 effects)

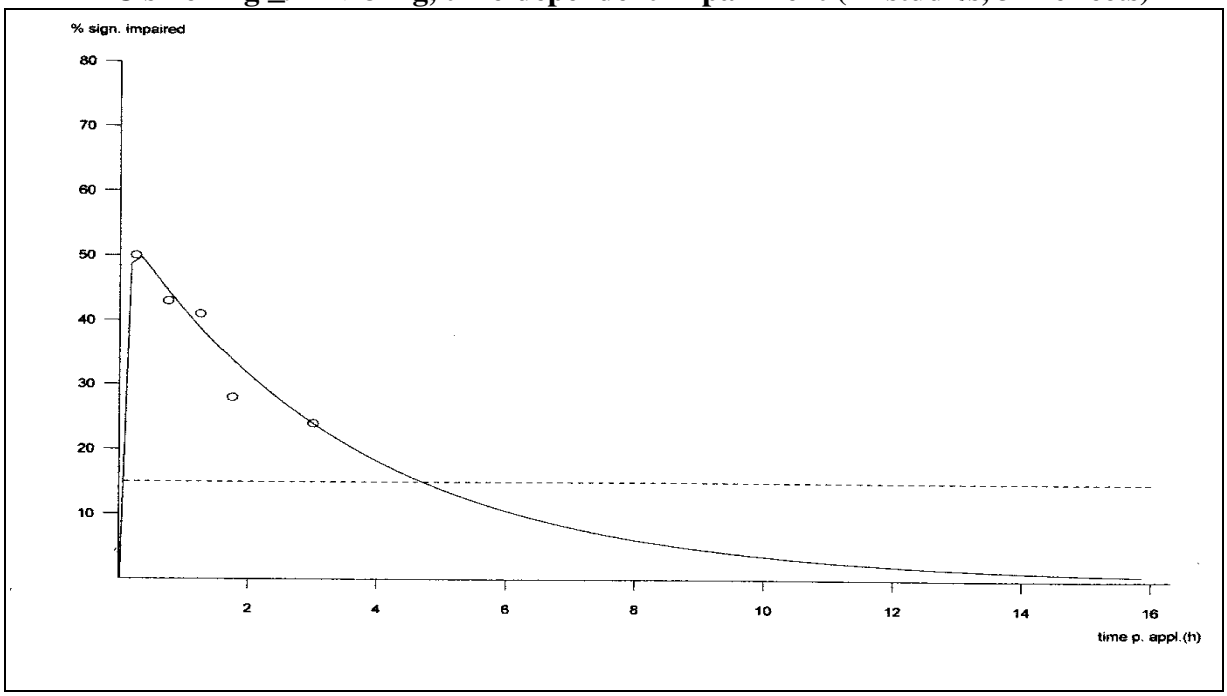

Figure 60: THC smoking ≥9 - <18 mg, time-dependent impairment.

THC smoking ≥18 mg, time-dependent impairment (22 studies, 154 effects)

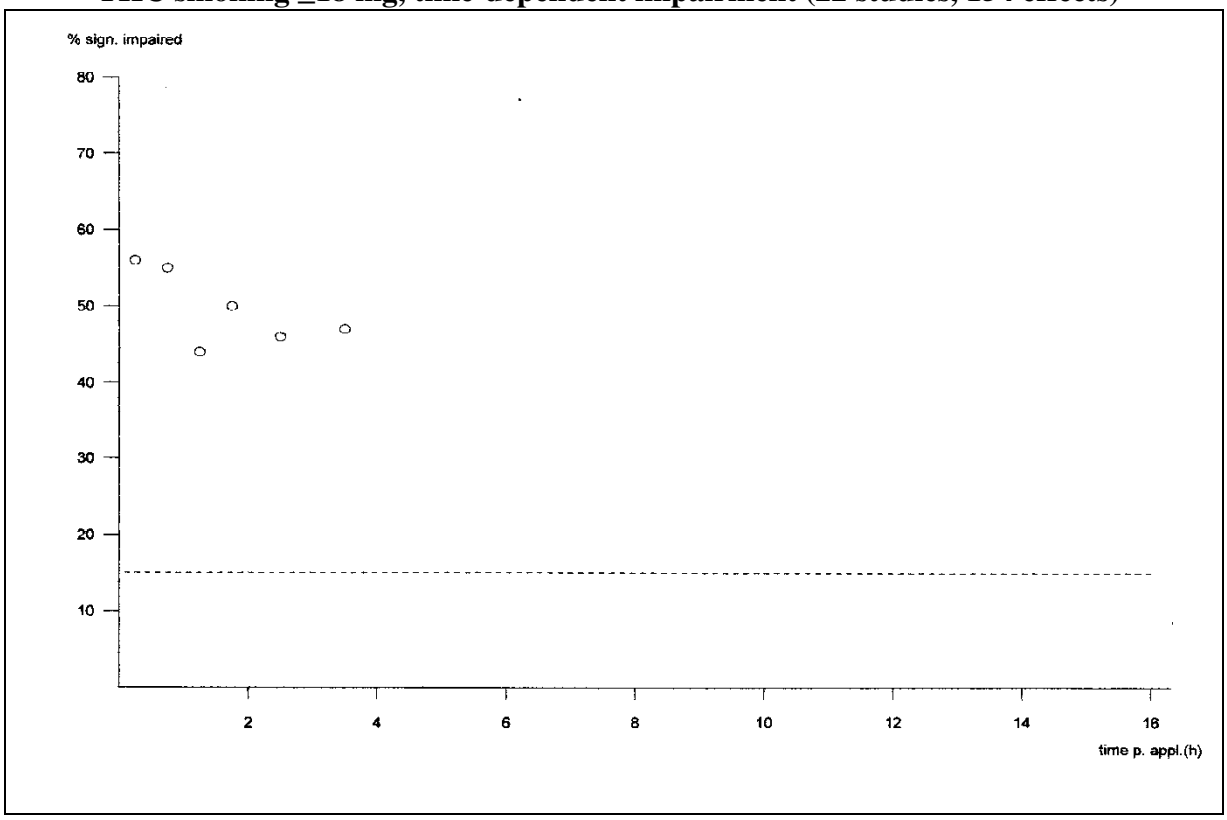

Figure 61: THC smoking ≥18 mg, time-dependent impairment.

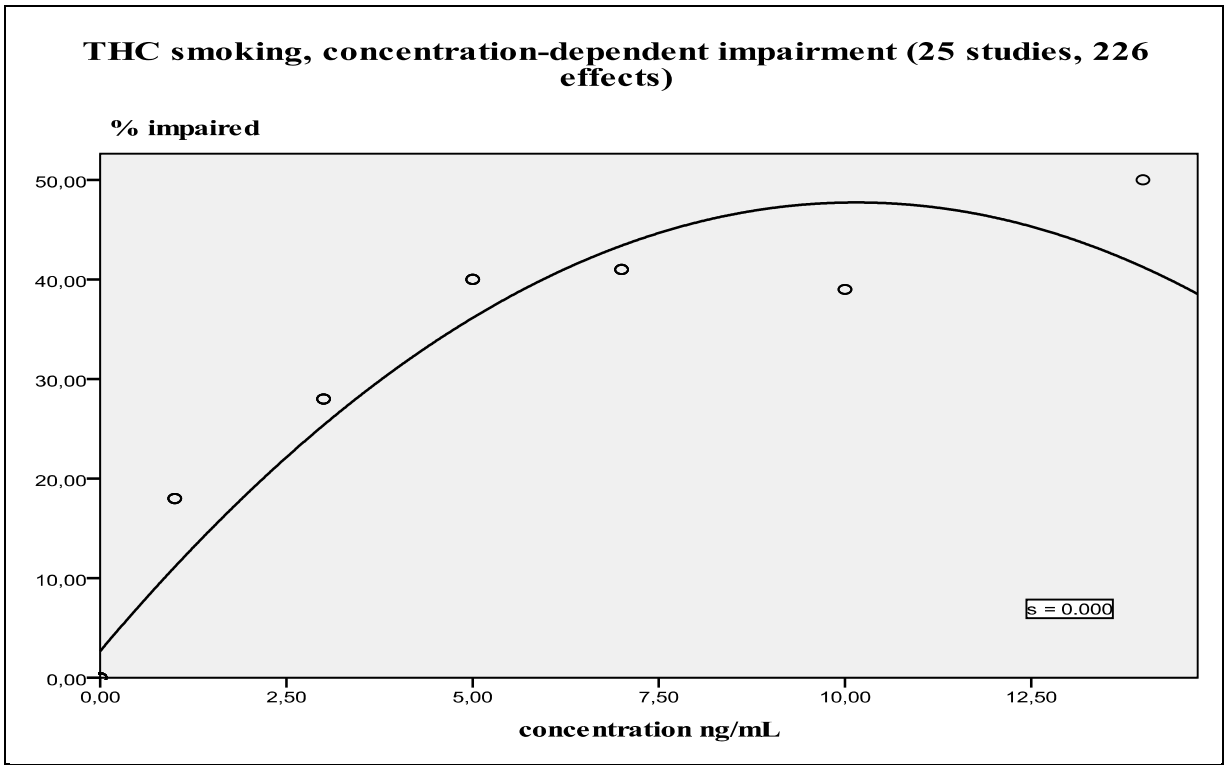

Figure 62: THC smoking, concentration-dependent impairment.

Table 57: THC smoking, summary of results.

Summary	THC Smoking		
Number of studies	78		
Number of effects	888		
Checked doses (mg)	ca.1 - 52		
Tabularly evaluable doses (mg)	1 - < 9	≥ 9 - <18	≥18 – 52 *)
No. Studies / no. effects	40 / 350	44 / 317	22 / 154
Max. sign. impaired test results (%)	69 (60 - 72)	50 (43 - 56)	55
Hour p.a. of maximum impairment	0.75 (0.50 - 0.75)	0.25 (0.25 - 0.5)	0.25
Alcohol equivalence of max. imp. (%)	>0.08	ca. 0.08	>0.08
Duration p.a. until <15% impairment (h)	2.5 (2,5 - 4.0)	4.75 (3.75 - 5.75)	
Degree of impairment	66 (57 – 92)	70 (47 – 92)	
0,05% alcohol equ. (ng/mL)	3.8 (3.3 - 4.5)		

*): no curve fitting due to too few data

3.6 Influencing factors on the degree of impairment including combination of drugs

Due to the predetermined designs of the experimental studies the report in the last chapters had to be restricted to the single administration to healthy subjects ≤60 years (meta-analytic approach possible) and to the multiple administrations to healthy subjects and patients (review approach). It goes without saying that the complexity of effect-determining factors could not be covered hereby. In real life there are a lot of more influencing factors that modify and change the degree of effects of a drug. It was, of course, impossible to specify all these influencing factors by giving experimental studies as examples, especially because a lot of influencing factors could hardly be realized in experimental studies. In this chapter we would like to draw the attention to some of the essential influencing factors especially to the simultaneous use of different drugs (combination of drugs) since one part of Task 1.1 should be to evaluate prominent combinations of drugs, medicines and alcohol for their impact on traffic safety.

3.6.1 Influencing factors

The following list summarizes some basic influencing factors without the claim to be complete.

Initial phase of therapy

- Agent, galenics, kind of administration
- Dose
- Time of administration (in the day, in the night)
- Time period between administration and performance requirement
- Compliance
- Disposition of the drug user
- Use of additional drugs
- Further influencing factors

After adaption

- Change of agent
- Change of dosage
- Compliance

- Disposition of the drug user
- Use of additional drugs
- Further influencing factors

The start of a therapy with medicaments is, of course, the most crucial phase with respect to performance impairment and change in feeling of patients. Concerning agent, dose and time period between administration and performance requirement we could give appropriate tables and figures for medicaments that demonstrated the dependence of effects on these variables. As we could demonstrate, it was, at most, more the dose than the agent itself that determines the degree of performance impairment. But all data were related to single administration and healthy test persons. Hence the conclusions concerning the degree of impairment and especially concerning the parameters calculated as for example the 0,05% alcohol equivalent concentration are restricted to these prerequisites. If one considers additionally other influencing factors like the disposition of a patient, the adaption or the additional use of drugs dynamics as well as kinetics of a drug and hence the parameters calculated may change. Besides the “agent” and the “dose” the “adaption” and “combination of drugs” are essential influencing factors of which we will discuss some aspects in the following. Concerning the “disposition” of the drug user we only would like to point to some aspects like the individual nature of the endocrine and hormonal system with implications for the absorption, distribution, metabolizing and elimination of agents; to inherent malfunction of metabolism with danger for adverse reactions, interactions and unwanted effects of medicaments; to constitutional and anatomic attributes like age, gender, weight, physique; to acute psychic and physical situation as for example tiredness, stress, concomitant diseases etc. etc.

3.6.2 Multiple administrations to healthy subjects (adaption) and patients

Degree of effects and concentration of a drug

Even if a meta-analytic evaluation of experimental studies with multiple administrations was impossible due to the described heterogeneities in the designs (chapter 3.1) and hence no quantitative figures could be presented, the reviews demonstrated in essence for all agents an adaption to the effects after different periods of time. That means that after some days of use of a drug the degree of performance impairment decreased. Besides the agent and the dose the adaption was one of the essential influencing factors on the degree of impairment. The adaption depended on many factors especially the degree of impairment after the first administration (at most very few deficits if already for the first administration there were few

deficits; apart from agents that establish their medicinal effects over a period of time), the dose and the frequency of use.

The recovery of performance with duration of treatment had essential impact on the correlation between concentration of the drug in serum/plasma and the degree of effects. In the following figure we tried to elucidate this fact using amitriptyline as an example.

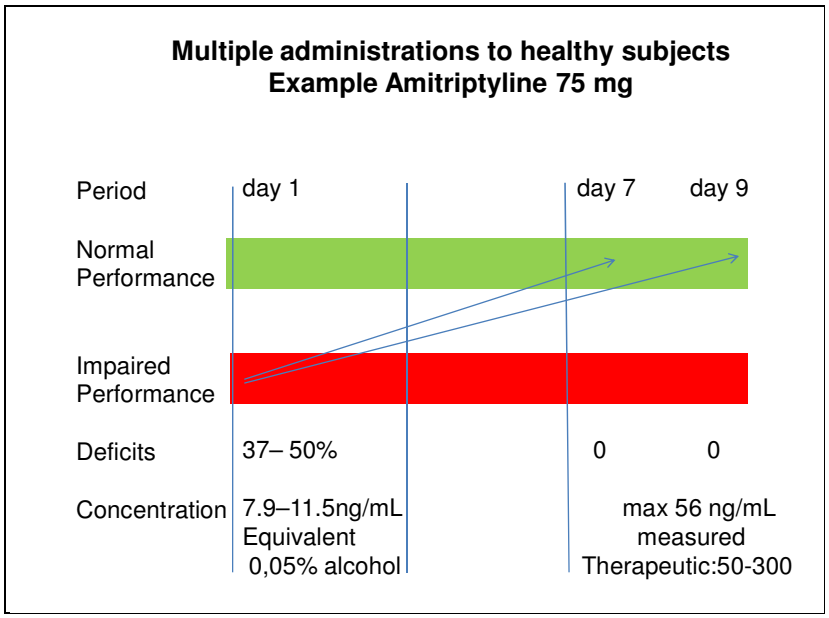

Figure 63: Influence of multiple administrations on performance (example amitriptyline).

For the beginning of the therapy (single use) we could demonstrate by means of the meta-analytic approach that the effects at a concentration of 7.9 to 11.5 ng/mL of amitriptyline corresponded to effects of 0,05% alcohol. But we cited a study that tested after 7 or rather 9 days of treatment in which there could not be found performance impairment. Since in this study concentrations were measured one realized the maximal concentration of a subject with 56 ng/mL, a value that corresponded very well to the therapeutic window of amitriptyline (50-300 ng/mL, Schulz and Schmoldt [2003]). That meant, with an essential higher concentration than after a single use there were no deficits. In a backwards conclusion one has to state that the well known fact that alone from a concentration of a drug in the serum/plasma there was no possibility to estimate the degree of effects – by the way a result that is even known for alcohol or illegal drugs.

This example made clear that the parameters calculated for single use could not be transferred to the situation of multiple administrations.

Situation in patients

The condition in patients is by far even more complex than the situation during adaption of healthy subjects. Unfortunately even the experimental studies using patients as subjects could not be analyzed meta-analytically due to the restrictions we summarized in chapter 3.1. Therefore even for the situation of patient we only can mention some experiences of the reviews.

The completely new aspect is the disease that should be treated with the medicament. One can differ between diseases with symptoms that themselves have negative influences on driving related performance and diseases that have no influence on performance. The next figure shows the different approaches.

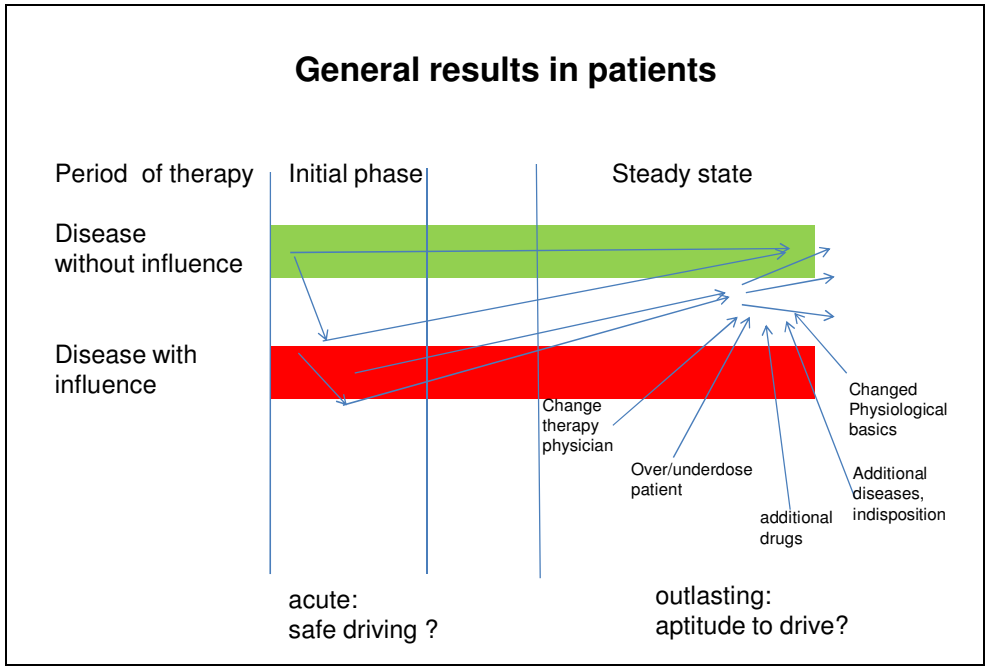

Figure 64: Different approaches concerning diseases.

If the disease itself has no impact on performance, eventually arising performance deficits will in general disappear with time of use of the medicament till the steady state. If, on the other hand, the disease has impairing effects it will, in general, demand some times till the agent show a benefit effect on the disease and herewith on the negative performance effect and in addition the adaption will reduce the degree of impairment. Since it is meaningful to start the therapy with dose gradually increasing medication it often will use some days till the dose is optimized correspondent to the disease. Hence, especially in the first days of a treatment the patient has to control his safe driving being under acute effect of his medicament.

If the patient is adapted to his medicine during the therapeutic, “normal” range of concentrations and if he is adjusted best with respect to the dosage of the medicament there

remain, in general, dependent on the disease, only marginal performance impairments. In this steady state the compliance of a patient, that means the correct taking of the medicament, is the basic requirement for driving safety. Afresh driving related performance impairment may emerge if the therapy is changed or another behaviour of the patient causes new deficits. Aspects that may influence performance during "steady state" may be:

- Change of therapy (dose or medicine) by the physician
- Overdose or even underdose by the patient
- Additional indispositions or diseases
- Additional use of alcohol and/or legal and/or illegal drugs
- Changed basic disposition

Therefore with chronic diseases it is no longer the question of driving safety in the sense of the acute disposition but the question of driving aptitude in the sense of the general aptitude to drive a car safely as prerequisite for the driving license.

3.6.3 Effects of simultaneous use of psychoactive drugs (Eva Schnabel & Günter Berghaus)

3.6.3.1 Importance of the simultaneous use

In the following, the consumption of different psychoactive substances within a time frame in which at least two substances have an effect simultaneously is named combined or simultaneous use.

The analysis of epidemiological studies seemed to indicate that the simultaneous use of different psychoactive substances is the rule rather than the exception. Augsburger and colleagues, for example, examined drivers who were suspected of driving under the influence of psychoactive substances. During a two years period ranging from 2002 to 2003, they analysed blood samples of 440 drivers in four Swiss cantons. In every second blood sample (50,7%), at least two psychoactive substances could be detected [Augsburger et al. 2005]. During the years 2000 to 2002, Holmgren and colleagues analysed alcohol, illicit drugs and pharmaceuticals in blood samples of fatally injured drivers (855 with a toxicological investigation) in Sweden. Within the investigation period, the percentage of cases with multiple drug intake increased from 10% to 26% [Holmgren et al. 2005]).

As far as we know, there are no systematic epidemiological studies up to now referring to the question of typical user groups of substance combinations. The following attempt of a

grouping therefore primarily was based on the practical experience of an expert activity within the frame of criminal proceedings.

Table 58: User groups of substance combinations.

Users	**Substance combinations**
Unintentional combination	Alcohol + medicines
Intentionally combined use	
Young people	Alcohol, cannabis, amphetamines
Elderly and ill people	Medicines, opioids
Addicted people	Alcohol, illicit drugs, benzodiazepines

Regarding the group of elderly people, paying attention to the problem of simultaneous use is even more important. With increasing age, the simultaneous intake of different medicines becomes more common. From the age of 60, an average intake of three medicines per day can be assumed. By the expected increasing aging of the population, the group of people who take different medicines simultaneously might become bigger and bigger.

Due to the importance of the simultaneous use of different psychoactive substances, one part of Task 1.1 is to evaluate prominent combinations of drugs, medicines and alcohol for their impact on traffic safety.

3.6.3.2 Impossibility of a meta-analytic approach

By collecting empirical knowledge about the major psychoactive substances, studies were found in which not only the effect of a single substance was tested but also the effect of substance combinations. The only substance for which more than just a few combination studies could be found was alcohol. However, a detailed analysis showed that even regarding alcohol there exist too few studies with the same second agent. We gathered 53 alcohol studies in which the combination with overall 35 different substances was tested. For most of these substances there are only one or two combination studies, with the exception of thioridazine (n = 3), cocaine (n = 3), MDMA (n = 4), cannabis (n = 10) and diazepam (n = 13). Thus, the number of studies is too low for most combinations to evaluate their effects by means of a meta-analysis. Even if there are some combinations with more studies, like for example for alcohol and THC, the designs of the different studies and hence the influencing factors on the results of performance tests are too heterogeneous to combine them meaningfully in a meta-analytic approach as this was possible with the single agents.

As an example, the effects of alcohol/cannabis combinations compared to placebo are summarized in the next table. The first digit shows the number of statistically significant impaired findings for the respective substance concentration and performance category, the second digit the number of all findings. The table illustrates some of the difficulties when trying to summarize the results of the different studies.

Table 59: Number of statistically significant impaired findings of the alcohol/cannabis group versus the placebo group in comparison to the number of all findings concerning different substance concentrations and performance categories.

BAC	THC dose given	Points in time of testing	Reac-tion time	Divided atten-tion	Psycho-motor skills	Visual func-tions	Trac-king	Dri-ving	Total
0,03%	1,75%	10-20min			0/1			0/1	0/2
0,03%	3,33%	10-20min			1/1			0/1	1/2
0,04%	100µg/kg	25-30min						5/9	5/9
0,04%	200µg/kg	30min						7/8	7/8
0,05%	170µg/kg	---					1/1	3/8	4/8
0,06%	1,75%	10-20min			0/1			1/1	1/2
0,06%	3,33%	10-20min			1/1			1/1	2/2
0,07%	215µg/kg	100min	2/2		1/1		1/1		4/4
0,08%	320µg/kg	100min			1/1		1/1		2/2
0,09%	3,6%	75min				0/1			0/1
0,10%	40µg/kg	---		2/2					2/2
0,11%	100µg/kg	5min				2/2			2/2
Total			2/2	2/2	4/6	2/3	3/3	17/29	30/45

First of all, different concentrations of alcohol as well as different concentrations of THC were used in the studies. Second, there were different points in time when performance testing took place. Thus, testing started in the absorptive or in the eliminative phase of alcohol or of THC. Summarizing is also difficult as some studies tested effects of the substance combination versus placebo and some versus the single substances (i.e. vs. alcohol or vs. cannabis).

Thus, a meta-analysis of experimental studies on combined effects cannot be conducted in a meaningful way. Even a review of experimental studies would go beyond the scope of this report due to the variety of possible combinations – alone the some hundreds of agents of pharmaceuticals would imply an immense number of substance combinations. Therefore in the following, only some basic information is presented for the comprehension of interactions

as well as some basic results of the experimental research on combined effects, referring in part word by word to Berghaus [2007].

3.6.3.3 Preliminary remarks on the combined effects of substances

First of all, interactions on the effect level can be separated from interactions in a physiological sense. The interaction on the effect level is illustrated by an example: If eye drops were administered to a patient who is sedated by the intake of a tranquillizer in order to investigate the eyeground for example, the two substances will not interact on the physiological level. Regarding the driving-relevant effects, however, an increased risk of the combined effects compared to the single effects can be assumed. In addition to the retardation induced by the sedation, the vision is clearly affected. Thus, there is an increased risk potential in a traffic situation in which a good vision and a normal reaction is required.

In a physiological sense, interactions mean the mutual influence of several substances in the organism. A diversity of mechanisms could cause this, for example chemical interactions or pharmacokinetic and pharmacodynamic interactions.

Interactions relevant for traffic safety become apparent by an increase or decrease of effects caused by substances which operate at different locations of the same system. Regarding the stimulation and sedation, which are the basic effects of psychoactive substances, this is illustrated in the next figure in a simplified way. If, for example, two sedative substances are taken simultaneously, a synergetic effect can result, either by an additive or an over-additive combined effect. Idealized, the additive effect of two substances with the sedation degree (-2) results in a combination with the sedation degree (-4), and the over-additive combined effect in a sedation degree higher than (-4). The effect combination is termed (non-competitive) antagonistic, if it leads to a lower effect than one of the single substances, like for example when consuming a sedative or stimulating substance [Krüger 1996, Möller 1998].

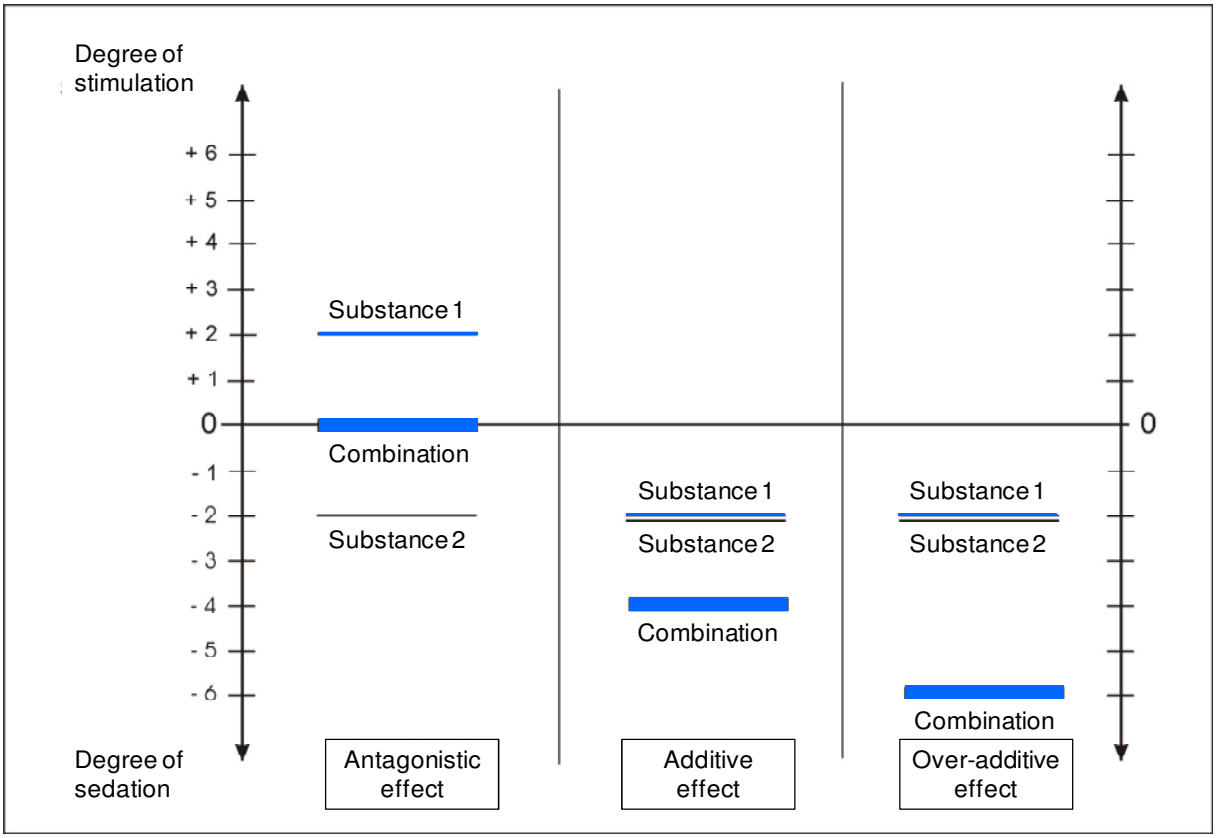

Figure 65: Interactions regarding stimulation and sedation.

Further, it should be pointed out that a general evaluation of a combined effect of two substances is not possible. The effect depends substantially on the time of performance testing and thus on the particular effect of the single substance at this point in time. For every single substance the effect firstly increases in the absorption phase and decreases in the elimination phase. When combining two substances, the kind of interaction and its size will therefore be continually changing. As an example, the kinetics and the expected combined effects after the simultaneous use of cocaine and rohypnol (long-acting hypnotic, sedative with the agent flunitrazepam) are presented in the next figure, modified according to [Möller 1998, p. 87]. First, the stimulating effect of cocaine is dominant due to the faster resorption (euphoric effect of cocaine). The stimulating effect increases, until the sedative effects of rohypnol become apparent and antagonistic effects occur. Finally, the effect of rohypnol increases more and more, and the euphorigenic effect of cocaine decreases more and more, so that the sedative effect becomes dominant over time. In the depressive phase after cocaine use (not presented in the figure), which is, for example, characterized by fatigue and exhaustion, effects might even be additive concerning sedation.

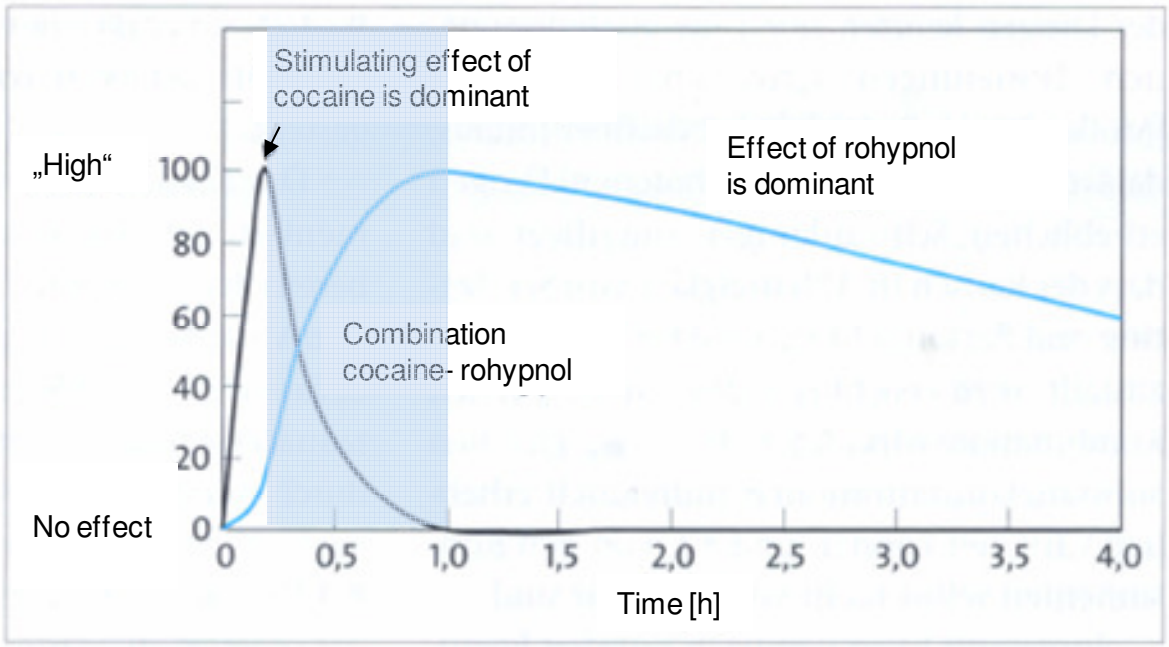

Figure 66: Simplified illustration of the interactions between cocaine and rohypnol (modified according to Möller [1998, p. 87].

Considering the effects-influencing factors – especially the dose and the adaptation to the single agents of a combination, but also the "setting" for drug consumption – it is evident that the following presented combined effects can only be rough references, which have to be modified in the concrete case according to dose, adaptation and time of testing.

3.6.3.4 Combined effects of substances

With the above mentioned limitations, interactions between medicines or between drugs are summarized as follows:

Table 60: Interactions between medicines regarding sedation and stimulation.

	Sedatives	**Antidepressants**	**Analgetics**	**Stimulants**
Sedatives	↓↓			
Antidepressants	↓↓	↓↓		
Analgetics	↓↓/↓↓↓	↓↓/↓↓↓	↓↓/↓↓↓	
Stimulants	↓↑	↓↑	↓↑	↑↑

↓↓ = additive sedative
↓↓↓ = over-additive sedative
↑↑ = additive stimulating
↓↑ = temporally different, difficult to predict

Table 61: Interactions between alcohol, illicit drugs and benzodiazepines regarding sedation and stimulation [modified according to [Möller 1998, p. 88; Möller 2005, p. 298]].

	Alcohol	Opiates	Cocaine	Cannabis	Amphetamines
Opiates	↓↓				
Cocaine	↓↑	↓↑			
Cannabis	↓↑	↓↑	↓↑		
Amphetamines	↓↑	↓↑	↑↑	↓↑	
Benzodiazepines	↓↓↓	↓↓	↓↑	↓↑	↓↑

↓↓ = additive sedative
↓↓↓ = over-additive sedative
↑↑ = additive stimulating
↓↑ = temporally different, difficult to predict

There are lots of experimental studies on the combined effects of medicines with alcohol. Krüger and colleagues evaluated in a meta-analytical approach 113 studies which meet defined quality requirements [Krüger 1996]. Thereby it is possible to describe the interactions quantitatively. The next table summarizes the results. It has to be considered that the experiments have not been conducted with comparable alcohol concentrations within the single substance classes. Therefore, the percentages are not comparable. Additional to the information in the table, the following combined effects were found: The more sedative the medicine, the more frequently occur interactions with alcohol. The more sedative the medicine, the lower are the alcohol concentrations at which interactions occur. Thus, the interaction with alcohol is particularly high for those medicine groups in which the medicinal agent itself has a strong performance-reducing effect.

Table 62: Percentages of statistically significant impaired alcohol-, medicine- and combined effects [modified according to Krüger 1996, p. 39].

Substance Class	Percentages of statistically significant impaired findings		
	Alcohol	Medicines	Alcohol + Medicines
Hypnotics / Sedatives	25,3	23,9	44,9
Tranquillizers	24,7	19,0	41,4
Antiallergics	29,8	8,5	36,2
Antidepressants	13,7	18,4	36,6
Neuroleptics	14,5	19,0	29,6
Analgetics	25,8	51,6	48,4
Stimulants	46,5	2,8	29,6
Beta-blocker	44,1	5,9	11,8
Spasmolytics	33,3	16,7	33,3

Especially for medicines, there is a huge body of literature concerning interactions between different agents from the physiological point of view, which are also partly relevant for performance behaviour.

4 DISCUSSION

4.1 General advantages of the meta-analytic approach to the evaluation of experimental studies

We think that meta-analysis in combination with the new aspects ‘calculation of concentrations’ and ‘curve fitting of the empirical data’ is the best approach to give an overview on the basic results of experimental studies on the effects of drugs on human performance related to driving safety.

There are obvtous advantages: For the first time this approach makes it possible to summarize data in dose- and time-dependent and concentration-dependent impairment courses. It would hardly be possible to establish such results by means of conventional reviews. Besides facts that one would expect, like for example the correlation between increasing doses and increasing performance impairment, a lot of new information could be presented. By calculation of parameters based on the approximated empirical data quantitative information like for example on degree of impairment, on maximum of impairment and on duration of impairment dependent on dose became possible. The curve fitting enables to recognize outliers and fills “gaps” of research by balancing of the original data for times p.a. for that no experimental studies exist. A completely new aspect is to be seen in the concentration-dependent performance impairment based on the evaluation of kinetic experimental studies.

Furthermore the meta-analytic approach offers the opportunity to compare the degree of effects of medicines and illegal drugs with the effects of alcohol. Since a lot of information on alcohol is well known, especially the effects of threshold concentrations for traffic safety, it even becomes possible to establish thresholds for drugs that can be compared to the limit-concentrations of alcohol.

Finally the possibility to upgrade the data pool without difficulty by further studies that had been or may be published in the future is an essential advantage compared to the conventional reviews. Hence, results on further agents, results concerning multiple administrations and results differed according to the kind of performance tests will be possible if enough studies can be encoded.

Of course, we will not keep quiet about shortcomings of the quality of studies on which the meta-analysis is based and, in consequence, about shortcomings of the method of processing the information. It is obvious that the results of the meta-analytic approach only reflect the results of the studies, hence, the better the studies the safer the findings and interpretations of

the meta-analytic evaluation. Therefore we would like to address the quality of the experimental studies and the procedure of handling the information encoded out of the experimental studies. We will concentrate on those considerations that are important for further research and important for the correct interpretation and generalization of the results.

4.2 Quality of experimental studies and their publication

The quality of experimental studies as well as their publications showed shortcomings that can be differentiated into three categories:

- **Design**
- **Execution of experiments**
- **Publication**

Concerning the design we illustrated already in chapter 3.1 that meta-analytically evaluable studies concentrated on single oral administration of drugs to healthy subjects aged ≤60 years (at most younger people, students). These aspects of the design are of course not generalizable to reality. The desperate differences in the test procedures chosen as realization of "driver fitness", especially the different levels of difficulty of the test batteries used, are a basic further shortcoming. Unfortunately there is no generally acclaimed agreement among experts on contents and duration of the test battery. Hence every researcher chooses his own tests to realize human performance related to safe driving and hence the results will often be very different depending on the test procedures.

Even the execution of experiments leaved a lot to be desired. In essence: too few subjects were integrated in relation to the number of test procedures (target variables), at most learning effects by performing the same test battery for several times could not excluded, at most subjects were carefully screened (understanding of tests and procedures, not uncooperative, not aggressive, not acutely ill, etc.) and hence it is unclear whether the medications and doses administered would have produced more impairment in "normal" subjects. Another aspect seems to be of fundamental importance. Unfortunately only in very few studies it is mentioned that subjects had to be excluded from performing the test battery due to serious side effects of the medicines. For example Bramness et al. [2006] reported that after using flunitrazepam some patients experienced, independent of their blood concentrations, unexpected, paradoxical reactions like agitation, talkativeness, disinhibition, aggression, violent behaviour, loss of impulse control etc. Analogues information is at most missing if

subjects do not tolerate illegal drugs. But in almost all publications the number of excluded subjects is not integrated in the statistical evaluation of the results of the performance tests.

Many of the above mentioned shortcomings are not mentioned or discussed in the publications. Furthermore essential information is often missing like for example the number of men and women and the weight of the subjects (compare chapter 3.1.1.3).

A selection of the studies according to these shortcomings would have been desirable, as even demanded by the work description of Task 1.1 of DRUID, but that was impossible because too many studies would have to be omitted so that a meaningful evaluation would have been impossible.

4.3 Procedure of handling extracted information

4.3.1 Missing population numbers and variability of test results and the impact on curve fitting

The quality of the curve fitting depends on the population number and the homogeneity of results within an individual time class (time-dependent analysis) or concentration class (concentration-dependent evaluation). Since the population number in a class frequently was too small we had to merge neighboring time- or concentration classes. In addition within a defined class we had to realize quite different results between studies that measured effects in this time class. It happened that in one study no effect was statistically significant impaired whereas in another study all effects were impaired even if both studies administered the same dose to the subjects. This is of course the consequence of different levels of test-difficulties and different numbers of subjects besides other aspects of the study design.

Missing values and heterogeneity of values between time classes are of course especially awkwardly concerning the first time p.a. and the late time spans p.a. The start of the curve (point in time where the curve crosses the x-axis) essentially depends on the empirical values for the very first time p.a. If, for example, no effects are measured in the first two hours and in the 3rd hour there will be a high percentage of impaired effects (may be in fact the maximum of impairment) it is very difficult to approximate these empirical data with respect to the question when the absorption curve starts p.a. At most the curve will start some times p.a. and, in general, this will reflect the kinetics of the agent (for example relatively slow absorption). But it can happen that in the first time classes there will be no impairment by chance (high variability, outliers that are not recognizable, only very few studies at hand) and hence for that reason the curve started later even if the kinetics may demand a start of the

curve immediately after administration of the medicine or illegal drug. Something similar holds true if for example the first effects p.a. (for example in the 2nd hour p.a.) will show a higher percentage of impaired tests than the second measurement (for example in the 3rd hour p.a.). In such a case the curve will go between the two values and hence will in general not start at time 0 p.a. In general if there are only one or two values in the absorption phase the absorption part of the approximation function has to be approximated in part by varying the parameters of the function. But this does not always mean that the reality is reflected. (By the way: the kinetic curve starts if the agent is detectable in blood. The dynamic curve can start earlier (if the drug quickly gets over the blood-brain barrier, lipophilic substances) or later (if a certain amount of a drug is necessary to show an effect).

All in all the point of time p.a. of the start of the fitted curve will not be sure in some agents due to the reasons mentioned above. But in our view this fact will not have essential consequences because the further course of the curve itself and the parameters calculated will change only marginally. Finally, the problem oft the curve fitting in the initial phase of effect of a drug is more a sophisticated problem and not so important in reality because it should be clear that a patient or illegal drug user should not drive immediately after taking a medicament or a drug.

The problem is serious in the elimination phase, especially if no effects are measured in the late elimination phase on which the approximation curve could be based like for example for THC. In such cases it is almost impossible to estimate the elimination curve exactly and in consequence the point in time when the curve crosses for example the 15% impairment threshold. It should be the task of research to close these gaps in the future.

4.3.2 Calculation of concentrations and the impact on allotting calculated concentrations to effects

Of course, we have to point out that the calculation of concentrations showed some shortcomings. **Basically there is an essential variability in calculating values for the time course of concentrations based on kinetic studies** as documented in the broad standard deviations of many drugs (chapter 7). This reflects the multitude of influencing factors on the concentration that will be measured after administration of a defined dose of a drug to a subject. As usual we calculated concentrations using the means of the kinetic curves and even the spreads we calculated in order to indicate the variations of the concentrations are calculated on the basis of the mean values of the kinetics. But, dependent on the level of safety that will be demanded by a special application (for example legal limits), even the

spread has to be widened by at least one standard deviation (compare curves in chapter 7) if one wants to be on the safe side.

Since dose, weight and time span between administration of a drug and measuring concentration in serum/plasma are essential influencing factors on the concentration we had taken into account these factors when calculating concentrations for the individual experiment. The concentrations given in chapter 7 hold true for a defined standard dose, the body weight of 70 kg and the defined time span between administration and point in time at which the concentration was of interest. To convert these standard values for the individual experiment we unfortunately did not know the weights of the subjects included and hence had to take “normal” values of 60 kg for women and 72 kg for men. If there were no information on the gender we took 66 kg. This means of course a certain inaccuracy. Even the adaption for the individual dose may produce a small shift if, for example, for higher doses the maximum of a kinetic curve will be situated after the maximum of the standard dose and hence, being some time longer under elimination, the maximum will be a little bit lower than calculated. But using therapeutic doses in general the differences will be marginally. Since in almost all studies the starting time p.a. and the duration of the individual performance tests of a test battery were not indicated it was impossible to allot concentrations to the individual tests. Because even the duration of the test battery was not mentioned in by far most of the studies we were forced to allot concentrations to the starting time of the test battery. But that meant that the concentration may even be another one when the individual performance test of a battery will be performed: during the absorption phase the concentration will be higher, in the elimination phase the concentration will be lower than at the beginning of the test battery. In order to limit this difference we only used data of the elimination phase for the curve fitting of empirical concentration values, because during elimination the decrease of the concentration curve in a defined time span is in general by far not so important than the increase in the absorption phase. A further limitation of this influencing factor is given by the fact that we merged concentrations in concentration classes and hence built up a certain adjustment.

4.4 Consequences for research and interpreting results

The shortcomings of the quality of experimental studies and of handling the extracted information must have, on the one hand, consequences for research and, on the other hand, for the interpretation of the results. In detail we would like to address several topics.

4.4.1 Necessity to improve and standardize research concerning experimental studies on human performance related to diving safety (test design, standardized test-battery)

An important aspect of the future must be the improvement of the quality and relevance of research in experimental studies in the field of driver fitness to reduce the variability of statistically significant impaired effects between individual studies. Guidelines for performing experimental studies, like for example those of a working group of ICADTS [2009], should be realized in all experimental studies (especially number of subjects, testing equivalence instead of statistical significance).

But ultra these guidelines, there is a basic necessity to develop a standardized, internationally acclaimed test battery to measure representatively the variable “safe driving behaviour”. Since experimental studies with a sufficient large subject panel are very expensive and the administration of drugs is not always nonhazardous for subjects the test battery should be so informative that sure statements on driving safety should be possible even if only a few studies or even a single one were performed on a special medicine. Especially for the seldom realized studies with multiple administrations or for studies with patients such a harmonized test battery is of fundamental importance concerning the safety of the results.

Concerning simultaneous use of drugs experiments are necessary that hold constant the concentration of one agent and measure effects during the whole action (absorption, distribution, elimination) of the second agent in order to learn something about the dynamics of the combinations.

With respect to illegal drugs like cocaine, amphetamine and THC a new approach should be established that includes beside performance tests even tests that measure subjective aspects like for example aggressive behaviour and its impact on safe driving.

4.4.2 Restrictions of informational value of the results of the meta-analysis

The results of the meta-analysis are valid only for single oral administration of agents to healthy subjects ≤60 years of age as it was determined by the design of the studies. That has several consequences.

<u>Single administration</u>

The single application of medicines in principle describes something like the “recreational use” in users of illegal drugs, that means the seldom use of a substance by people who do not take a medicament prescribed by a physician but only for short term demand. In essence this

situation can be characterized as "worst case scenario" because only the negative effects of the medicine on human performance will often be realized. In contrast, the use of a medicine by a patient at the initial phase of the treatment will probably produce, besides the negative effects, even positive effects with respect to those symptoms of a disease that may have negative effects on performance. And even for those groups of medicines that develop the full effect till the steady state the adaption will inhibit stronger performance deficits.

Administrations to healthy subjects ≤60 years of age

Using healthy people as subjects with the above mentioned additional selection (cooperative, no adverse reactions etc.) causes that the negative effects on performance in experiments will be less explicitly as in real life. In general the age of the user, his physical and psychological health and the existence of further factors that influence performance (compare chapter 3.6.1) will delimit his basic degree of performance. Hence, the administration of a drug will cause additional impairment that for example realizes in higher impairment and/or longer time periods till the performance is restored. Hence one has to include a certain safety interval, like it was done in the categorization of medicines within DRUID, that means the time period till a medicine will show no impairment has to be longer than based on the experimental results alone.

Broad variation of empirical values

Due to the variability of the designs, especially the differences between "simple" and "complex" performance tests, even the empirical data showed a broad variation that, in part, will be the reason for unsatisfactory results. Within a defined time class percentages of statistically significant reduced effects varied considerably. We tried indeed to handle these variations by calculating lower as well as higher approximation curves (10% variation of the number of statistically significant reduced effects per time class). But it leaves unknown if this 10% variation will really suffice to capture the variation.

0,05% alcohol equivalence, limit concentration

The best approach to establish limit concentration is of course an adequate epidemiological study. But since for most medicines this approach is impossible due to the low exposure in drivers the comparison of results of experimental studies on drugs with experimental studies on alcohol may help to give first impressions about limit concentrations for medicines and illegal drugs. Concerning **the calculation of 0,05% alcohol equivalent concentrations we have to point out that the calculated values only can be a rough lead**. On the one hand, as

reported above, this hold true due to the variation of the calculated kinetics and on the other hand because of the fact that the concentrations were calculated for the starting time of the test battery. Hence a certain shift could not be excluded. Furthermore the calculations are based on single administration and will of course change with multiple administrations as described in chapter 3.6.2. In addition one has to take into account a lot of more aspects for the construction of such limits like for example the variation of the toxicological measuring methods or safety margins.

4.5 Concluding remarks

In spite of the shortcomings listed above we think that we could offer a lot of valuable information that may be helpful for patients, physicians and for judging the degree of impairment of medicines and illegal drugs in relation to the performance impairments under the influence of alcohol.

Patients and physicians

Our results offer an optimization of the initial phase of a therapy with medicaments concerning degree and duration of performance impairment. In general a physician will not start his considerations about the optimal therapy for a disease with the question which agent will influence performance fewest. From the point of view of a physician it is by far more important to prescribe a medicament that ‘matches’ the patient and the illness. Primarily he will judge the benefit of a therapy and hence of a special medicament according to its power to cure a disease and not according to the fact if this medicament will impair the performance of the patient. Hence the benefit of the meta-analysis is to be seen in the fact that for many agents parameters were calculated that may help patients and physicians to get an impression on the course of the degree of performance impairments at the initial phase of a therapy with medicines. By starting the therapy with a small dose that indicates only marginal negative effects and by uptitration of dosage during the course of the treatment the danger of a medicine in relation to traffic safety can be limited.

The risk of a medicine concerning driving safety depends on more influencing factors than on its effect on human performance alone

The effect of drugs on human performance related to driving safety measured by experimental studies was the central theme of our task within this part of the DRUID project. The comparison of effects of illegal drugs with the effects of alcohol may give a first impression on the ranking of agents according to the danger for traffic safety.

But it is very important to state that the risk of an agent concerning traffic safety depends on more influencing variables than only on its performance impairment. The effect of drugs on driving related skills is one aspect out of a very complex pattern of determining aspects. These other aspects are in part more important than the effects of the agent itself.

Since other working packages of DRUID deal with such influencing factors a short compilation may suffice:

- Number of patients (acute, chronic) treated with the medicine
- Number of prescriptions and number of really used tablets
- Number of side effects with relevance to traffic safety (nausea, dizziness, … as mentioned in the package leaflet and even voluminous books on this topic)
- Number of interactions with other medicines, foods (even voluminous books on this topic)
- Number of unexpected intolerance, incompatibility

These influencing factors are additional reasons that a ranking of medicaments according to their danger for patients (categorization of medicines) must be another one than according to performance impairment alone.

5 REFERENCES

In the following at first the experimental studies of those agents that are included in the meta-analysis are documented and then other studies and experimental studies of agents that are at least not integrated.

Studies labeled with "**BAST**" were selected within the earlier study [Berghaus 1997], studies labeld with "**DRUID**" were gathered for this project.

A * before the authors means that this study met the inclusion criteria and hence was included in the data base.

Hypnotics and sedatives

Brotizolam

BAST

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Lormetazepam

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Temazepam

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Flunitrazepam

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Flurazepam

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Zolpidem

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Antidepressants

Amitriptyline

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Imipramine

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Trazodone

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Fluoxetine

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Paroxetine

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Anxiolytics

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Lorazepam

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Buspirone

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Meprobamate

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Antihistamines

Diphenhydramine

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Triprolidine

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6 APPENDIX

6.1 Detailed description of the data base

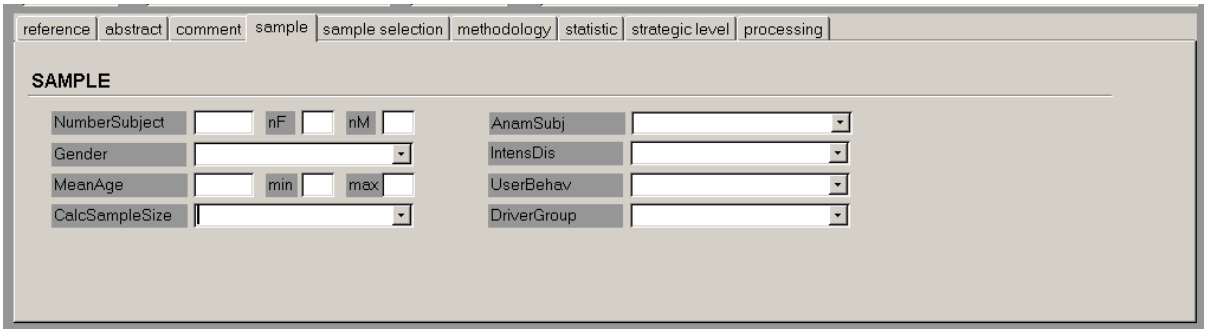
In addition to the detailed description of the database chapter 8.1 of the Alcohol Deliverable we would like to give the list of variables, categories and explanations used for the Drug Deliverable with focus on those variables that especially are of interest for administrations of medicines and illegal drugs.

Publication Level

Comment:

Main Question	Rules
1) single medicament effect	only the effect of medicaments is of interest
2) different dosages of 1 medicament	at least two different dosages of medicaments are given to the subjects and differences in effects are of interest
3) different points in time	time of day, absorptive vs. eliminative
4) alcohol and med., drugs	if combination of alcohol and other substances is of interest (also caffeine, sucrose, acamprosate, nicotine…)
5) different subject groups	e.g. gender, age, aggressive/anxiety dispositions, drinking behaviour, family history of alcoholism, driving/cognitive performance
6) med and other influence	time of day, absorptive vs. eliminative
7) other	e.g. alcohol tolerance, genetic factors, social/environmental condition, drug expectancy, food intake, reward, feedback
8) different medicaments	the effect of more than one medicaments are of interests

Samples:



- Number Subject (nF, nM): sample size (number of females, number of males)
- Gender: only female, only male, mixed
- Mean Age (min, max): mean age of the sample (minimum, maximum age)
- Age Group: the chosen category refers to the mean age of the sample

- Anamnesis Subject: medical history of subjects (only studies with healthy subjects were excerpted!)

Anamnesis Subject	Rules
1) no specification possible	if nothing is mentioned, most probably healthy subjects (medical screening performed)
2) healthy	subjects with no diseases
3) acute disease	subjects with an acute disease
4) chronic disease	subjects with a chronic disease
5) acute and chronic	subjects with a combination of an acute and a chronic disease
6) healthy and ill	healthy subjects and subjects with a disease are considered
7) addicted on substance	subjects are addicted to the substance
8) other	unlisted options

- Intensity Disease: intensity of the disease (subjects have to be healthy!)

Intensity Disease	Rules
1) no specification possible	if nothing is mentioned
2) no disease	subjects are healthy
3) light	disease is light distinct
4) medium	disease is medium distinct
5) heavy	disease is heavy distinct
6) no information	there is no information in the study
7) not relevant	disease is not relevant for the study

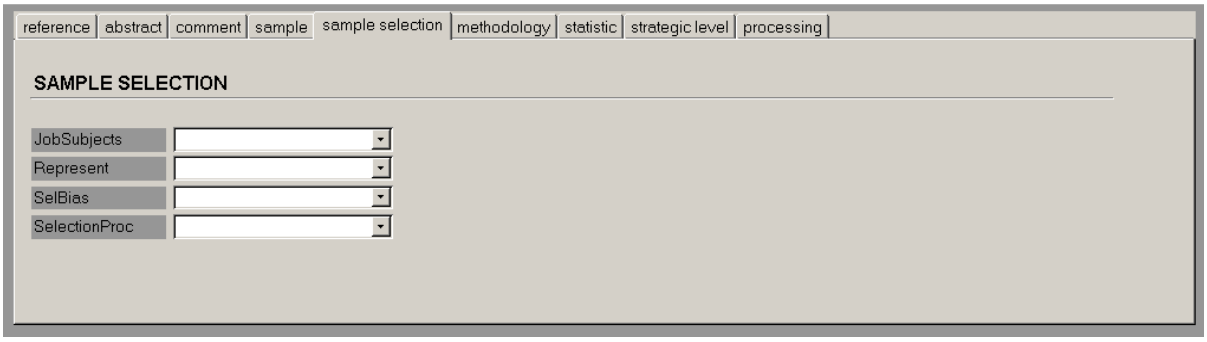
- User Behaviour: intake behaviour of a substance

User Behaviour	Rules
1) no specification possible	if nothing is mentioned
2) no use	no use of medicaments or if subjects are healthy and there is no information concerning medication
3) less than 1x month	intake of the relevant substance less than 1 a month
4) less than 1x week	intake of the relevant substance less than 1 a week
5) 1x week	intake of the relevant substance 1 a week
6) more than 1x week	intake of the relevant substance more than 1 a week
7) 1x day	intake of the relevant substance 1 a day
8) more than 1x day	intake of the relevant substance more than 1 a day
9) recreational use	no routine use of the relevant substance
10) addicted	subjects are addicted to the relevant substance
11) other	unlisted options
12) not relevant	intake of another substance is not relevant

- Driver Group: driving experience of the subjects (only to be filled out in driving studies)

Driver Group	Rules
1) no specification possible	for pilots or if nothing is mentioned
2) novice	drivers or pilots with a licence since less than 2 years
3) amateur	for drivers, if nothing is mentioned
4) professional	professional drivers or pilots

Sample selection:



- Job Subjects: occupation of the subjects

Job Subjects	Rules
1) no specification possible	if nothing is mentioned
2) not relevant	information is not relevant
3) at most students	most of the subjects are students
4) at most professional drivers	most of the subjects are professional drivers
5) at most pilots	most of the subjects are pilots
6) at most one job-group	most of the subjects in one job sector
7) different jobs	subjects work in different jobs
8) other	unlisted options
9) no information	there is no information in the study

- Represent: subjects are representatively concerning one or more attributes compared to the population

Represent	Rules
1) no specification possible	if nothing is mentioned
2) conc disease	subjects are representable concerning a disease
3) conc med use	subjects are representable concerning use of a medicament
4) conc other	subjects are representable concerning something else
5) conc several aspects	subjects are representable concerning several aspects
6) no information	there is no information in the study
7) not relevant	information is not relevant

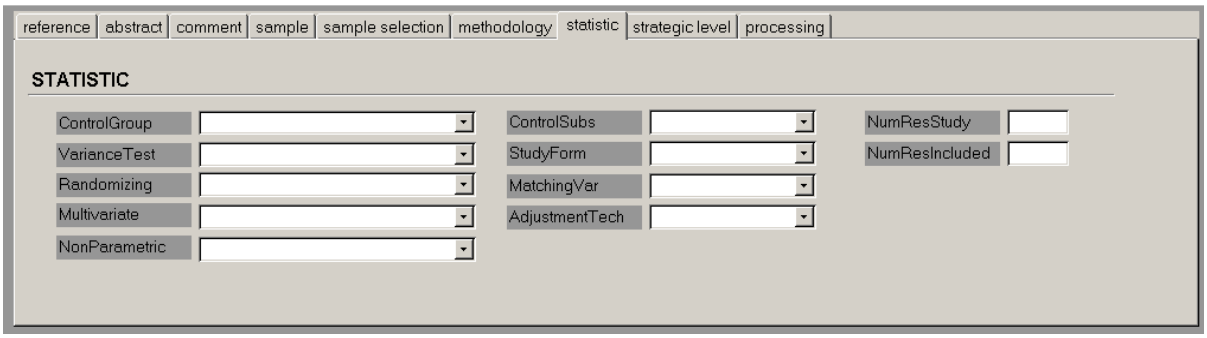
- Selection Bias: characteristics regarding the selection of probands

Selection Bias	Rules
1) no specification possible	if nothing is mentioned
2) disease	Is the subject healthy?
3) use of drugs	Takes the subject drugs?
4) hearing	Has the subject hearing problems?
5) seeing	Has the subject a problem with the eyes?
6) other	unlisted options
7) combination	More than one of the characteristics are analysed
8) no information	there is no information in the study

- Selection Procedure: checking of in- and exclusion criteria regarding the subjects

Selection Procedure	Rules
1) no specification possible	if nothing is mentioned
2) yes, on inquiry	inquiry or instruction (e.g. abstinence of alcohol/nicotine) or if selection is made, but no specification concerning selection process
3) yes, medical screening	e.g. testing of seeing, hearing, EEG and ECG
4) yes, lab parameters	e.g. testing of body fluids
5) other	unlisted options
6) no information	there is no information in the study
7) not relevant	information is not relevant

Statistics:



- Control Group: characteristics of group which receives no medicaments

Control Group	Rules
1) no specification possible	if nothing is mentioned
2) healthy sample itself without medication	subjects are in both groups (group, who intake the medicament and control group)
3) other healthy without med	different subjects in control group
4) ill sample itself without disease and med	comparison with ill sample itself without disease and medicaments
5) ill sample itself with disease, without med	comparison with ill sample itself with disease and without medicaments
6) other	unlisted options

- Multivariate: refers to the analysis of variance for testing the effect of medicaments

Multivariate	Rules
1) no specification possible	if nothing is mentioned
2) no	if no multivariate analysis of variance is conducted
3) yes	if a multivariate analysis of variance is conducted

- Non Parametric: refers to the statistical test

Non Parametric	Rules
1) no specification possible	if nothing is mentioned or if both parametric and non-parametric tests are used
2) no	if a parametric test is used
3) yes	if a non-parametric test is used for at least one variable

- Control Substance: substance given to the control group

Control Substance	Rules
1) no specification possible	if nothing is mentioned
2) placebo	placebo as control substance
3) no substance	No control substance

- Study Form: design of the study

Study Form	Rules
1) no specification possible	if nothing is mentioned
2) Cross-over	subjects are in both groups (treated and untreated with medicaments)
3) matched pairs	if matching concerning any factor, for example age
4) non matched pairs	if between condition, but randomizing or nothing is mentioned concerning matching
5) other	unlisted option

- Matching Variance: matching parameters, only relevant for matched/non matched pairs or between design

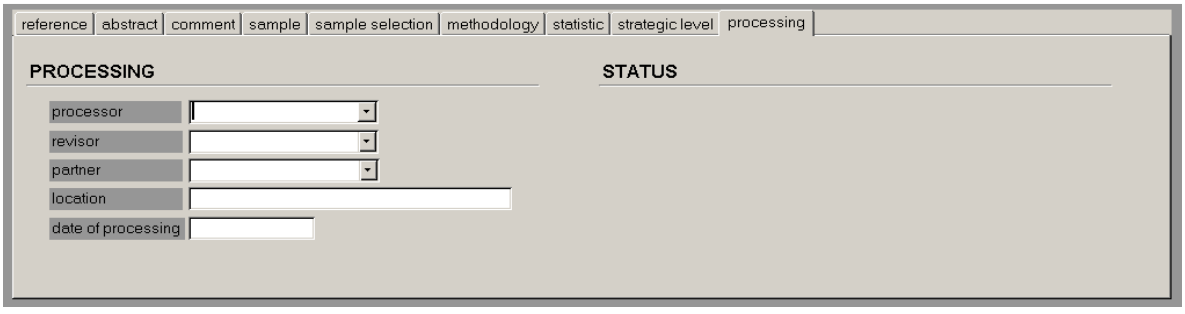
Matching Variance	Rules
1) no specification possible	if nothing is mentioned
2) age	matched by age
3) gender	matched by gender
4) education	matched by education
5) other	e.g. IQ
6) combination	Combination of matching parameters
7) not relevant	for within/cross-over condition

- Adj Tech: refers to the adjustment of the alpha-level

Adj Tech	Rules
1) no specification possible	if nothing is mentioned
2) none	if authors say they did not make an adjustment
3) Bonferroni	Bonferroni adjustment technique
4) Bonferroni Holm	Bonferroni Holm adjustment technique
5) others	e.g. Dunn's technique

- Num Res Study: Number of relevant and statistically significant findings concerning medicament reported in the study
- Num Res Included: number of findings of the study included into the database

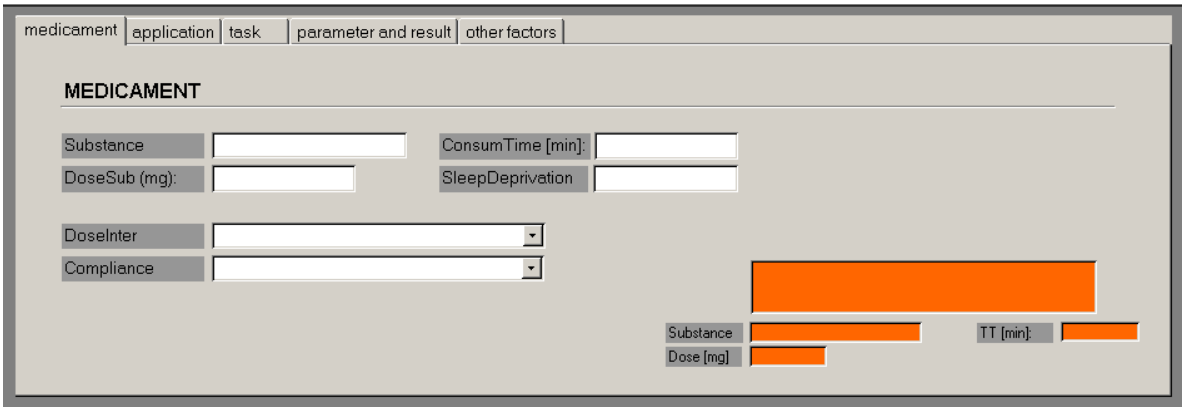
Processing:



- Status: no entries for medicaments studies

Findings Level

Medicament:



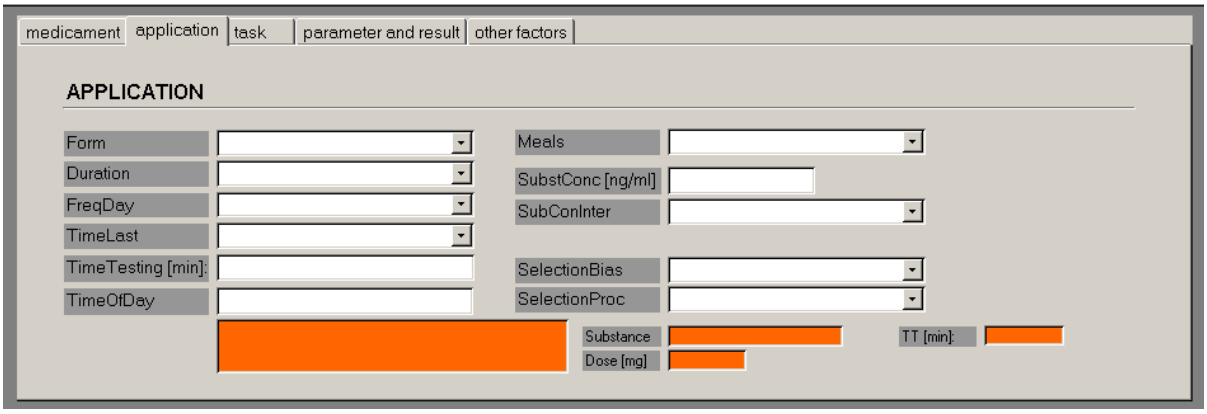
- Substance: name of active agent, INN (international non proprietary name)
- Dose Substance (mg): Dose of active agent/substance in mg
- Consume Time (min): Duration of drug consumption in min, especially if drug is smoked (e.g. marihuana)
- Sleep Deprivation: *Yes*, if sleep duration of all subjects is restricted or if they are awake longer than about 16 hours (and if study speaks of "sleep deprivation")
- Dose Inter: Dose or dose per body weight and whether body weight is given or not

Dose Inter	**Rules**
1) no specification possible	if nothing is mentioned
2) dose given in mg	description in mg
3) dose given in mg/kg without kg of sample	description in mg per body weight, basis of calculation is the average of body weight for women or men
4) dose given in mg/kg with kg of sample	description in mg per body weight

- Compliance: specifications concerning compliance testing

Compliance	**Rules**
1) no specification possible	if it is mentioned that "the subjects received their capsules …", "drugs were administered...", …
2) on inquiry	information was inquired
3) sured by lab tests or other	Ensured by lab tests (e.g. urine/and or plasma level determination)
4) other	if drug intake was observed by a supervisor, or any other confirmation of compliance
5) no information	there is no information in the study

Application:



- Form: form of application

Form	Rules
1) no specification possible	if it is mentioned
2) oral	oral intake
3) i.v.	intravenous
4) i.m.	intramuscular
5) supp	suppository
6) combination	combination
7) smoking	inhalation
8) nose	sniffing
9) other	unlisted option
10) no information	there is no information in the study

- Duration: Duration of application

Duration	Rules
1) no specification possible	if nothing is mentioned
2) single	single intake of substance
3) up to 1 week	period of application up to 1 week
4) up to 1 month	period of application up to 1 month
5) up to 1 year	period of application up to 1 year
6) more than 1 year	period of application over 1 year
7) other	unlisted option

- Frequency Day: Applications per day

Frequency Day	Rules
1) no specification possible	if nothing is mentioned
2) single	single intake of substance
3) 2 times	intake of substance twice a day
4) 3 times	intake of substance 3 times a day
5) 4 times	intake of substance 4 times a day
6) more than 4 times	intake of substance more than 4 times a day
7) no information	there is no information in the study

- Time Last: Period of last application before testing

Time Last	Rules
1) no specification possible	if nothing is mentioned
2) morning (6 - 11)	morning
3) mid (11 - 15)	midday
4) afternoon (15 - 18)	afternoon
5) evening (18 - 22)	evening
6) night (22 - 6)	night
7) other	unlisted option
8) no information	there is no information in the study

- Time Testing (min): approximate duration of the performed test
- Time of Day: approximate point in time of the performed test
- Meals:

Meals	Rules
1) no specification possible	if meals are offered or if there is a standardization of meals or instruction, but no information whether according leaflet or not
2) no information	generally no information concerning meals
3) other	unlisted option
4) according leaflet	According leaflet

- Substance Concentration (ng/mL): serum/plasma level of active agent during test
- Sub Con Inter: source of information of substance concentration

Sub Con Inter	Rules
1) no specification possible	if nothing is mentioned
2) given in study	Information given in study
3) calculated	calculated

- Selection Bias: exclusion parameters of test persons (with reference to the particular test)

Selection Bias	Rules
1) no specification possible	if nothing is mentioned
2) diseases	subject is not healthy
3) use of drugs	also alcohol or nicotine
4) tiredness	subject is not vigilant
5) other aspects	other options
6) combination	combination of exclusion parameters
7) no information	if generally no information concerning selection process prior application
8) not relevant	exclusion parameters are not relevant for the test

- Selection Procedure: check of exclusion parameters

Selection Procedure	Rules
1) no specification possible	if nothing is mentioned
2) yes, on inquiry	inquiry or instruction (e.g. abstinence of alcohol/nicotine) or if selection made, but no specification concerning selection process
3) yes, medical screening	e.g. testing of seeing, hearing, EEG and ECG
4) yes, lab parameters	e.g. testing of body fluids
5) others	unlisted option
6) no information	if generally no information concerning selection process prior application
7) not relevant	exclusion parameters are not relevant for the test

6.2 Raw data concerning dose- and time-dependent data base

Outliers are not excluded.

Antipsychotics

Agent: Haloperidol, 3 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	0	0	0
< 3	0	15	0	15
< 4	0	5	0	5
< 5	11	14	0	25
< 6	2	5	0	7
< 7	3	12	0	15
< 8	0	0	0	0
< 9	2	13	0	15
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	3	21	0	24
Overall	21	85	0	106

Agent: Sulpiride, 400 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	12	0	12
< 3	1	14	1	16
< 4	0	0	0	0
< 5	0	9	0	9
< 6	0	0	0	0
< 7	0	9	0	9
< 8	0	0	0	0
< 9	0	9	0	9
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	2	16	0	18
Overall	3	69	1	73

Agent: Promethazine, 25 + 30 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	2	14	0	16
< 2	3	25	0	28
< 3	17	18	0	35
< 4	24	4	0	28
< 5	12	8	0	20
< 6	11	3	0	14
< 7	15	13	0	28
< 8	5	0	0	5
< 9	6	17	0	23
< 10	1	2	0	3
< 11	0	6	0	6
< 12	0	0	0	0
< 15	1	8	0	9
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	1	2	0	3
Overall	98	120	0	218

Anxiolytics

Agent: Oxazepam, 15 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	5	0	8
< 2	12	19	0	31
< 3	10	19	0	29
< 4	7	17	0	24
< 5	8	14	0	22
< 6	0	3	0	3
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	1	0	1
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	40	78	0	118

Agent: Oxazepam, 30 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	1	0	1
< 2	16	22	0	38
< 3	14	14	0	28
< 4	10	6	0	16
< 5	6	11	0	17
< 6	0	6	0	6
< 7	0	7	0	7
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	2	0	2
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	46	69	0	115

Agent: Lorazepam, 1 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	8	0	11
< 2	11	32	0	43
< 3	7	19	0	26
< 4	15	23	0	38
< 5	1	15	0	16
< 6	2	2	0	4
< 7	0	13	0	13
< 8	1	4	0	5
< 9	0	10	0	10
< 10	0	0	0	0
< 11	0	3	0	3
< 12	0	0	0	0
< 15	0	6	0	6
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	8	0	8
Overall	40	143	0	183

Agent: Lorazepam, 2 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	2	7	0	9
< 2	62	25	0	87
< 3	88	29	0	117
< 4	52	27	0	79
< 5	42	12	0	54
< 6	4	1	0	5
< 7	24	13	0	37
< 8	0	0	0	0
< 9	15	12	0	27
< 10	0	0	0	0
< 11	0	6	0	6
< 12	0	0	0	0
< 15	0	4	0	4
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	5	6	0	11
Overall	294	142	0	436

Agent: Lorazepam, 2.5 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	8	4	0	12
< 2	29	24	0	53
< 3	44	28	0	72
< 4	40	8	0	48
< 5	29	8	0	37
< 6	6	4	0	10
< 7	18	12	0	30
< 8	3	3	0	6
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	1	0	0	1
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	12	0	12
Overall	178	103	0	281

Agent: Bromazepam, 6 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	6	0	6
< 2	5	36	0	41
< 3	1	7	0	8
< 4	0	0	0	0
< 5	0	0	0	0
< 6	0	6	0	6
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	2	0	2
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	6	57	0	63

Agent: Bromazepam, 12 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	3	0	6
< 2	8	33	0	41
< 3	6	2	0	8
< 4	0	0	0	0
< 5	0	0	0	0
< 6	3	3	0	6
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	20	41	0	61

Agent: Alprazolam, 1 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	3	0	3
< 2	36	16	0	52
< 3	20	5	0	25
< 4	12	9	0	21
< 5	5	3	0	8
< 6	6	5	0	11
< 7	2	4	0	6
< 8	0	0	0	0
< 9	2	1	0	3
< 10	0	0	0	0
< 11	0	4	0	4
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	83	50	0	133

Agent: Diazepam, 5 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	7	34	0	41
< 2	27	88	0	115
< 3	15	47	0	62
< 4	7	30	1	38
< 5	6	34	0	40
< 6	0	7	0	7
< 7	0	10	0	10
< 8	0	1	0	1
< 9	0	12	0	12
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	7	0	7
< 18	0	0	0	0
< 24	0	7	0	7
≥ 24	0	13	0	13
Overall	62	290	1	353

Agent: Diazepam, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	38	85	4	127
< 2	87	133	5	225
< 3	34	88	0	122
< 4	24	83	1	108
< 5	7	50	0	57
< 6	3	24	0	27
< 7	3	36	0	39
< 8	0	12	0	12
< 9	3	23	0	26
< 10	6	3	0	9
< 11	0	3	0	3
< 12	1	2	0	3
< 15	0	7	0	7
< 18			0	
< 24	0	3	0	3
≥ 24	0	21	0	21
Overall	206	573	10	789

Agent: Diazepam, 15 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	48	27	0	75
< 2	60	84	0	144
< 3	26	27	0	53
< 4	19	51	0	70
< 5	6	51	0	57
< 6	0	13	0	13
< 7	5	27	0	32
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	3	0	3
≥ 24	1	8	0	9
Overall	165	291	0	456

Agent: Diazepam, 20 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	32	15	1	48
< 2	51	32	0	83
< 3	25	20	1	46
< 4	20	17	0	37
< 5	2	21	0	23
< 6	1	12	0	13
< 7	0	12	0	12
< 8	0	4	0	4
< 9	0	10	0	10
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	131	143	2	276

Agent: Chlordiazepoxid, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	1	8	1	10
< 2	2	18	2	22
< 3	3	14	1	18
< 4	0	10	0	10
< 5	1	7	0	8
< 6	3	5	0	8
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	10	62	4	76

Agent: Clobazam, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	4	29	3	36
< 3	2	17	0	19
< 4	2	28	0	30
< 5	0	9	0	9
< 6	0	10	0	10
< 7	0	6	0	6
< 8	0	9	0	9
< 9	0	4	0	4
< 10	0	0	0	0
< 11	0	4	0	4
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	4	0	4
Overall	8	120	3	131

Agent: Clobazam, 20 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	1	21	0	22
< 3	2	11	0	13
< 4	1	24	1	26
< 5	0	4	0	4
< 6	0	8	0	8
< 7	0	4	0	4
< 8	0	4	0	4
< 9	0	4	0	4
< 10	1	1	1	3
< 11	3	4	1	8
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	4	0	4
Overall	8	89	3	100

Agent: Meprobamate, 400 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	3	0	3
< 2	3	27	0	30
< 3	4	10	0	14
< 4	1	9	1	11
< 5	0	11	0	11
< 6	0	9	0	9
< 7	0	1	0	1
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	8	70	1	79

Agent: Meprobamate, 800 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	25	0	25
< 2	5	38	0	43
< 3	0	8	0	8
< 4	0	3	0	3
< 5	0	0	0	0
< 6	0	3	0	3
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	5	77	0	82

Agent: Meprobamate, 1200 - 3600 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	3	0	6
< 2	12	14	0	26
< 3	12	9	0	21
< 4	5	4	0	9
< 5	8	4	0	12
< 6	0	0	0	0
< 7	9	3	0	12
< 8	0	0	0	0
< 9	4	2	0	6
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	5	7	0	12
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	12	0	12
Overall	58	58	0	116

Agent: Buspirone, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	4	0	4
< 2	5	41	0	46
< 3	2	6	0	8
< 4	2	40	0	42
< 5	0	4	0	4
< 6	0	18	0	18
< 7	1	3	0	4
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	1	3	0	4
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	11	119	0	130

Agent: Buspirone, 20 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	4	36	0	40
< 3	0	4	0	4
< 4	2	30	0	32
< 5	0	4	0	4
< 6	0	8	0	8
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	6	82	0	88

Hypnotics and sedatives

Agent: Triazolam, .25 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	5	41	0	46
< 2	54	79	1	134
< 3	23	37	0	60
< 4	21	32	1	54
< 5	15	47	0	62
< 6	2	11	0	13
< 7	3	47	0	50
< 8	1	2	0	3
< 9	4	42	0	46
< 10	0	13	0	13
< 11	0	43	0	43
< 12	0	0	0	0
< 15	4	0	0	4
< 18	0	0	0	0
< 24	0	6	0	6
≥ 24	11	10	0	21
Overall	143	410	2	555

Agent: Triazolam, 0.50 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	11	20	0	31
< 2	64	28	0	92
< 3	47	17	0	64
< 4	29	21	0	50
< 5	17	32	0	49
< 6	7	8	0	15
< 7	3	19	0	22
< 8	0	5	0	5
< 9	2	8	0	10
< 10	1	12	0	13
< 11	2	13	0	15
< 12	0	5	0	5
< 15	2	16	0	18
< 18	1	12	0	13
< 24	1	10	0	11
≥ 24	1	6	0	7
Overall	188	232	0	420

Agent: Lormetazepam, 1 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	3	0	3
< 2	6	15	0	21
< 3	1	5	0	6
< 4	1	4	0	5
< 5	0	12	0	12
< 6	1	2	0	3
< 7	0	3	0	3
< 8	1	0	0	1
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	16	0	16
< 12	2	14	0	16
< 15	0	9	0	9
< 18	1	7	0	8
< 24	0	0	0	0
≥ 24	0	1	0	1
Overall	13	91	0	104

Agent: Temazepam, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	1	7	0	8
< 2	2	20	0	22
< 3	2	24	1	27
< 4	0	9	0	9
< 5	1	12	0	13
< 6	0	20	0	20
< 7	0	11	0	11
< 8	1	4	0	5
< 9	0	22	1	23
< 10	0	0	0	0
< 11	0	14	0	14
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	7	143	2	152

Agent: Temazepam, 20 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	9	8	0	17
< 2	23	32	0	55
< 3	19	27	0	46
< 4	7	21	0	28
< 5	1	12	0	13
< 6	1	14	0	15
< 7	0	24	0	24
< 8	0	6	0	6
< 9	0	18	0	18
< 10	0	10	0	10
< 11	0	19	0	19
< 12	0	0	0	0
< 15	6	16	0	22
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	66	207	0	273

Agent: Flurazepam, 15 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	5	4	0	9
< 3	0	0	0	0
< 4	8	2	0	10
< 5	4	4	0	8
< 6	0	0	0	0
< 7	1	1	0	2
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	1	18	0	19
< 12	0	0	0	0
< 15	8	5	0	13
< 18	2	6	0	8
< 24	1	12	0	13
≥ 24	0	0	0	0
Overall	30	52	0	82

Agent: Flurazepam, 30 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	0	0	0
< 3	2	2	0	4
< 4	8	2	0	10
< 5	0	4	0	4
< 6	0	0	0	0
< 7	4	12	0	16
< 8	1	0	0	1
< 9	8	4	0	12
< 10	1	0	0	1
< 11	13	7	0	20
< 12	0	0	0	0
< 15	7	9	0	16
< 18	2	9	0	11
< 24	2	11	0	13
≥ 24	0	5	0	5
Overall	48	65	0	113

Agent: Nitrazepam, 5 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	2	12	0	14
< 2	7	21	0	28
< 3	6	22	0	28
< 4	0	2	0	2
< 5	0	4	0	4
< 6	0	4	0	4
< 7	0	2	0	2
< 8	0	1	0	1
< 9	1	8	0	9
< 10	5	10	0	15
< 11	1	28	0	29
< 12	7	15	0	22
< 15	5	10	0	15
< 18	0	12	0	12
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	34	151	0	185

Agent: Nitrazepam, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	7	7	0	14
< 2	26	12	0	38
< 3	15	15	0	30
< 4	0	10	0	10
< 5	0	3	0	3
< 6	0	3	0	3
< 7	0	4	0	4
< 8	0	1	0	1
< 9	3	7	0	10
< 10	9	7	0	16
< 11	2	15	0	17
< 12	9	6	0	15
< 15	5	24	0	29
< 18	2	8	0	10
< 24	0	0	0	0
≥ 24	0	4	0	4
Overall	78	126	0	204

Agent: Flunitrazepam, 1 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	2	1	0	3
< 2	15	8	0	23
< 3	6	12	0	18
< 4	4	12	0	16
< 5	3	13	0	16
< 6	0	0	0	0
< 7	0	12	0	12
< 8	0	0	0	0
< 9	0	12	0	12
< 10	0	0	0	0
< 11	8	38	0	46
< 12	0	3	0	3
< 15	0	12	0	12
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	1	3	0	4
Overall	39	126	0	165

Agent: Flunitrazepam, 2 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	7	2	0	9
< 2	17	10	0	27
< 3	18	1	1	20
< 4	7	9	1	17
< 5	17	5	0	22
< 6	6	3	0	9
< 7	4	10	0	14
< 8	0	0	0	0
< 9	7	15	0	22
< 10	1	8	0	9
< 11	7	18	0	25
< 12	2	6	0	8
< 15	3	3	0	6
< 18	1	0	0	1
< 24	0	0	0	0
≥ 24	1	5	0	6
Overall	98	95	2	195

Agent: Zopiclone, 7.5 mg

4Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
<10 1	3	5	0	8
< 2	31	25	0	56
< 3	5	7	0	12
< 4	15	16	0	31
< 5	14	9	0	23
< 6	6	13	0	19
< 7	7	18	0	25
< 8	0	0	0	0
< 9	3	17	0	20
< 10	3	7	0	10
< 11	8	37	0	45
< 12	3	16	0	19
< 15	1	22	0	23
< 18	0	4	0	4
< 24	0	4	0	4
≥ 24	0	5	0	5
Overall	99	205	0	304

Agent: Zolpidem, 5 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	14	0	14
< 2	3	38	0	41
< 3	0	23	0	23
< 4	0	5	0	5
< 5	0	2	0	2
< 6	0	6	0	6
< 7	0	7	0	7
< 8	0	5	0	5
< 9	0	0	0	0
< 10	0	8	0	8
< 11	0	0	0	0
< 12	0	8	0	8
< 15	0	5	0	5
< 18	0	10	0	10
< 24	0	10	0	10
≥ 24	0	0	0	0
Overall	3	141	0	144

Agent: Zolpidem, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	5	13	0	18
< 2	51	44	0	95
< 3	13	29	0	42
< 4	12	9	0	21
< 5	12	30	0	42
< 6	5	17	0	22
< 7	0	28	0	28
< 8	0	5	0	5
< 9	3	28	0	31
< 10	0	16	0	16
< 11	1	22	0	23
< 12	0	15	0	15
< 15	0	19	2	21
< 18	0	21	0	21
< 24	0	20	1	21
≥ 24	2	2	0	4
Overall	104	318	3	425

Agent: Zolpidem, 20 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	8	5	0	13
< 2	34	19	0	53
< 3	9	15	0	24
< 4	3	6	0	9
< 5	4	5	0	9
< 6	0	2	0	2
< 7	9	8	0	17
< 8	0	5	0	5
< 9	4	8	0	12
< 10	0	14	0	14
< 11	0	1	0	1
< 12	0	8	0	8
< 15	0	5	0	5
< 18	0	10	0	10
< 24	0	10	0	10
≥ 24	1	1	0	2
Overall	72	122	0	194

Agent: Zaleplon, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	1	3	0	4
< 2	12	22	0	34
< 3	8	14	0	22
< 4	1	38	0	39
< 5	1	35	0	36
< 6	1	34	1	36
< 7	1	35	0	36
< 8	0	17	1	18
< 9	1	20	0	21
< 10	0	6	0	6
< 11	0	4	0	4
< 12	0	4	0	4
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	2	0	2
Overall	26	234	2	262

Antidepressants

Agent: Imipramine, 75 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	1	9	0	10
< 3	2	18	0	20
< 4	1	4	0	5
< 5	5	16	0	21
< 6	1	9	0	10
< 7	6	19	0	25
< 8	0	0	0	0
< 9	5	15	0	20
< 10	0	5	0	5
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	21	95	0	116

Agent: Amitriptylin, 25 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	5	6	0	11
< 2	14	15	0	29
< 3	7	14	0	21
< 4	9	7	0	16
< 5	4	8	0	12
< 6	0	0	0	0
< 7	4	10	0	14
< 8	0	0	0	0
< 9	0	0	0	0
< 10	2	3	0	5
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	2	0	2
Overall	45	65	0	110

Agent: Amitriptyline, 50 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	17	27	0	44
< 3	11	20	0	31
< 4	19	9	0	28
< 5	30	23	0	53
< 6	1	10	0	11
< 7	16	14	0	30
< 8	0	0	0	0
< 9	8	4	0	12
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	102	107	0	209

Agent: Amitriptyline, 75 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	8	0	8
< 3	12	9	0	21
< 4	6	8	0	14
< 5	7	8	0	15
< 6	0	0	0	0
< 7	7	14	0	21
< 8	0	0	0	0
< 9	7	7	1	15
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	1	7	0	8
Overall	40	61	1	102

Agent: Fluoxetine, 60 + 75 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	10	0	10
< 3	2	19	0	21
< 4	0	0	0	0
< 5	0	31	0	31
< 6	0	8	0	8
< 7	0	21	0	21
< 8	0	0	0	0
< 9	0	32	0	32
< 10	0	0	0	0
< 11	5	16	0	21
< 12	0	0	0	0
< 15	1	2	0	3
< 18	0	3	0	3
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	8	142	0	150

Agent: Paroxetine, 30 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	0	4	0	4
< 3	1	12	0	13
< 4	0	0	0	0
< 5	1	15	0	16
< 6	0	0	0	0
< 7	0	12	0	12
< 8	0	0	0	0
< 9	0	12	0	12
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	12	0	12
Overall	2	67	0	69

Agent: Mianserin, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	4	0	7
< 2	8	11	0	19
< 3	3	8	0	11
< 4	3	3	0	6
< 5	3	7	0	10
< 6	0	0	0	0
< 7	3	7	0	10
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	4	8	0	12
< 18	4	8	0	12
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	31	56	0	87

Agent: Trazodone, 100 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	3	11	0	14
< 3	11	16	1	28
< 4	5	1	0	6
< 5	3	17	0	20
< 6	0	0	0	0
< 7	0	12	0	12
< 8	0	0	0	0
< 9	0	6	0	6
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	22	63	1	86

Antihistamines

Agent: Diphenhydramine, 25 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	3	7	0	10
< 2	7	9	0	16
< 3	9	24	0	33
< 4	1	7	0	8
< 5	0	19	0	19
< 6	0	0	0	0
< 7	0	14	0	14
< 8	0	0	0	0
< 9	0	2	0	2
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	6	0	6
Overall	20	88	0	108

Agent: Diphenhydramine, 50 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	2	7	0	9
< 2	23	35	1	59
< 3	21	53	2	76
< 4	21	22	1	44
< 5	3	13	0	16
< 6	6	30	0	36
< 7	0	14	0	14
< 8	3	9	0	12
< 9	0	2	0	2
< 10	0	3	0	3
< 11	0	0	0	0
< 12	1	2	0	3
< 15	0	10	0	10
< 18	0	3	0	3
< 24	0	0	0	0
≥ 24	0	9	0	9
Overall	80	212	4	296

Agent: Triprolidine, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	2	0	2
< 2	5	15	0	20
< 3	9	6	0	15
< 4	5	10	0	15
< 5	0	0	0	0
< 6	0	15	0	15
< 7	4	1	0	5
< 8	0	0	0	0
< 9	0	10	0	10
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	10	0	10
Overall	23	69	0	92

Agent: Terfenadine, 60 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	3	0	3
< 2	1	68	2	71
< 3	0	29	0	29
< 4	0	37	2	39
< 5	0	20	0	20
< 6	0	24	1	25
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	8	2	10
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	10	0	10
Overall	1	199	7	207

Agent: Loratadine, 10 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	1	56	1	58
< 3	0	10	0	10
< 4	1	26	0	27
< 5	0	6	0	6
< 6	0	17	0	17
< 7	0	14	0	14
< 8	0	0	0	0
< 9	0	6	0	6
< 10	0	13	0	13
< 11	0	6	0	6
< 12	0	0	0	0
< 15	0	9	0	9
< 18	0	0	0	0
< 24	0	0	0	0
≥ 24	0	3	0	3
Overall	2	166	1	169

THC

Agent: THC oral, < 9 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	0	0	0
< 2	3	45	0	48
< 3	5	36	0	41
< 4	1	12	0	13
< 5	0	8	1	9
< 6	0	0	0	0
< 7	0	11	0	11
< 8	0	0	0	0
< 9	1	8	0	9
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	10	0	10
< 18	0	8	0	8
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	10	138	1	149

Agent: THC oral , 9 ≤ x < 18 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	1	2	0	3
< 2	27	43	0	70
< 3	18	31	0	49
< 4	3	14	0	17
< 5	1	8	0	9
< 6	0	0	0	0
< 7	1	10	0	11
< 8	0	0	0	0
< 9	0	9	0	9
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	20	0	20
< 18	0	16	0	16
< 24	0	0	0	0
≥ 24	0	0	0	0
Overall	51	153	0	204

Agent: THC oral, ≥18 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	6	0	6
< 2	28	22	1	51
< 3	9	14	0	23
< 4	5	10	0	15
< 5	5	6	0	11
< 6	0	0	0	0
< 7	0	0	0	0
< 8	0	0	0	0
< 9	0	0	0	0
< 10	0	0	0	0
< 11	0	0	0	0
< 12	0	0	0	0
< 15	0	0	0	0
< 18	0	0	0	0
< 24	0	3	0	3
≥ 24	0	0	0	0
Overall	47	61	1	109

Agent: THC smoking, <9 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .5	102	63	0	165
< 1.0	63	51	1	115
< 1.5	4	13	0	17
< 2.0	8	10	0	18
< 3.0	4	6	1	11
< 4.0	0	10	0	10
< 5.0	0	11	0	11
< 7.0	0	3	0	3
Overall	181	167	2	350

Agent: THC smoking, 9 ≤ x < 18 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .5	62	61	1	124
< 1.0	51	68	0	119
< 1.5	16	23	0	39
< 2.0	5	13	0	18
< 3.0	4	5	0	9
< 4.0	0	8	0	8
< 5.0	0	2	0	2
< 6.0	0	2	0	2
< 7.0	0	1	0	1
< 12	2	10	0	12
< 24	0	9	0	9
≥ 24	1	6	0	7
Overall	141	208	1	350

Agent: THC smoking, ≥18 mg

Time p.a. (h)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .5	25	20	0	45
< 1.0	24	20	0	44
< 1.5	11	14	0	25
< 2.0	6	6	0	12
< 3.0	5	6	0	11
< 4.0	8	9	0	17
< 5.0	2	1	0	3
< 6.0	0	2	0	2
< 12.0	4	5	0	9
< 24	5	5	0	10
≥ 24	3	7	0	10
Overall	93	95	0	188

6.3 Raw data concerning concentration-dependent analysis

Concentrations in ng/mL serum.

Antipsychotics

Agent: Haloperidol, ≥5.75 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .4	1	10	0	11
< .6	2	15	0	17
< .8	0	6	0	6
< 1.2	5	25	0	30
< 1.4	0	6	0	6
< 2.0	0	5	0	5
< 3.4	3	8	0	11
Overall	11	75	0	86

Agent: Promethazine, ≥ 2.75 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 2	1	2	0	3
< 5	1	8	0	9
< 6	9	20	0	29
< 7	14	11	0	25
< 8	11	6	0	17
< 9	22	10	0	32
< 10	7	0	0	7
< 20	17	6	0	23
Overall	82	63	0	145

Anxiolytics

Agent: Oxazepam, ≥2.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 100	0	10	0	10
< 200	9	36	0	45
< 300	9	36	0	45
< 400	4	23	0	27
< 500	17	19	0	36
< 600	1	5	0	6
< 700	0	3	0	3
< 800	2	4	0	6
< 900	1	2	0	3
Overall	43	138	0	181

Agent: Lorazepam, ≥3 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 5	5	44	0	49
< 10	24	103	0	127
< 15	115	69	0	184
< 20	132	56	0	188
< 25	21	20	0	41
< 30	16	6	0	22
< 35	2	0	0	2
< 40	5	0	0	5
< 45	11	2	0	13
< 50	1	0	0	1
< 55	4	0	0	4
< 63	11	0	0	11
Overall	347	300	0	647

Agent: Bromazepam, ≥1.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 20	0	12	0	12
< 40	2	26	0	28
< 60	2	8	0	10
< 80	0	14	0	14
< 100	3	5	0	8
< 140	3	3	0	6
< 160	4	2	0	6
< 180	6	2	0	8
Overall	20	72	0	92

Agent: Alprazolam, ≥2.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 3	0	8	1	9
< 6	3	33	1	37
< 9	5	28	0	33
< 12	18	16	0	34
< 15	16	10	0	26
< 18	26	14	0	40
< 21	9	8	0	17
< 24	8	1	0	9
< 27	9	1	0	10
< 30	3	0	0	3
Overall	97	119	2	218

Agent: Diazepam, ≥1 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 50	2	35	0	37
< 100	6	104	0	110
< 150	26	120	1	147
< 200	47	233	0	280
< 250	37	141	1	179
< 300	34	142	0	176
< 350	79	188	5	272
< 400	33	66	0	99
< 450	33	25	0	58
< 500	36	65	0	101
< 550	38	34	0	72
< 600	24	16	1	41
< 650	11	2	0	13
< 700	24	21	0	45
< 1250	25	8	0	33
Overall	455	1200	8	1663

Agent: Chlordiazeüpxide, ≥1.75 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 400	4	20	0	24
< 600	3	16	1	20
< 800	0	3	0	3
< 1000	0	3	0	3
< 2400	0	3	0	3
Overall	7	45	1	53

Agent: Clobazam, ≥2.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 100	0	4	0	4
< 150	0	31	0	31
< 200	4	47	0	51
< 250	4	26	2	32
< 300	0	12	0	12
< 350	1	15	0	16
< 400	1	20	1	22
< 450	3	10	0	13
< 550	0	5	0	5
< 650	0	5	0	5
< 700	4	4	0	8
< 1320	6	4	0	10
Overall	23	183	3	209

Agent: Meprobamate, ≥2.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 10000	1	48	2	51
< 20000	1	32	0	33
< 30000	5	12	0	17
< 40000	7	8	0	15
< 50000	7	1	0	8
< 60000	4	0	0	4
< 70000	4	0	0	4
< 80000	6	0	0	6
Overall	35	101	2	138

Agent: Buspirone, ≥1.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .3	2	21	0	23
< .6	1	70	0	71
< .9	3	59	0	62
< 1.2	3	59	0	62
< 1.5	5	26	0	31
< 1.8	0	16	0	16
< 2.1	1	18	0	19
< 2.4	2	14	0	16
< 2.7	2	14	0	16
< 3.0	1	1	0	2
< 6.7	0	10	0	10
< 13.5	0	4	0	4
Overall	20	312	0	332

Hypnotics and sedatives

Agent: Triazolam, ≥1.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	41	314	0	355
< 2	86	198	2	286
< 3	73	98	2	173
< 4	68	47	0	115
< 5	47	16	0	63
< 6	1	3	0	4
< 7	10	3	0	13
< 8	7	2	0	9
< 10	5	2	0	7
< 23	16	1	0	17
Overall	354	684	4	1042

Agent: Brotizolam, ≥1.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< .5	1	3	0	4
< ^1.0	1	13	0	14
< 1.5	1	8	0	9
< 2.0	3	6	0	9
< 2.5	2	9	1	12
< 3.0	3	6	1	10
< 3.5	2	7	0	9
< 4.5	2	2	0	4
< 6.0	2	2	0	4
Overall	17	56	2	75

Agent: Lormetazepam, ≥1.75 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 2	4	31	1	36
< 4	3	39	0	42
< 6	1	18	0	19
< 8	4	10	0	14
< 10	3	4	0	7
< 14	3	3	0	6
< 16	2	2	1	5
Overall	20	107	2	129

Agent: Temazepam, ≥1.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 100	0	52	1	53
< 200	10	149	0	159
< 300	11	94	1	106
< 400	18	60	0	78
< 500	25	48	0	73
< 600	1	11	0	12
< 700	11	14	0	25
< 800	1	1	0	2
< 900	11	7	0	18
< 1300	9	0	0	9
Overall	97	436	2	535

Agent: Flunitrazepam, ≥1.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 1	0	3	0	3
< 2	1	19	0	20
< 3	4	43	0	47
< 4	1	37	0	38
< 5	10	24	0	34
< 6	14	32	0	46
< 7	20	14	0	34
< 8	12	21	0	33
< 9	20	9	0	29
< 10	19	3	0	22
< 22	47	2	2	51
Overall	148	207	2	357

Agent: Zopiclone, ≥2.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 5	0	14	0	14
< 10	0	20	0	20
< 15	8	36	0	44
< 20	14	56	0	70
< 25	2	7	0	9
< 30	7	18	0	25
< 35	8	14	0	22
< 40	12	8	0	20
< 45	16	23	0	39
< 50	4	0	0	4
Overall	71	196	0	267

Agent: Zolpidem, ≥1.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 20	5	198	3	206
< 40	3	87	0	90
< 60	17	95	0	112
< 80	26	45	0	71
< 100	39	51	0	90
< 120	19	22	0	41
< 140	14	5	1	20
< 160	15	10	1	26
< 180	2	2	0	4
< 206	31	29	0	60
Overall	171	544	5	720

Agent: Zaleplon, ≥1.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 2	4	117	1	122
< 4	3	51	1	55
< 6	0	41	0	41
< 8	0	21	0	21
< 10	1	15	0	16
< 12	1	11	0	12
< 14	1	9	0	10
< 16	6	7	0	13
< 18	2	6	0	8
< 20	0	12	0	12
< 42	16	10	0	26
Overall	34	300	2	336

Antidepressants

Agent: Amitriptyline, ≥4.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 6	0	2	0	2
< 9	2	3	0	5
< 12	4	10	0	14
< 15	1	7	0	8
< 21	8	4	0	12
< 24	19	23	0	42
< 27	0	2	0	2
< 30	3	5	0	8
< 33	9	5	1	15
< 36	2	11	0	13
Overall	48	72	1	121

Agent: Mianserin, ≥2.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 4	6	12	0	18
< 8	2	4	0	6
< 12	6	10	0	16
< 16	6	11	0	17
< 20	4	6	0	10
< 28	5	5	0	10
< 32	6	4	0	10
Overall	35	52	0	87

Agent: Trazodone, ≥1.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 300	0	6	0	6
< 600	3	19	0	22
< 900	2	20	0	22
< 1200	3	17	0	20
< 1500	10	9	1	20
< 1800	9	13	0	22
< 3100	4	12	0	16
Overall	31	96	1	128

Antihistamines

Agent: Diphenhydramine, ≥2.5 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 10	0	15	0	15
< 20	0	5	0	5
< 30	1	26	0	27
< 40	3	44	0	47
< 50	8	33	0	41
< 60	4	18	0	22
< 70	26	44	2	72
< 80	1	1	0	2
< 90	0	3	0	3
< 100	0	12	0	12
< 120	0	6	0	6
< 130	1	11	0	12
< 140	1	5	0	6
Overall	45	223	2	270

Agent: Triprolidine, ≥2.25 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 3	0	22	0	22
< 6	3	18	0	21
< 9	3	10	0	13
< 12	11	17	0	28
< 15	7	6	0	13
< 18	4	5	0	9
< 21	0	10	0	10
< 24	5	15	0	20
< 30	2	3	0	5
Overall	35	106	0	141

THC

Agent: THC oral, ≥1.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 2	13	203	1	217
< 4	55	92	0	147
< 6	15	22	1	38
< 8	12	10	0	22
< 10	10	7	0	17
Overall	105	334	2	441

Agent: THC smoking , ≥1.0 hours p.a. and <10.0 hours p.a.

Concentration class (ng/mL)	Sign. impaired effects	No difference	Sign. improved effects	Overall
< 2	7	33	0	40
< 4	16	40	1	57
< 6	21	32	0	53
< 8	16	23	0	39
< 10	5	11	0	16
< 12	7	8	0	15
< 14	1	3	0	4
< 16	2	0	0	2
< 30	2	1	0	3
Overall	77	151	1	229

7 META-ANALYSIS OF PHARMACOKINETIC STUDIES (BY GUIDO STICHT)

7.1 Methods of evaluation

7.1.1 Introduction

Extensive tables of therapeutic and toxic concentrations in human plasma have been published (Baselt et al., 2002; Pentz et al., 1979; Stead & Moffat, 1983; Schultz & Schmoldt 2003). For giving an expert`s opinion about subjects, who have been under the influence of drugs or narcotics during carrying out criminal acts, blood concentrations of active agents are suitable for pointing to specified pharmacological effects. However blood specimens are often drawn several hours after the actions. Pharmacokinetic data make it possible to calculate the concentration of the active agent at action time and to explain the effects at the time of the incident. Furthermore statements concerning dose of the drug and time of intake can be calculated by using the pharmacokinetic equations:

7.1.2 Basics of pharmacokinetics after oral administration

The course of drug concentrations in blood plasma after oral administration can be fitted by a one or a two-compartment model (Dost 1953, Dost, 1968; Gibaldi & Perrier, 1975; Wellhöner, 1982). The absorption of an immediate-release oral solution or other pharmaceutical preparation is rapid and can be described by a first order absorption process with a lag time t_0.

$$(1) \quad C = Cp0 * e^{-Ka * (t - t_0)}$$

C means the plasma concentration at the time t, Cp0 the fictitious initial concentration at the time $t = t_0$, and Ka the absorption rate constant. The plasma concentration-time profile is characterized with equation (2), assuming a one compartment model with an elimination rate constant β, but without a distribution phase.

$$(2) \quad C = Cp0 * e^{-\beta * (t - t0)} - Cp0 * e^{-Ka * (t - t_0)}$$

Plasma concentration-time curves of substances with high absorption rate constants and lipophilic properties are characterized by increased peak concentrations. This can be

interpreted as absorption of a substance into a central compartment with a volume expressed in this publication as percent of the total volume of distribution. A low value of V% means a high increase of the peak concentration, caused by a small volume of a central compartment. But V% is to be regarded as a parameter, specific for the used computer program and is not identical with the real extent of the central compartment. Values of V% near 100% mean that, the course of the concentration-time curve is to be described by a one compartment model too. The distribution rate constant α controls the slope of the curve subsequent to the peak concentration C_{max} at the time t_{max} up to the part of the curve, which is controlled only by the first order elimination process.

$$(3)\quad C = Cp0 * e^{-\beta * (t - t0)} - Cp0 * e^{-Ka * (t - t0)}$$

$$+ Cp0 * ((100-V\%)/V\%) * (e^{-\alpha * (t - t0)} - e^{-Ka * (t - t0)})$$

The fictitious initial concentration Cp0 is proportional to dose D and bioavailability B and inversely proportional to body weight G and volume of distribution V_β. This is demonstrated by equation (4).

$$(4)\quad Cp0 = \frac{D * B}{G * V\beta} * \frac{Ka}{Ka - \beta} * 10$$

The distribution factor V_β represents the ratio of the volume of distribution in which the substance is dissolved and the body weight. The distribution volumes of lipophilic active agents have high values and result in low plasma concentrations. Pharmacokinetic studies with only oral intake of a drug are not appropriate for calculating the bioavailability. But evaluations of plasma concentration-time curves after intravenous and oral administration allow to determine the bioavailability by forming the quotient of the areas under the plasma concentration-time curves (equ. 5).

$$(5)\quad B = \frac{AUC\infty(p.o.)}{AUC\infty(i.v.)} * \frac{D(i.v.)}{D(p.o.)} * \frac{G(p.o.)}{G(i.v.)} * 100\ [\%]$$

AUC_∞ denotes the area below the concentration-time curve of a substance between time zero and time infinity, given orally (p.o.) and intravenously (i.v.) (Rowland and Tucker 1982). In

the case of failing results of studies with intravenous administration or in default of the possibility of intravenous application, volume of distribution and bioavailability are combined to the apparent volume of distribution V/B. From this the fictitious initial concentration is calculable using dose and body weight as further parameters.

Only few pharmacokinetic studies contain numerical values of concentrations. In most cases the course of concentration is demonstrated as plot, and the characteristic parameters C_{max} , t_{max}, β, and AUC are listed for pointing out influences on the pharmacokinetics as for instance age, sex or gender of volunteers. These parameters are very useful for comparing different studies with a group of volunteers, but are not appropriate for describing the complete course of a concentration-time curve. Therefore in most cases, the curves had to be re-handled and evaluated with a computer program. The new re-evaluated values are assigned in the tables with (!).

7.1.3 Evaluation of pharmacokinetic studies

Pharmacokinetic parameters can be arranged in a first group of data which control the course of drug concentration and a second group of parameters which can be derived from this curve. In the following, both groups are listed containing additionally the measuring units of the parameters.

Basic pharmacokinetic parameters

Ka	[h^{-1}]	Absorption rate constant
α	[h^{-1}]	Distribution rate constant
β	[h^{-1}]	Elimination rate constant
t_0	[h]	Lag time
Cp0	[ng/mL]	Fictitious initial concentration
V%	[%]	Part of the central compartment

Further basic parameters which determine the value of Cp0 beside absorption and elimination rate constant:

D	[mg]	Dose
G	[kg]	Body weight
B	[%]	Bioavailability
$V_β$	[L/kg]	Distribution factor

Derived pharmacokinetic parameters

$\mathbf{C_{max}}$	[ng/mL]	Peak concentration
$\mathbf{t_{max}}$	[h]	Time of peak concentration
AUC_∞	[ng*h/mL]	Total area under the plasma concentration-time curve extrapolated to infinity

Further pharmacokinetic parameters as for instance clearance or protein binding do not affect directly the plasma concentration-time curve and are not dealed with in the following. Most of pharmacokinetic publications contain plots from which the numerical values of plasma concentration-time pairs could be taken. These data were base of calculating the basic pharmacokinetic parameters using a self-made computer program (Sticht et al.1986, Graß 1989, Sticht and Käferstein 1998). First the terminal of log linear part of the plasma concentration v. time curve is determined by least regression analysis resulting in values of Cp0 and β. After that Ka, $t_{0,}$ and α are varied one after another following the principles of least square regression analysis. After every iteration V% is calculated at the least sum of deviations.

The determined pharmacokinetic parameters are arranged in tabulations belonging to each drug. AUC_∞ is calculated with aid of the computer program. Cp0, C_{max} and AUC_∞ are dependent on dose and body weight, and were converted into values at body weight of 70 kg and a typical therapeutic dose, which is given in front of each table. Self-calculated values are supplied with a call-sign in brackets together with a weighting factor between 1 and 3. Most peak plasma concentrations and time of the peak concentrations originate from the evaluated studies. Additionally listed are the evaluated studies of the publications, number, age, gender, and body weights of the volunteers, the administrated doses and some remarks on the studies. Arithmetic averaging was performed according to a formula of Sheiner et al. (1981), which has been used in the work of Graß (1989) too (equation 6).

$$(6) \qquad P = \sum_{k=1}^{k=n} N * Q * p \Big/ \sum_{k=1}^{k=n} N * Q$$

This equation contains the following variables:

P = Average of parameters from the evaluated studies

p = Parameter of a study

k = Number of evaluated studies

N = Number of volunteers of a study

Q = Weighting factor of the single parameter

Several criterions are to be taken into account for laying down the weighting factors (1-3). Pharmacokinetic parameters or plasma concentration-time curves originating from single studies with volunteers are to be rated higher than those deriving from average curves. Personal data of the test persons as age, gender, and body weight are important too. In the case of failing body weight the parameters Cp0, $\mathbf{C_{max}}$, and AUC_∞ which depend on the body weight, a weighting factor of 1 was taken. The rate constants Ka, α, and β were averaged in form of the half lives which are connected with the constants via the formula:

$$t1/2k = \ln 2/k$$

7.1.4 Formation of the mean pharmacokinetic profile

Mean values of the pharmacokinetic parameters result in the average plasma concentration-time curve. The standard deviations influence the course of the curve in a very different matter so that maximal or minimal curves cannot be developed by adding the SD to the average or subtract from it. But the following combinations are used for calculating the maximal and minimal curves which are limiting lines of a multitude of curves. Each point of the limiting lines is created by proving all combinations until maximal or minimal value of a concentration is reached.

Cp0, t0, Ka, V%, α, β : mean + SD
Cp0, t0, Ka, V%, α, β : mean - SD
Ka : mean + SD ; the other parameters as mean
Ka, α : mean + SD : „ „ „ „ „
Ka, α, β : mean + SD „ „ „ „ „
Ka, β : mean + SD „ „ „ „ „
α : mean + SD „ „ „ „ „
α, β : mean + SD „ „ „ „ „
β : mean + SD „ „ „ „ „
Ka : mean - SD; the other parameters as mean
Ka, α : mean -SD „ „ „ „ „
Ka, α, β : mean - SD „ „ „ „ „
Ka, β : mean - SD „ „ „ „ „
α : mean - SD „ „ „ „ „
α, β : mean - SD „ „ „ „ „
β : mean - SD „ „ „ „ „

7.1.5 Pharmacokinetics of metabolites

A plasma concentration-time curve of metabolites can be described in the same manner as that of the mother substance. But the calculated pharmacokinetic parameters are not identical with those after oral intake of the metabolite. In the following only pharmacologic active metabolites which contribute essentially to the effect of the mother substance are evaluated. Another method of describing the course of the metabolite concentration is a self-made program which starts from the Cp0 of the mother substance and calculates the percentage which is transformed to the metabolite. Further parameters are formation rate constant and elimination rate constant. These values are listed and averaged in the same way as those of the drugs.

7.1.6 Pharmacokinetics of other administration forms

Substances, administrated by inhalation like Δ^9-tetrahydrocannabinol, are incorporated with high absorption rate constant and rapid distribution, but the course of the plasma concentration curve can be described as well as after oral intake.

An absorption phase failed after intravenous application of an agent and a complete incorporation is to be assumed (bioavailability B = 100%). A plasma concentration-time curve after intravenous administration can be described by an elimination function supplemented with two distribution functions which simulate the distribution from two compartments with different volumes V_1 and V_2, expressed by % of the distribution volume of the elimination phase, and different distribution rate constants K_1 and K_2 (fast and slow distribution constants).

$$(7)\quad C = Cp0 * e^{-\beta * t} + (Cp0 * (100-V1)/V1) * e^{-K1 * t} + (Cp0 * (100-V2)/V2) * e^{-K2 * t}$$

7.2 Hypnotics/sedatives

7.2.1 Benzodiazepines

7.2.1.1 Short-acting benzodiazepines

The first compound with an additional heterocyclic pentagonal ring across the 1,2-position of the diazepine was triazolam, triazolo-1,4-benzodiazepine. Two other benzodiazepines, alprazolam, and brotizolam, contain a ring system with a triazolo group, but midazolam an imidazolo- and loprazolam an imidazolon-ring. The benzodiazepines of this group have effective sleep inducing properties. The courses of absorption and elimination show large differences. Because of such different duration of pharmacological activity, triazolam, midazolam, and brotizolam with elimination half-lives of less than 5 hours are counted among short acting hypnotic/sedative, whereas loprazolam with a value of 7-15 hours is classified as intermediate active and alprazolam as long active substance.

7.2.1.1.1 Brotizolam

Application: Brotizolam, chemically related to clotiazepam and triazolam, is a triazolo-1,4-thienodiazepin with effective sleep inducting property. Doses of 0.5 to 1.5 mg led in linear dependence to peak concentrations of 6.8 to 25.5 ng per mL plasma (Bechtel, 1983). An accumulation of brotizolam was not observed, even at daily administration of 0.25 mg brotizolam to elderly subjects (58-81 yr). The elimination half-life was not enhanced by chronic intake and corresponded to the upper limit of the range of young people (Bechtel & Goetzke, 1986). In another study with elderly volunteers but with an average age of 81 years (71-93 yr) the elimination half-lives were still more elevated to 9.3 (4.0-19.5 h (Jochemsen, 1983c).

Biotransformation: Caused by the chemical structure of brotizolam with various positions in the molecule for metabolic changes the biotransformation and secretion precede so rapidly that after a dose of 0.25 mg no dose-related side-effects or rebound symptoms are expected (Nicholson et al., 1980; Fritz-Osner et al., 1983; Demling, 1992). Several hydroxy-derivatives preferably α-hydroxy- and 6-hydroxy-brotizolam are formed. All compounds exhibited a profile of action quite similar to brotizolam. None of the examined metabolites had a longer duration of action than the parent substance, since rapid glucuronidation and excretion in the urine occur. Only up to 1% of brotizolam is excreted unchanged in the urine. All findings

favor the conclusion that the various actions of brotizolam are mainly caused by the latter itself and not by its active metabolites (Bechtel, 1983; Danneberg et al., 1986).

Interaction: An in vitro study with human liver microsomes showed that the transformation to the main metabolites is catalyzed by the isoenzyme cytochrome P450 (ZYP) 3A4, because the biotransformation was inhibited almost completely by an anti-CYP3A4 antiserum (Senda et al., 1997). These findings were confirmed by in vivo experiments. An inhibitor of CYP3A4, the fungicide itraconazole led to a considerable slowing down of brotizolam degradation, after itraconazole had been administered during 4 days in a dose of 200 mg, finally 1 hour before brotizolam intake. The elimination half-life was enhanced from 4.56 h to 23.27 h. Corresponding to these results, the area under the plasma concentration-time curve was elevated 5-fold and the clearance diminished to a fourth (Osanai et al., 2004). In similar way pretreatment during one week with erythromycin retarded the metabolism of brotizolam, so that $t_{1/2}\beta$ and AUC_{∞} were more than duplicated (Tokairin et al., 2005).

The antituberculosis drug rifampicin induces several drug-metabolizing enzymes with its greatest effect on CYP3A4 (Niemi et al., 2003). After treatment of a group of 13 male subjects with a daily dose of 450 mg rifampicin the biotransformation of brotizolam was accelerated to such an extend that only a fourth of the peak concentration in the placebo group was formed. The area under the curve decreased from 75.3 to 6.4 $ng_{*}h/mL$ and the elimination half-life from 9.1 to 1.6 h. Accordingly the hypnotic effect was decreased. A combined administration of these drugs is therefore not recommendable.

Patients with liver cirrhosis showed a twofold prolongation of the elimination half-life, which was likely due to a decrease in clearance and an increase in volume of distribution (Jochemsen et al., 1983d). In addition the plasma protein binding, which is normally 89-95% (Bechtel, 1983), was diminished and the part of free brotizolam elevated. Renal failure had as expected no influence on the pharmacokinetics of brotizolam. No decelerated elimination was observed in 18 patients with different degrees of renal failure. There was no indication of drug accumulation (Evers et al., 1983).

Evaluation of the studies: Table 63 demonstrates that brotizolam is quickly absorbed. The time of peak concentration was 0.9 ± 0.54 h and the lag time 0.117 ± 0.100 h. The ranges of peak concentration and elimination half-life are comparatively large and therefore the ranges of concentrations at different times too. The V% values obtained by evaluation of the studies are about 90%. Course of the plasma concentration-time curve can therefore be described by a one compartment model and is not influenced by the value of α.

7.2.1.1.2 Triazolam

Application: Triazolam is widely used as hypnotic agent (Pakes et al., 1981). Studies with triazolam were performed with doses of 0.25 up to 0.5 mg (Table 64), demonstrating that it is pharmacological active in low doses. Intravenous and sublingual administrations are connected with a higher bioavailability than an oral intake. The absorbed part of triazolam relative to intravenous was in the case of sublingual administration 20% higher than after oral intake. The mean absolute bioavailability was 44% (oral) and 53% (sublingual) (Kroboth et al., 1995).

Biotransformation: The low bioavailability is caused by the first-pass metabolism in the liver, and a fraction may be degraded in the gut wall (Kroboth et al., 1995). 85% of 0.88 mg given as ^{14}C-triazolam was excreted in the urine and 8% in feces. The major urinary metabolites were α-hydroxy- and 4-hydroxy-triazolam for 69% and 11% of the urinary ^{14}C. These were excreted in conjugated form. Nonconjugated hydroxy-triazolam was present in plasma in insufficient amounts for kinetic analysis. The elimination half-lives were 1.3 resp. 3.8 h (Eberts et al., 1981). The table contains a study of Kinirons et al. (1996), in which the pharmacokinetics of two ethnic groups was compared. Statistically significant differences between the pharmacokinetic parameters $t_{1/2}\beta$ and AUC_{∞} young male Caucasians and southern Asians were not observed. A further investigation of Lang et al. (1996) revealed inter-ethnic differences. After oral administration of triazolam the mean AUC of Afro-Americans was twice as large as that of the Caucasians, pointing to a higher activity of CYP3A4 in Afro-Americans than in Caucasians. The influence of age and gender on the pharmacokinetics was investigated by Smith et al. (1983) and Greenblatt et al. (2004). The former study showed no statistically significant age or gender dependent differences. Greenblatt et al. compared groups of young, intermediate aged, and elderly men and women. Among women age had no statistically significant effect on area under the triazolam concentration-time curve, but the group of elderly men showed elevated values of AUC and elimination half-life.

Interaction: A major number of active agents have been proved to have influence on the pharmacokinetics of triazolam. Thus two investigations in Table 64 (Varhe et al., 1996; 1996a) demonstrated that the fungicide fluconazole leads to a marked retardation of the biotransformation and thus to enhancement of the hypnotic effect. In contrary the fungicide terbinafine had no inhibitory effect, because it is an inhibitor of squalene epoxidase and not of a P450 enzyme as fluconazole. The antihypertensive diltiazem, which is a potent inhibitor of the CYP3A4 isoenzyme, showed in combination with triazolam almost a duplication of the

elimination half-life and the peak concentration. The area under the triazolam plasma curve was more than twice as high as that of the placebo group (Kosuge et al. 1997). Further active agents interacting with triazolam and other hypnotics/sedatives are listed in the review article of Wang und DeVane (2003).

On the other hand pretreatment with rifampicin accelerated the biotransformation of triazolam to such an extent that the area under the plasma concentration curve exhibited only 5% of the area concerning the placebo group. Practically no more hypnotic effect existed.

Evaluation of the studies: As shown in Table 64, 20 studies with 143-183 observations were used for evaluation of pharmacokinetic parameters. Distribution half-lives and V% values were averaged, but the amount of V% is in the range of 90% and a one compartment model describes the plasma concentration-time curve approximately.

7.2.1.1.3 Midazolam

Application: Midazolam is a water-soluble benzodiazepine preferably used in the emergency medicine as intravenously administrated sedative before unpleasant procedures. In higher dosage it can be applied for induction of anesthesia. Absorption after oral intake is rapid. After taking tablets or solutions of midazolam drowsiness appeared after 0.38 h (range 0.25-0.55 h). The time of the peak concentration after a 10 mg tablet was higher than after solution administration (0.74 h vs. 0.37 h). Heizmann et al. (1983) determined an absolute bioavailability of 31-72% after taking midazolam in doses of 10, 20, and 40 mg (Table 65). Linear dependence exists between 10 and 20 mg. After a dose of 40 mg the peak concentration and the area under the plasma concentration-time curve are elevated even after normalization on a 10 mg dose and a body weight of 70 kg. Thus these values were not used for averaging. Similar results are obtained by Bornemann et al. (1985) by investigations with solutions of 7.5, 15, and 30 mg. In the range of the dosage until 15 mg an increase of C_{max} and AUC proportional to the dose was observed. The more than proportional to the dosage elevated values after taking 30 mg midazolam appears to be caused by saturation effects of enzyme systems during first-pass metabolism.

Biotransformation: The mean metabolite is 1-hydroxy-midazolam, stated in animal experiments as pharmacologically active, is quickly detoxified by glucuronidation and excreted in the urine, so that the action of midazolam is mainly caused by the latter itself and not by its active metabolite. Influence of gender on the pharmacokinetics was proved as of negligible clinical importance by Chen et al. (2006). Women exhibited only 11% higher mean

body weight corrected total body clearance and 28% higher total clearance than men. In the same way AUC values of male subjects were elevated.

Dundee et al. (1986) found after intravenous administration of a fixed dose of 0.3 mg/kg midazolam to 115 healthy volunteers and patients 9 subjects with prolonged elimination half-life, 8-22 hours in contrary to 3.3 ± 1.5 hours. Klotz et al. (1986) compared the elimination half-lives of midazolam in poor and extensive metabolizers of sparteine and found the same tendency concerning the pharmacokinetic parameters of both substances. They pointed to the polymorphism of the enzyme involving degradation of both drugs. Harper et al. (1985) observed retarded elimination in more than 50 years old patients undergoing minor surgery in comparison to younger patients (4.5 ± 0.36 vs. 2.5 ± 0.15 h). Major operative procedures led to enhanced elimination half-lives even in young subjects.

Interaction: Caused by predominant metabolism to one degradation product catalyzed by CYP3A4 all the substances reacting with this isoenzyme have influence on the pharmacokinetics. This was demonstrated with the calcium channel blockers diltiazem and verapamil by Backman et al. (1994). The effect was proved to be such intensive that reducing of the dosage is recommended, if a concomitant treatment with diltiazem or verapamil is not avoidable. The orally active growth hormone tabimorelin, which is an inhibitor of CYP3A4 too, led to a statistically significant increase in exposure of midazolam, Even after a washout period AUC was statistically significant higher (45%) than baseline levels (Zdravkovic et al. 2003). Results of combined treatment with midazolam und clarithromycin (Gorski et al. (1998) indicated that in addition to the liver, the intestine is a major side of interaction between oral midazolam und clarithromycin.

Evaluation of the studies: The determined standard deviation of V% is higher than the mean value. A usage is ineffective, because a negative value would be formed from calculating the difference between mean and standard deviation. Therefore a calculation was performed without a standard deviation of V%.

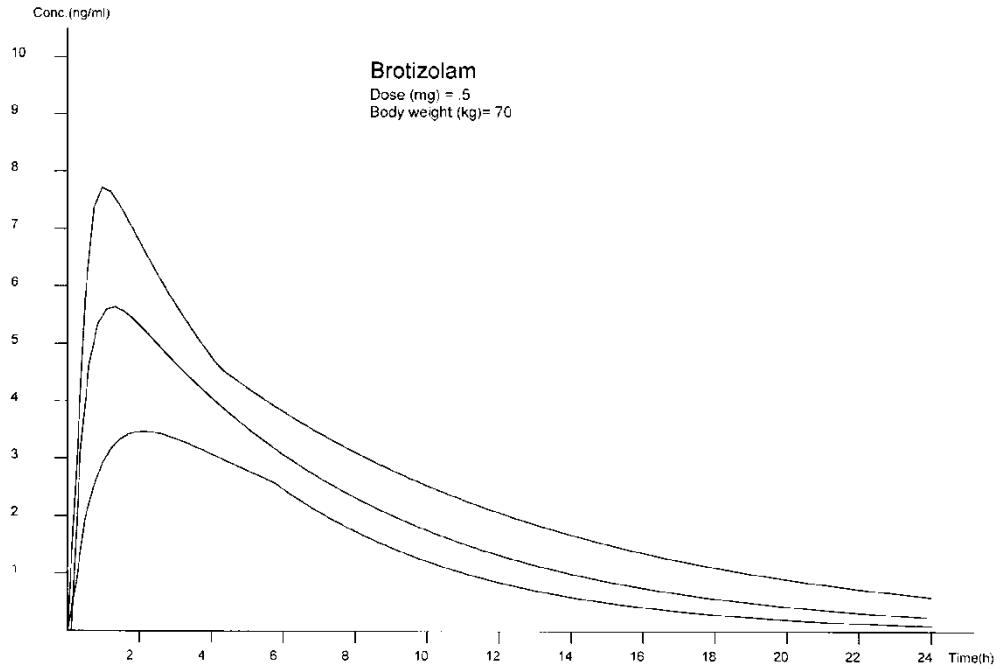


Figure 67: Plasma concentration-time curve of brotizolam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	6.97	±	2.31	ng/mL	
Ka:	2.74	±	1.41	h^{-1}	
α:	0.5	±	0.0	h^{-1}	
β:	0.139	±	0.037	h^{-1}	
t_0	:0.117	±	0.10	h	
V%:	100%				
B:	70%				
					derived from time-course of plasma concentrations
C_{max}:	8.71	±	3.49 ng/mL		5.64 (3.48-7.72) ng/mL
t_{max}:	5.6	±	1.6 h		1.32 (0.96-2.16) h
AUC_{∞}:	58.4	±	15.9 ng*h/mL		47.5 (31.3-69.8) ng*h/mL
V_{β}/G:	0.56	±	0.21 L/kg		0.756±0.375 L/kg

Table 63: 0.5 mg Brotizolam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Jochemsen et al. 1983a	healthy volunteers (1F)	21	0.5	10.8 (2)	0.50 (2)		3.6 (3)	0 (2)	
„	(1F)	23	0.5	10.3(2)	0.017(3)		3.3(3)	0(2)	
„	(1F)	26	0.5	8.29(2)	0.40(2)		5.9(3)	0.6(2)	
„	(1M)	24	0.5	4.44(2)	0.25(2)		6.7(3)	0.233(2)	
„	(1M)	22	0.5	12.8(2)	0.050(2)		3.5(3)	0.067(2)	
„	(1M)	23	0.5	8.28(2)	0.017(3)		6.2(3)	0(2)	
„	(1M)	24	0.5	10.9(2)	0.12(2)		4.6(3)	0.009(2)	
„	intravenous (5M/3F)	21-26	0.25				4.8 (2)		
„	oral (5M/3F)	21-26	0.5		0.74 (2)		5.1 (2)	0.133(2)	
Jochemsen et al. 1983b	(1F)	26	0.5	6.29 (3!)	0.067 (3!)	(1.26)	5.75 (3!)	0.374(3!)	90.8 (3!)
„	(1M)	22	0.5	8.17 (3!)	0.50 (3!)	(1.39)	3.11 (3!)	0.001(3!)	100 (3!)
„	(5M/3F)	21-26	0.5				5.2 (2)		
Osanai et al. 2004	placebo (10M) (itraconazole)	33.75.2	0.5	4.11 (2!)	0.10 (2!)	(1.39)	4.86 (2!)	0.11 (2!)	(99.8)
Tokairin et al. 2005	placebo (14M) (erythromycin)	28.1	0.5	6.74 (1)	0.12 (2)	(1.07)	6.92 (2)	0.033 (2)	(61.7)
Jochemsen et al. 1983c	young (and eld.) vol. (5M/3F)	21-26	0.25				5.0 (2)		
Bechtel u. Weber 1985	(8M/F)		0.25	10.86 (1!)	0.24 (2!)	(1.26)	4.5 (2!)	0.108 (2!)	(98.4)
Greenblatt et al.1983b	(1M)	24	0.25		0.13 (3)		2.6 (3)	0.46 (3)	
„	(1M)	25	0.25		0.015(3)		4.9 (3)	0.25 (3)	
„	(1M)	28	0.25		0.035(3)		3.8 (3)	0.13 (3)	
„	(1M)	22	0.25		0.14(3)		3.0 (3)	0.09 (3)	
„	(1M)	24	0.25		0.28 (3)		6.9 (3)	0.02 (3)	
„	(1M)	23	0.25		0.94 (3)		5.0 (3)	0.05 (3)	
„	(1M)	24	0.5		0.19 (3)		3.0 (3)	0.16 (3)	
„	(1M)	25	0.5		0.40 (3)		4.9 (3)	0.08 (3)	
„	(1M)	28	0.5		1.54(3)		3.7 (3)	0.13 (3)	
„	(1M)	22	0.5		0.12 (3)		2.8 (3)	0.03 (3)	
„	(1M)	24	0.5		0.15 (3)		5.3 (3)	0.15 (3)	

„	(1M)	23	0.5		0.010(3)		6.3 (3)	0.25 (3)	
Ujiie et al. 2006	placebo (rifampicin) (13M)	28±5.8	0.5	6.74 (2)	0.092 (2)	(1.22)	7.41(2)	0.14 (2)	(87.2)
	Mean			6.97	0.25		5.0	0.117	
	± SD			±2.31	±0.27		±1.8	±0.100	
	Number of trials			6	7		8	7	
	Number of observations			54	74		98	74	

Continuation of Table 63: 0.5 mg Brotizolam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{∞} (ng*h/mL)	G (kg)	B (%)	V_{β}/B (L)	V_{β}/G (L/kg)
Jochemsen et al. 1983a	healthy volunteers (1F)	6.72(2)	1.8 (2)	63.9 (3)	52			0.54 (2)
„	(1F)	9.61(2)	0.3(2)	47.5(2)	58			0.49(2)
„	(1F)	6.35(2)	2.4(2)	61.4(2)	72			0.65(2)
„	(1M)	3.76(2)	1.43(2)	41.4(2)	63			0.96(2)
„	(1M)	11.8(2)	0.37(2)	59.7(2)	73			0.40(2)
„	(1M)	8.01(2)	0.3(2)	62.7(2)	76			0.61(2)
„	(1M)	8.8(2)	0.8(2)	56.1(2)	76			0.26(2)
„	intravenous (5M/3F)				69±10.3			
„	oral (5M/3F)				69±10.3	70 (2)		
Jochemsen et al. 1983b	(1F)	4.0 (3!)	4.0 (3!)	46.1 (3!)	72			
„	(1M)	7.34 (3!)	0.3 (3!)	34.9 (3!)	73			
„	(5M/3F)			67.2 (2)	76.0±11.1			
Osanai et al. 2004	placebo (10M) (itraconazole)	4.29(2!)	0.75 (2!)	28.0 (2!)	62.3±4.6			
Tokairin et al. 2005	placebo (14M) (erythromycin)	8.2 (1!)	0.8 (2!)	67.0 (2!)	69.8			
Jochemsen et al. 1983c	young (and elderly) volunteers(5M/3F)	14.6 (2)	1.1 (2)		69	0.70 (2)		
Bechtel u. Weber 1985	(8M/F)	9.2 (1!)	0.9 (2!)	66.4 (1!)				
Greenblatt et al.1983b	(1M)	6.03 (3)	1.0 (3)		70.4			
„	(1M)	11.6 (3)	0.5 (3)		75.0			
„	(1M)	15.8 (3)	0.25 (3)		65.9			
„	(1M)	9.86 (3)	0.75 (3)		70.4			
„	(1M)	12.5 (3)	0.5 (3)		68.2			
„	(1M)	11.3 (3)	1.5 (3)		80.2			
„	(1M)	16.0 (3)	0.5 (3)		70.4			
„	(1M)	6.54 (3)	0.5 (3)		75.0			
„	(1M)	3.39 (3)	1.5 (3)		65.9			
„	(1M)	6.35 (3)	0.75 (3)		70.4			
„	(1M)	11.2 (3)	0.5 (3)		68.2			

„	(1M)	10.2 (3)	0.5 (3)		80.2	
Ujiie et al. 2006	placebo (rifampicin) (13M)	7.9 (2!)	0.84 (2!)	72.1 (2!)	69.1±11.2	
	Mean ± SD	8.71 ±3.49	0.90 ±0.54	58.4 ±15.9		70
	Number of trials	8	8	6		2
	Number of observations	74	74	62		16

Table 64: 0.5 mg Triazolam (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Greenblatt et al. 1983a	young and (1M)	25	0.5	4.06 (2!)	0.456 (3!)	(1.38)	3.04 (3!)	0.256 (3!)	(65.1)
„	(elderly) volunteers (1F)	21	0.5	4.64 (2!)	0.124 (3!)	(0.52)	3.26 (3!)	0.167 (3!)	(32.3)
„	male (8M)	23-33	0.5				3.0(2)		
„	female (8F)	21-31	0.5				2.7 (2)		
Otani et al. 1997b	comparison with alprazolam(10M)	29.8	0.5	2.83 (2!)	0.147(2!)	(1.48)	2.73(2!)	0.204(2!)	(93.0)
Smith et al. 1983	influence of (5M)	25	0.5	8.72 (2!)	0.256(2!)	(0.28)	3.41(2!)	0.21(2!)	(70.3)
„	age (5M)	45	0.5	9.06 (2!)	0.219(2!)	(0.63)	2.87(2!)	0.19(2!)	(99.2)
	and (5M)	72	0.5	8.58(2!)	0.488(2!)	(1.96)	3.59(2!)	0.14(2!)	(98.4)
„	gender (5F)	27	0.5	8.40 (2!)	0.465(2!)	(0.78)	2.95(2!)	0.14(2!)	(70.3)
„	(5F)	47	0.5	8.26 (2!)	0.513(2!)	(0.77)	2.18(2!)	0.058 (2!)	(87.5)
„	(5F)	67	0.5	9.46(2!)	0.294(2!)	(0.37)	2.18(2!)	0.16(2!)	(87.5)
Greenblatt et al. 2000	comparison with (10M)	26	0.25	7.53 (2!)	0.237(2!)	(1.39)	2.66(2!)	0.034(2!)	(99.8)
„	zolpidem (10F)	28	0.25	5.8 (2!)	0.340(2!)	(1.04)	3.01(2!)	0.0064(2!)	(98.4
Jochemsen et al. 1983b	comparison with (1F)	26	0.5	2.39 (3!)	0.396(3!)	(1.73)	1.83(3!)	0.49(3!)	(96.9)
«	brotizolam (1M)	22	0.5	3.88 (3!)	0.044(3!)	(1.39)	2.34(3!)	0.021(3!)	(99.8)
«	(5M/3F)	21-26	0.5	-	-	-	2.60(2)	-	-
Greenblatt et al. 2005	EEG-test (13M)		0.375	4.57 (1!)	0.355(2!)	(1.72)	3.33(2!)	0.153(2!)	(70.3)
Varhe et al. 1996	placebo (2M/10F)	19-31	0.25	5.02 (1!)	0.564(2!)	(1.33)	3.64(2!)	0.21(2!)	(69.2)
„	+ terbinafine (2M/10F))	19--31	0.25	5.62 (1!)	0.555(2!)	(1.33)	2.70(2!)	0.009(2!)	(99.6)
Varhe et al. 1996a	+(fluconazol) (2M/10F)	20-32	0.25	4.96 (1!)	0.506(2!)	(1.39)	2.92(2!)	0.01(2!)	(98.4)
Kosuge et al. 1997	+(diltiazem)(7M)	20-22	0.25	4.46 (2)	0.325(2!)	(0.54)	3.57(2!)	0.013(2!)	(93.0)
Kinirons et al. 1996	Caucasians (8M)	28	0.375	-	-	-	3.32 (2)	-	-
„	Southern-Asians (8M)	22	0.375	-	-	-	3.36 (2)	-	-
Greenblatt et al. 2004	young-(old) CYP3A (10M)	20-36	0.25	5.87(2!)	0.325(2!)	(1.39)	2.82(2!)	0.086(2!)	(98.4)
„	young-(old) CYP3A (13F)	20-36	0.25	6.22(2!)	0.317(2!)	(1.33)	2.69(2!)	0.151(2!)	(98.1)
	Mean ± SD			**6.17 ±1.88**	**0.369 ±0.134**		**2.96 ±0.40**	**0.110 ±0.088**	
	Number of trials			20	20		25	20	
	Number of observations			143	143		183	143	

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Greenblatt et al. 1983a	young and (1M)	3.99 (2!)	1.55 (3!)	18.01 (2!)	52			
„	(elderly) volunteers (1F)	10.3 (2!)	0.5 (3!)	26.1 (2!)	58			
„	male (8M)	4.6 (2)	1.8 (2)		70			
„	female (8F)	3.6 (2)	2.1 (2)		57			
Otani et al. 1997b	comparison with alprazolam(10M)	2.8(2!)	0.9 (2!)	11.0(2!)	60.8			
Smith et al. 1983	influence of (5M)	7.3(2)	1.05 (2)	39.7(2!)	79.9			
„	age (5M)	6.7(2)	0.75 (2)	33.8(2!)	79.3			
	and (5M)	6.6(2)	0.75(2)	37.8(2!)	76.7			
„	gender (5F)	5.28(2)	1.85 (2)	30.42(2!)	60.4			
„	(5F)	4.48(2)	1.6 (2)	20.2(2!)	60.1			
„	(5F)	6.49(2)	0.65(2)	25.8(2!)	59.3			
Greenblatt et al. 2000	comparison with (10M)	6.45 (2)	1.25 (2)	26.2 (2!)	75.3			
„	zolpidem (10F)	4.4 (2)	1.25 (2)	22.2 (2!)	66.8			
Jochemsen et al. 1983b	comparison with (1F)	1.85 (3)	1.33 (3)	5.09 (3!)	72			
“	brotizolam (1M)	3.50 (3)	0.33 (3)	12.8 (3!)	73			
“	(5M/3F)	5.0(1)	1.2(2)	15.4(1!)	52-82			
Greenblatt et al. 2005	EEG-test (13M)	3.7 (1)	1.2 (2)	19.7(1!)	-			
Varhe et al. 1996	placebo (2M/10F)	4.0 (1)	1.8 (2)	22.4(1!)	48-80			
„	+ terbinafine (2M/10F))	3.4 (1)	1.5 (2)	17.06(1!)	48-80			
Varhe et al. 1996a	+(fluconazol) (2M/10F)	3.0 (1)	1.3 ()	17.3(1!)	53-83			
Kosuge et al. 1997	+(diltiazem)(7M)	4.2 (2)	1.6 (2)	21.2(2!)	71.1			
Kinirons et al. 1996	Caucasians (8M)	7.12 (2)	1.5 (2)	34.2 (2)	77.9			
„	Southern-Asians (8M)	10.4 (2)	0.75 (2)	34.9 (2)	68.0			
Greenblatt et al. 2004	young-(old) CYP3A (10M)	5.48(2)	1.0(2)	22.2(2!)	76.7			
„	young-(old) CYP3A (13F)	5.0(2)	1.3(2)	21.5(2 !)	65.0			
Kroboth et al. 1995	intravenous. oral. sublingual					44 %		
	Mean **± SD**	**5.23** **±1.85**	**1.30** **±0.38**	**24.0** **±7.8**		**44 %**		
	Number of trials	25	25	23				
	Number of observations	183	183	167				

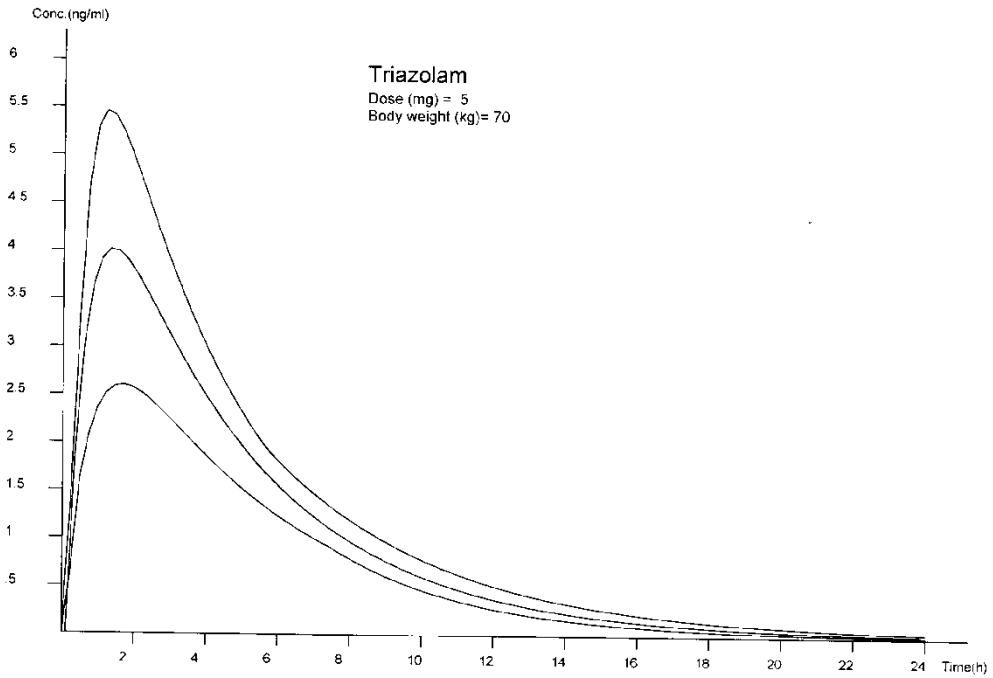


Figure 68: Plasma concentration-time curve of triazolam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	6.17	±	1.88	ng/mL	
Ka:	1.88	±	0.50	h^{-1}	
α:	0.5	±	0.0	h^{-1}	
β:	0.234	±	0.028	h^{-1}	
t_0:	0.110	±	0.088	h	
V%:	100%				
B:	44%				
					derived from time-course of plasma concentrations
C_{max}:	5.23	±	1.85 ng/mL		4.01 (2.60-5.46) ng/mL
t_{max}:	1.30	±	0.38 h		1.31 (1.20-1.68) h
AUC_{o-oo}:	24.0	±	7.8 ng*h/mL		23.0 (16.6-29.6) ng*h/mL
Vβ/G	:				0.582 ± 0.255 L/kg

Table 65: 10 mg Midazolam (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Heizman et al. 1983	determination of (1)	22-27	10	54.0(3!)	0.073(3!)	1.40(3!)	1.45(3!)	0.100(3!)	84.8(3!)
„	bioavailability (1)	22-27	10	36.9(3!)	0.078(3!)	0.16(3!)	1.81(3!)	0.017(3!)	6.25(3!)
„	and of the (1)	22-27	10	57.9(3!)	0.022(3!)	0.42(3!)	2.01(3!)	0.000(3!)	25.0(3!)
„	distribution volume (1)	22-27	10	46.7C	0.059(3!)	0.19(3!)	1.87(3!)	0.015(3!)	12.1(3!)
„	after (1)	22-27	20	69.1(3!)	0.148(3!)	0.200(3!)	1.51(3!)	0.093(3!)	21.2(3!)
„	intravenous (1)	22-27	20	60.1(3!)	0.115(3!)	0.181(3!)	1.64(3!)	0106(3!)	35.2(3!)
„	and oral (1)	22-27	20	77.0(3!)	0.025(3!)	0.630(3!)	2.24(3!)	0.011(3!)	99.6(3!)
„	administration (1)	22-27	20	39.8(3!)	0.065(3!)	0.137(3!)	1.66(3!)	0(3!)	6.25(3!)
„	(1)	22-27	20	63.3(3!)	0.034(3!)	0.185(3!)	2.30(3!)	0(3!)	17.6(3!)
„	(1)	22-27	20	93.9(3!)	0.081(3!)	0.242(3!)	2.59(3!)	0.001(3!)	21.7(3!)
„	(1)	22-27	40	78.3(3!)	0.034(3!)	0.135(3!)	2.13(3!)	0(3!)	10.9(3!)
„	(1)	22-27	40	57.4(3!)	0.023(3!)	0.165(3!)	3.96(2)	0(3!)	5.47(3!)
„	intravenous (6)	22-27	0.15 mg/kg	-	-	-	2.29±0.42 (3)	-	-
Klotz et al. 1986	extensive metabolizer (6)	23-37	-	-	-	-	2.2±0.9(2)	-	-
Backman et al. 1994	placebo + (diltiazem u. verapamil) (9F)	19-28	15	18.3(1!)	0.355(2!)	0.533(2!)	3.84(2!)	0.040(2!)	10.8(2!)
Nassr et al. 2006	placebo + (roflumilast) (18M)	<50	2	56.9(2!)	0.237(2!)	0.502(2!)	3.47(2!)	0.158(2!)	5.86(2!)
Dundee et al. 1986	(20)	<50					2.1±0.11(2)		
Allonen et al. 1981	(6)		7.5		0.23±0.37(2)		2.4±08(2)		
„	(6)		15		0.23±0.37(2)		2.4±0.8(2)		
Smith et al. 1981	solution (6)		10				1.77±0.83(2)		
„	tablet (6)		10				1.77±0.83(2)		
	Mean ± SD			**54.5 ±16.8**	**0.199 ±0.104**	**0.442 ±0.238**	**2.51 ±0.72**	**0.083 ±0.067**	**16.0 ±0.21.7**
	Number of trials			3	5	3	10	3	3
	Number of observations			39	51	39	95	39	39

Continuation of Table 65: 10 mg Midazolam (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Heizman et al. 1983	determination of (1)	64.0(3)	0.5 (3)	125.0(3!)	54.6	31	38.6	
„	bioavailability (1)	170.7(3)	0.25(3)	160.6(3!)	76.1	57	59.9	
„	and of the (1)	155.4(3)	0.25(3)	261.5(3!)	64.0	48	41.9	
„	distribution volume (1)	123.7(3)	0.25(3)	139.0(3!)	61.0	46	67.8	
„	after (1)	87.0(3)	0.5(3)	153.9(3!)	54.6	38	47.9	
„	intravenous (1)	68.5(3)	0.5(3)	141.9(3!)	76.1	45	45.0	
„	and oral (1)	74.1(3)	0.25(3)	242.9(3!)	64.0	32		
„	administration (1)	160.3	0.25(3)	150.2(3!)	61.0	61		
„	(1)	173.6	0.25(3)	260.7(3!)	72.1	49		
„	(1)	203.2(3)	0.25(3)	413.2(3!)	77.5	64		
„	(1)	(245.4)	0.25(3)	(305.4)	72.1	63		
„	(1)	(401.1)	0.25(3)	(488.3)	77.5	72		
„	intravenous (6)	-	-	-	55-77			
Klotz et al. 1986	extensive metabolizer (6)	-	-	-	-	-		-
Backman et al. 1994	placebo + (diltiazem u. verapamil) (9F)	43.3(1)	1.1(2)	129.1(1!)	55-80	-		
Nassr et al. 2006	placebo + (roflumilast) (18M)	98.1(2)	0.5(2)	594.5(2!)	78			
Dundee et al. 1986	(20)							
Allonen et al. 1981	(6)					44		
„	(6)					44		
Smith et al. 1981	solution (6)		0.37±0.45(2)			36		
„	tablet (6)		0.74±0.45(2)			36		
	Mean ± SD	**103.5 ±40.7**	**0.55 ±0.28**	**231.0 ±138.2**		**44.5 ±10.2**	**50.2 ±10.6**	
	Number of trials	3	5	3		5	**1**	
37	Number of observations	37	51	37		36	**6**	

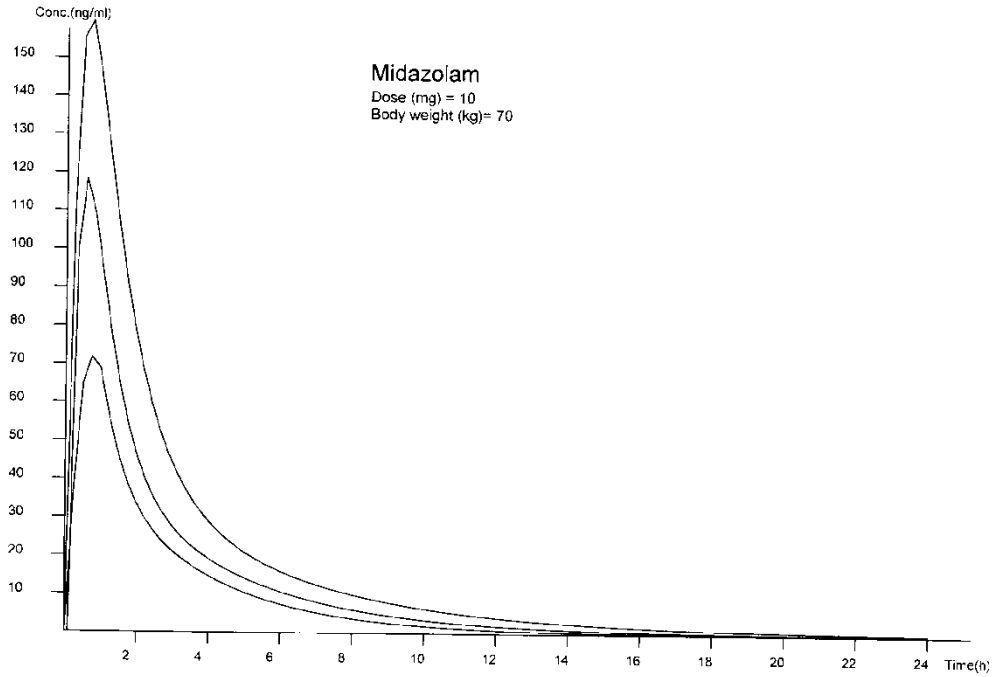


Figure 69: Plasma concentration-time curve of midazolam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	54.5	±	16.8	ng/mL
Ka:	3.48	±	1.19	h^{-1}
α:	1.57	±	0.55	h^{-1}
β:	0.276	±	0.061	h^{-1}
t_0:	0.083	±	0.067	h
V%:	16.0			%
B:	44.5	±	10.2%	

				derivedfromtime-courseof plasmaconcentrations
C_{max}:	103.5	±	40.7 ng/mL	115.5 (71.8-159.8) ng/mL
t_{max}:	0.55	±	0.28 h	0.67 (0.67-0.72) h
AUC_{o-oo}:	231.0	±	138.2 ng*h/mL	276.5 (187.2-440.4) n*h/mL
Vβ	:0.56	±	0.21 L/kg	1.266 ± 0.565 L/kg

7.2.1.2 Medium-length acting benzodiazepines

Medium-length acting hypnotics/sedatives are developed for avoiding disadvantages of slowly metabolised active agents with long plasma half-lives, which may cause daytime sedation and accumulation on multiple dosages. On the other hand very rapidly eliminated hypnotics have been implicated in causing rebound anxiety the morning after administration (Morgan & Oswald 1982) and pronounced insomnia on withdrawal after repeated usage (Kales et al. 1979).

7.2.1.2.1 Lormetazepam

Application: Depending on individual conditions, lormetazepam was found to have pronounced depressant effects on the central nervous system at oral doses of 0.5 to 2 mg, which are lower than that used for most of the benzodiazepines. Pierce et al. (1984) compared two formulations of lormetazepam, a wet granulation tablet (Noctamid®) and a soft gelatin capsule (Loramet®, Wyeth Laboratories). Lormetazepam was more rapidly absorbed from the capsule than from the tablet (t_{max} =1 hr vs. 2.4 h). Accordingly the lag times (0.13 hr vs. 0.29 hr) and the absorption half-lives (0.40 hr vs. 0.80 hr) were shorter. For effective antianxiety therapy, lormetazepam should be administrated as the other hydroxylated benzodiazepines 2-3 times daily.

Biotransformation: As other hydroxylated benzodiazepines, the mean metabolism pathway is conjugation to the pharmacologically glucuronide, which is detectable not only in urine, but also in plasma after intravenous or oral administration. The concentration of lormetazepam glucuronide increased for about 3 hours and remained constant for 3-9 hours at a level of 5 ng per mL plasma after injection of 0.2 mg and at 60 ng/mL after oral intake of 2 mg lormetazepam (Hümpel et al. 1979). The comparatively high concentrations of lormetazepam glucuronide are due to the low distribution volume of 0.31 L/kg compared with that of the parent drug. (6.8 L/kg). After enzymatic hydrolysis of urine or plasma samples, about 90% of the radioactivity derived from a 5-^{14}C-lormetazepam administration was extractable with ether. Extracts from plasma contained only the parent drug, whereas in the urine up to 6% was identified as the demethylated product lorazepam (Hümpel et al. 1979).

Interaction: Pharmacokinetics of 3-hydroxylated benzodiazepines, metabolized nearly exclusively by phase-II metabolism (conjugation), are not statistically significant affected by severe liver disease in contrast to drugs degraded by phase-I metabolism (e.g. oxidation, demethylation). Thus Hildebrand et al. (1990) concluded from a pharmacokinetic study,

comparing patients with liver cirrhosis and healthy volunteers, that the pharmacokinetics were not altered in cirrhotic patients, even though plasma levels and peaks under the plasma curves were increased. But alterations were not so large that a lower dosage than usable should be chosen for treatment of cirrhotic patients.

In elderly subjects (65.8 ± 3-3 yr), there was a trend only to a slower elimination phase of the parent drug: $t_{½}\beta$ = 11.5 hr (i.v.), 14.2 hr (1 mg oral), and 15.2 hr (3 mg oral) in comparison to young subjects: $t_{½}\beta$ = 10.6 (i.v.), 9.9 (1 mg oral), and 10.7 (3 mg oral) (Hümpel et al. 1980). Doenicke et al. (1991) investigated the influence of cimetidine on the pharmacokinetics of lormetazepam. The volunteers received 5 cimetidine tablets á 200 mg at intervals of 6 hours, the last tablet together with 1 mg lormetazepam. No interaction of the drugs was observed.

Evaluation of studies: In the dosage range of 1 to 3 mg lormetazepam, linear dependence of pharmacokinetic parameters on the dose has been shown by the studies of Hümpel et al. (1980), because the body weight and dose normalized values are in good conformity (tables 4). The standard deviation of V% was not used for calculations of minimal and maximal curves, because these curves would have taken courses with too much deviating of peak concentrations and areas under the plasma concentration-time curves.

7.2.1.2.2 Temazepam

Application: Temazepam, the 3-hydroxyl derivative of diazepam, is useful in doses of 20 to 40 mg in treatment of insomnia. It is rapidly absorbed with a mean absorption half-life of 22 minutes (Table 67), though several pharmacokinetic parameters are affected as is the case at day-time or night-time administration (Müller et al. 1987). The absorption was slower after evening administration, the absorption half-life 32 vs. 23 minutes and time at peak concentration 1.67 vs. 1.02 hours. Peak plasma concentrations were lower and the distribution half-life was increased comparing with day-time administration. However the authors stated that these alterations are unlikely to have any clinical significance. Different formulations were tested, suspension, uncoated tablets, soft and hard gelatin capsules. Soft gelatin capsules seemed to be somewhat more effective than tablets or hard gelatin capsules, but all the formulations were found to be acceptable.

In patients requiring minor surgery, temazepam can be used as premedication, because the pharmacokinetic parameters evaluated in such patients were found to be statistically not different from that derived from healthy volunteers (Indalo & Kokwaro, 1995).

Biotransformation: Metabolism of temazepam occurs nearly exclusively by conjugation at the 3-hydroxy position yielding temazepam glucuronide as the major metabolite. A minor

metabolic pathway is N-demethylation yielding oxazepam, which is conjugated to oxazepam glucuronide. After daily administration of 0.41 mg/kg radiolabeled temazepam, at or near the steady-state peak, 36.1% of the radioactivity in blood was determined as temazepam and 44.9% as temazepam glucuronide. Only 1.8% was present as oxazepam glucuronide (Schwarz 1979). 80% of a dose of 0.41 mg/kg was excreted into the urine and 12% into the feces.

Interaction: Smith et al. (1983) have investigated the influence of age and gender on the pharmacokinetics of temazepam. 30 healthy volunteers were divided into three groups of men and 5 women according to age. None of the pharmacokinetic variables of the groups derived from young, middle-aged, and elderly men showed statistically significant differences, but in the group of elderly women (63-71 yr), altered elimination half-lives were observed: women $t_{½}\beta$ = 18.4 hr, men (68-76 yr) $t_{½}\beta$ = 9.9 hr. Divoll et al. (1981) found against that prolonged elimination half-lives in younger women. Thus age does not affect the pharmacokinetics of temazepam statistically significant. In cirrhotic patients, Ochs et al. (1986) observed a smaller distribution volume, but no differences in the clearance of temazepam.

The bioavailability was unchanged by 1 day's treatment with cimetidine, ranitidine, or a common emulsion antacid (Elliott et al. 1984). Greenblatt et al. (1984) observed in the same way that pharmacokinetics of temazepam was not affected by the coadministration of cimetidine. Erythromycin, a strong inhibitor of cytochrome P450 (CYO3A4), did not change the pharmacokinetics and pharmacodynamics of temazepam to a statistically significant degree (Luurila et al. (1994). Also rifampin, a potent inducer of the hepatic microsomal enzyme system, did not alter the pharmacokinetics of temazepam, as well as probenecid, which decreases the tubular secretion of many substances (Brockmeyer et al. 1990). This is in agreement with the fact that the biotransformation of temazepam occurs mainly by conjugation and not by an oxidative mechanism.

Evaluation of studies: Comparing the pharmacokinetic parameters of temazepam with those of its demethylation product, oxazepam, the faster absorption is obvious: T_{max} = 1.6 vs. 2.6 hr, Ka = 1.9 vs. 0.93 h^{-1}, and the distribution phase is more pronounced. These properties are due to the higher lipophilicity of temazepam compared with oxazepam and give reasons for temazepam being a more appropriate hypnotic than oxazepam.

7.2.1.2.3 Loprazolam

Application: Loprazolam is an imidazole benzodiazepine with anxiolytic, sedative, anticonvulsant, and skeletal muscle relaxing properties. For treatment of insomnia the dosage is usually 1 mg but can be increased to 2 mg if necessary. Investigations of McInnes (1985)

demonstrate that multiple administrations did not influence the course of plasma concentration-time curve after intake of 1 mg loprazolam. Similar results have been referred by Stevens et al. (1983) after administration of 2 mg loprazolam. No indications have been found that the active agent or active metabolites accumulate. Bareggi et al. (1988) have proved effects of after-dinner administration of oral loprazolam. The absorption was pronouncely retarded. C_{max} was diminished from 8 to 5.2 ng/mL and t_{max} elevated from 2.2 up to 5.8 h, but the mean elimination half-life and area under the plasma concentration-time curve was not altered.

Biotransformation: In contrary to other imidazo or triazo benzodiazepines, loprazolam forms predominantly only one metabolite, which is identified as loprazolam-N-oxide. This pharmacologically active degradation product has after intake of o.5 or 1 mg loprazolam its mean peak concentration at 4.5 h in blood plasma (Ford et al. 1987). Mean times to plasma concentrations of loprazolam did not differ statistically significant between young and elderly subjects and ranged from 1.6 to 2.7 h, the time to plasma concentration of the N-oxide was slightly elevated in elderly subjects to 6.5 h. Similar results have been obtained by Dorling and Hindmarch (2001). These authors observed no prolongation of the elimination half-lives or elevation of the areas under the plasma concentration-time curves, whereas the investigations of Ford et al. (1987) revealed greater areas under the plasma concentration-time curves for both loprazolam and its N-oxide in the elderly, 50-68% above those found in young subjects. There was a trend towards somewhat longer elimination half-lives of loprazolam and its N-oxide in the elderly too.

Interaction: While in animal experiments at high doses of loprazolam over 6-12 months was evidence of an enzyme induction following administration of 1 mg loprazolam for up to 30 nights no signs of hepatic microsomal induction were found in healthy volunteers (Ankier et al. 1983). An enhancement of hepatic microsomal oxidation of the many other drugs by loprazolam is therefore regarded as unlikely by the authors.

Evaluation of studies: Comparing the pharmacokinetic parameters of loprazolam listed in Table 68, obviously time to peak concentrations and normalised peak concentrations are in good accordance and independent on the dose. The fictive initial concentrations show modest deviations, whereas the range of the elimination half-life is large (7-20 h) and as expected the areas under the plasma concentration-time curves, too.

Table 66: 1 mg Lormetazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Hildebrand et al. 1990	healthy + (cirrhotic patients) (5M)	20-21	0.03 mg/kg	4.22(2!)	0.321(2!)	1.61 (2!)	7.81(2!)	0.022(2!)	43.2(2!)
Pierce et al. 1984	comparison (1M)	21-34	1	4.95 (1!)	1.27(2!)	1.39(2!)	7.61(2!)	0.16(2!)	8.80(2!)
„	tablet (1M)	21-34	1	4.30 (2!)	0.529(2!)	0.94(2!)	9.67(2!)	0.23(2!)	21.7(2!)
„	„ (1M)	21-34	1	5.84 (2!)	0.784(2!)	1.36(2!)	7.27(2!)	0.36(2!)	37.5(2!)
„	„ (1M)	21-34	1	7.22 (2!)	0.459 (2!)	1.26(2!)	4.53(2!)	0.12(2!)	98.4(2!)
„	„ (1M)	21-34	1	5.03 (2!)	0.462(2!)	0.77(2!)	6.76(2!)	052(2!)	21.2(2!)
„	„ (1M)	21-34	1	5.76 (2!)	1.03(2!)	1.54(2!)	8.28(2!)	0.33(2!)	35.2(2!)
„	„ (1M)	21-34	1	6.00(2!)	1.03(2!)	1.48(2!)	11.3(2!)	0.31(2!)	35.2(2!)
„	and capsule (1M)	21-34	1	7.30(2!)	0.392(2!)	1.93(2!)	4.78(2)	0.11(2!)	93.8(2!)
„	„ (1M)	21-34	1	3.08(2!)	0.172(2!)	1.58(2!)	10.0(2!)	0.014(2!)	49.6(2!)
„	„ (1M)	21-34	1	4.54(2!)	0.303(2!)	1.76(2!)	12.0(2!)	0.14(2!)	90.8(2!)
„	„ (1M)	21-34	1	3.33(2!)	0.578(2!)	1.16(2!)	10.2(2!)	0.009(2!)	21.5(2!)
„	„ (1M)	21-34	1	5.11(2!)	0.263(2!)	0.73(2!)	6.94(2!)	0.23(2!)	64.6(2!)
„	„ (1M)	21-34	1	4.71(2!)	0.722(2!)	1.18(2!)	8.21(2!)	0.13(2!)	17.6(2!)
„	„ (1M)	21-34	1	5.92(2!)	0.357(2!)	0.64(2!)	10.8(2!)	0.29(2!)	24.2(2!)
Hümpel et al. 1979	5-^{14}C-Lormetazepam (5M)	23-30	2	4.62(2!)	0.030(2!)	1.24(2!)	10.8(2!)	0.016(2!)	6.8(2!)
Hümpel et al 1980	young and (3M/3F)	24.2±1.2	1	-	0.5±0.2(3)	2.3±0.8(3)	9.9±2.4(3)	-	-
„	(elderly) volunteers (3M/3F)	24.2±1.2	3	-	0.8±0.3(3)	2.4±0.9(3)	10.7±2.1(3)	-	-
	Mean ± SD			**4.89 ±1.01**	**0.519 ±0.294**	**1.77 ±0.56**	**9.45 ±1.72**	**0.131 ±0.141**	**36.3 ±27.4**
	Number of trials			4	6	6	6	4	4
	Number of observations			24	36	36	36	24	24

Continuation of Table 66: 1 mg Lormetazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Cmax (ng/mL)	Tmax (h)	AUCo-oo (ng*h/mL)	G (kg)	B (%)	Vβ/B (L)	Vβ/G (L/kg)
Hildebrand et al. 1990	healthy + (cirrhotic patients) (5M)	27.2(2)	0.33 (2)	55.8(2!)	63.2	82(3)		
Pierce et al. 1984	comparison (1M)	4.71(2)	4.0(2)	54.6(2!)	42-72			
„	tablet (1M)	5.65(2)	1.0(2)	69.3(2!)	= 56.8			
„	„ (1M)	5.44(2)	3.0(2)	57.2(2!)	„			
„	„ (1M)	5.52(2)	2.0(2)	32.5(2!)	„			
„	„ (1M)	7.06(2)	2.0(2)	53.8(2!)	„			
„	„ (1M)	5.36(2)	3.0(2)	68.1(2!)	„			
„	„ (1M)	5.76(2)	2.0(2)	95.8(2!)	„			
„	and capsule (1M)	5.44(2)	0.67(2)	47.7(2!)	„			
„	„ (1M)	4.71(2)	1.0(2)	49.9(2!)	„			
„	„ (1M)	4.46(2)	0.67(2)	77.2(2!)	„			
„	„ (1M)	5.36(2)	2.0(2)	56.2(2!)	„			
„	„ (1M)	4.87(2)	0.67(2)	51.0(2!)	„			
„	„ (1M)	6.73(2)	1.0(2)	65.2(2!)	„			
„	„ (1M)	8.68(2)	1.0(2)	96.9(2!)	„			
Hümpel et al 1979	5-^{14}C-Lormetazepam (5M)	6.54(2)	2.0(2)	79.1(2!)	73.8±4.8			
Hümpel et al 1980	young and (3M/3F)	5.06(3)	2.2±0.8(3)	55.2(3)	63.3±6.8	73±16(3)		
„	(elderly) volunteers (3M/3F)	4.87(3)	3.0±1.5(3)	59.7(3)	63.3±6.8	80±12(3)		
	Mean	**6.21**	**2.0**	**61.5**		**78**		
	± SD	**±2.22**	**±0.96**	**±12.3**		**±4**		
	Number of trials	6	6	6		3		
	Number of observations	36	36	36		17		

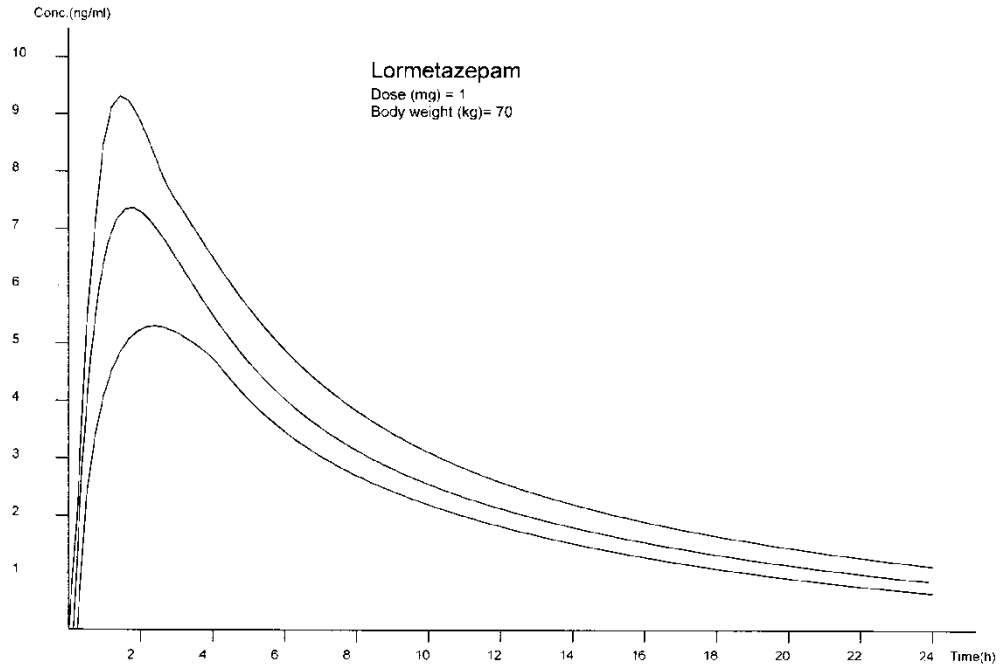


Figure 70: Plasma concentration-time curve of lormetazepamam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	4.89	±	1.01	ng/mL
Ka:	1.77	±	0.56	h^{-1}
α:	0.392	±	0.095	h^{-1}
β:	0.0733	±	0.0112	h^{-1}
t_0	:0.131	±	0.141	h
V%:	36.3			%
B:	78	±	4	

				derived from time-course of plasma concentrations
C_{max}:	6.21	±	2.22 ng/mL	7.36 (5.30-9.31) ng/mL
t_{max}:	2.0	±	0.96 h	2.10 (1.68-3.84) h
AUC_{o-oo}:	61.5	±	12.3 ng*h/mL	78.5 (61.4-100.0) ng*h/mL

Table 67: 20 mg Temazepam (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Indalo, Kokwaro 1995	male (1M)	50	40	231(3!)	0,111(3!)	0.564(3!)	5.70(3!)	0.034(3!)	17.6(3!)
„	surgical (1M)	52	40	547(3!)	0.170(3!)	0.598(3!)	5.06(3!)	0.009(3!)	37.4(3!)
„	Patients (1M)	30	40	246(3!)	0.180(3!)	0.686(3!)	5.32(3!)	0.045(3!)	16.4(3!)
„	(1M)	57	40	410(3!)	0.215(3!)	0.982(3!)	5.72 (3!)	0.008(3!)	24.9(3!)
„	(1M)	47	40	247(3!)	0.254(3!)	0.697(3!)	5.66 (3!)	0.208(3!)	21.9(3!)
„	(1M)	49	40	90(3!)	0.057(3!)	0.888(3!)	8.88 (3!)	0.068(3!)	8.20(3!)
„	(1M)	55	40	281(3!)	0.131(3!)	0.711(3!)	4.67 (3!)	0.016(3!)	24.8(3!)
„	(1M)	36	40	333(3!)	0.042(3!)	0.648(3!)	6.61(3!)	0.022(3!)	24.0(3!)
„	(1M)	28	40	382(3!)	0.436(3!)	0.573(3!)	5.45(3!)	0.009 (3!)	17.6(3!)
Schwarz et al. 1979	Suspension (24)		0.41mg/kg	275(1!)	0.465(2!)	1.18(2!)	9.74(2!)	0.022 (2!)	48.4(2!)
„	hard gelatin capsule (24)		0.41mg/kg	235(1!)	0.405(2!)	2.96(2!)	10.8(2!)	0.470(2!)	69.8(2!)
Matilla et al. 1985	uncoated tablet (5M/7F)	22-28	20	272.6(2!)	0.363(2!)	1.51(2!)	11.5(2!)	0.030(2!)	24.9(2!)
„	soft gelatin capsule (5M/7F)	22-28	20	319.7(2!)	0.248(2!)	0.814(2!)	9.51(2!)	0.090(2!)	18.8(2!)
Smith et al. 1983	gender (5M)	22-28	30	215(2!)	0.537(2!)	1.69(2!)	15.5(2!)	0.265(2!)	24.9(2!)
«	age (5M)	42-52	30	351(2!)	0.802(2!)	0.885(2!)	10.7(2!)	0.458(2!)	9.38(2!)
«	(5M)	68-76	30	273(2!)	0.271(2!)	1.53(2!)	9.41(2!)	0.398(2!)	69.2(2!)
«	(5F)	20-35	30	251(2!)	0.248(2!)	0.937(2!)	15.5(2!)	0.400(2!)	64.6(2!)
„	(5F)	40-58	30	314(2!)	0.247(2!)	2.24(2!)	12.2(2!)	0.300(2!)	69.8(2 !)
Bittencourt et al. 1979	soft gelatin capsule (6M)	20-30	20	-	0.215(2)	0.815(2)	8.30(2)	-	-
Fucella 1979	soft gelatin capsule (4)		20	329(1!)	0.318(2!)	0.573(2!)	7.27(2!)	0.003(2!)	12.4(2!)
«	hard gelatin capsule (4)		20	222(1!)	0.525(2!)	0.924(2!)	8,27(2!)	0.210(2!)	10.6(2!)
Greenblatt et al. 1989	(triazolam, flurazepam) (6M/7F)	27±1	15	259(2!)	0,343(2!)	1,67(2!)	10,6(2!)	0,662(2!)	35,2(2!)
	Mean ± SD			**280 ±58**	**0.365 ±0,138**	**1.50 ±0.78**	**10.1 ±2.2**	**0.247 ±0,228**	**40.6 ±21.2**
	Number of trials			13	14	14	14	13	13
	Number of observations			124	130	130	130	124	124

Continuation of Table 67: 20 mg Temazepam (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	T_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Indalo, Kokwaro 1995	male (1M)	402(3)	1.5(3)	2518(3!)	75			
„	surgical (1M)	845(3)	0.5(3)	4385(3!)	68			
„	patients (1M)	743(3)	0.5(3)	2623(3!)	55			
„	(1M)	966(3)	0.5(3)	4586(3!)	82			
„	(1M)	491(3)	1.0(3)	2468(3!)	80.5			
„	(1M)	813(3)	0.5(3)	2278(3!)	63			
„	(1M)	728(3)	0.5(3)	2513(3!)	66.5			
„	(1M)	931(3)	0.5(3)	3955(3!)	77.5			
„	(1M)	436(1)	1.5 (3)	3103(3!)	87			
Schwarz et al. 1979	suspension (24)	317(1)	2.0(2)	3960(1!)				
„	hard gelatine capsule (24)	260(1)	2.0(2)	3540(1!)				
Matilla et al. 1985	uncoated tablet (5M/7F)	726(2)	1.1(2)	5727 (2!)	50-85			
„	soft gelatine capsule (5M/7F)	935(2)	0.9(2)	5357(2!)	50-85			
Smith et al. 1983	gender (5M)	463(2)	1.7(2)	5680(2!)	79.9			
«	age (5M)	427(2)	3.1(2)	5367(2!)	79.2			
«	(5M)	363(2)	2.3(2)	3790(2!)	76.7			
«	(5F)	355(2)	2.2(2)	4070(2!)	60.4			
„	(5F)	431(2)	2.4(2)	5047(2!)	60.1			
Bittencourt et al. 1979	soft gelatin capsule (6M)	668(2)	0.75(2)	4970(2)				
Fucella 1979	soft gelatin capsule (4)	892(1)	0.83 (2)	3879(1)				
«	hard gelatin capsule (4)	668(1)	1.44(2)	3515(1)				
Greenblatt et al. 1989	(triazolam, flurazepam) (6M/7F)	420(2)	1.5(2)	4040(2!)	62±2			
	Mean	**544**	**1.6**	**4407**				
	±SD	**±233**	**±0.6**	**±942**				
	Number of trials	14	14	14				
	Number of observations	130	130	130				

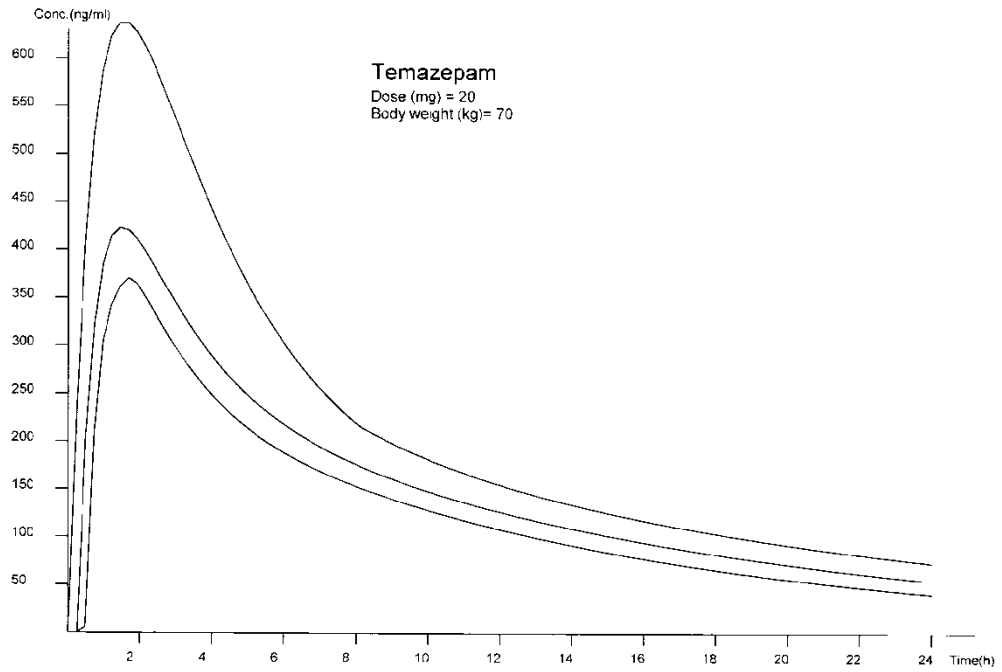


Figure 71: Plasma concentration-time curve of temazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	280	±	58	ng/mL	
Ka:	1.90	±	0.52	h^{-1}	
α:	0.46	±	0.15	h^{-1}	
β:	0.0686	±	0.0122	h^{-1}	
t_0:	0.247	±	0.228	h	
V%:	40.6	±	21.2	%	
					derived from time-course of plasma concentrations
C_{max}:	544	±	233 ng/mL		423 (370-638) ng/mL
t_{max}:	1.6	±	0.6 h		1.45 (1.20-1.68) h
AUC_{o-oo}:	4407	±	942 ng*h/mL		460 (3680-6644) ng*h/mL

Table 68: 1 mg Loprazolam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Bareggi et al. 1988	fasting + (after dinner) (8)	22-25	2	3,1(1!)	1,26(2!)	1,39(2!)	20,0(2!)	0,290(2!)	4,54(2!)
McInnes et al. 1985	At night (6)	22-37	1	3,17(1!)	1,58(2!)	1,65(2!)	18,1(2!)	0,330(2!)	4,70(2!)
Swift et al. 1985	young (5M/5F))	23-39	1	3,05(2!)	0,201(2!)	1,54(2!)	9,67(2!)	0,500(2!)	65,1(2!)
„	elderly (4M/5F))	67-83	1	3,43(2!)	0,478(2!)	1,10(2!)	13,5(2!)	0,160(2!)	42,4(2!)
„	Alter (5M/5F))	23-39	0,5	4,14(2!)	0,450 (2!)	1,31(2!)	8,94(2!)	0,340(2!)	74,4(20!)
„	Influence (5M/5F))	67-83	0,5	4,42(2!)	0,268(2!)	0,564(2!)	11,1(2!)	0240(2!)	65,1(2!)
„	of dose (5M/5F))	23-39	1	4,90(2!)	0,338(2!)	0,660(2!)	8,06(2!)	0,260(2!)	96,9(2!)
„	(5M/5F))	67-83	1	4,98(2!)	0,444(2!)	0,707(2!)	8,22(2!)	0,270(2!)	43,1(2!)
Stevens et al. 1983	healthy volunteers (8)		2				7,06±1,98(2)		
	Mean ±SD			**4,06 ±0,75**	**0,560 ±0,425**	**1,08 ±0,39**	**11,2 ±4,1**	**0,299 ±0,095**	**53,3 ±29,1**
	Number of trials			8	8	8	8	8	8
	Number of observations			73	73	39	73	73	73

Continuation of Table 68: 1 mg Loprazolam (absorption, distribution and elimination).

Evaluated studies	**Data from comparative single dose studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{o-oo} (ng_*h/mL)**	**G (kg)**	**B (%)**	**V_β/B (L)**	**V_β/G (L/kg)**
Bareggi et al. 1988	fasting +.(after dinner) (8)	4,4(1)	2,2 (2)	96,5(1!)	54,6			
McInnes et al. 1985	At night (6)	3,25(1)	3,0(2)	81,6(1!)	60,3-91,4			
Swift et al. 1985	young (5M/5F))	4,3(2)	2,4(2)	45,5(2!)	67,3±11,1			
„	elderly (4M/5F))	4,2(2)	2,4(2)	67,8(2!)	70,0±9,1			
„	Alter (5M/5F))	3,99(2)	2,0(2)	52,3(2!)	67,1±11,1			
„	Influence (5M/5F))	4,12(2)	2,0(2)	70,4(2!)	68,4±10,4			
„	of dose (5M/5F))	4,11(2)	2,0(2)	54,6(2!)	67,1±11,1			
„	(5M/5F))	4,75(2)	2,0(2)	58,3(2!)	68,4±11,4			
Stevens et al. 1983	healthy volunteers (8)	5,0(2)	2,5(2)	18-95				
	Mean	**4,30**	**2,24**	**61,4**				
	±SD	**±0,39**	**±0,29**	**±13,1**				
	Number of trials	9	9	8				
37	Number of observations	81	81	73				

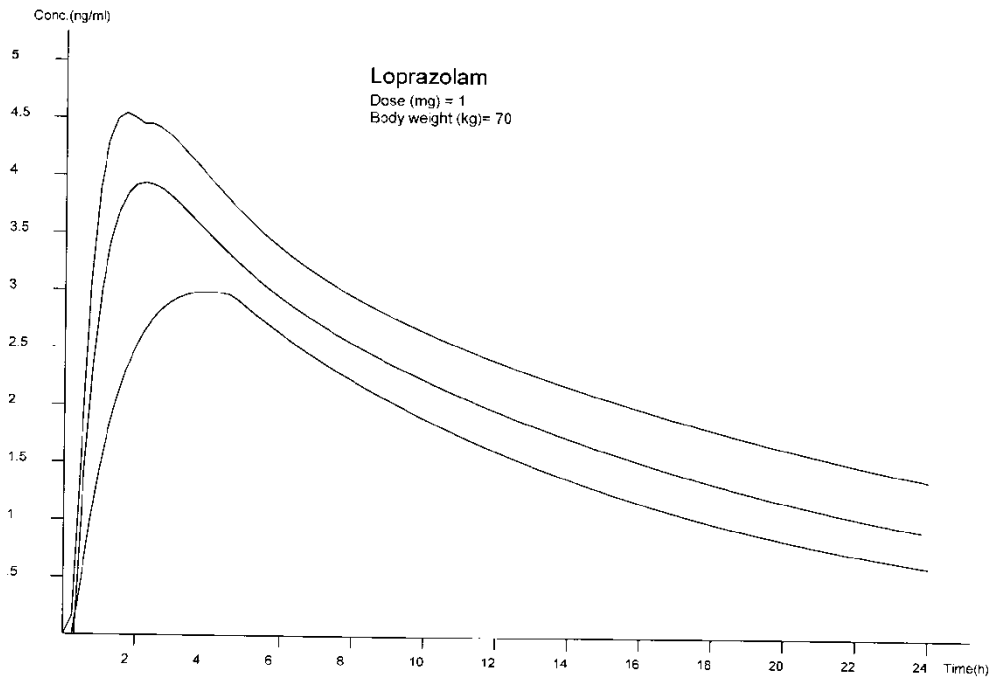


Figure 72: Plasma concentration-time curve of loprazolam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	4,06	±	0,75	ng/mL
Ka:	1,24	±	0,54	h^{-1}
α:	0,64	±	0,17	h^{-1}
β:	0,0619	±	0,0166	h^{-1}
t_0:	0,299	±	0,095	h
V%:	53,3	±	29,1	%

					derived from time-course of plasma concentrations
C_{max}:	4,30	±	0,39	ng/mL	3,93 (2,99-4,54) ng/mL
t_{max}:	2,24	±	0,29	h	2,10 (1,68-3,84) h
AUC_{o-oo}:	61,4	±	13,1	ng*h/mL	64,9 (47,2,2-91,8) ng*h/mL

7.2.1.3 Long-acting benzodiazepines

7.2.1.3.1 Nitrazepam

Application: Nitrazepam is one of the most widely used hypnotics in Western Europe. Since the elimination half-life is about 30 hours, the duration of action may extend into the next day even after a single dose of 5 mg (Borland & Nicholson 1975, Hindmarch & Clyde 1980). Holm et al. (1982) investigated the influence of age and food intake on the pharmacokinetics on nitrazepam in 8 young and 8 elderly volunteers after single-dose intake. Concomitant food intake had no apparent influence on the absorption rate or on the bioavailability and there was no statistically significant difference in nitrazepam pharmacokinetics between young and elderly subjects, whereas Jochemsen et al. (1983e) observed a prolongation of the half-life by 40%, but not an alteration of the clearance of total or unbound nitrazepam. The authors explain these findings by a larger volume of distribution. Yamazaki et al. (2007) achieved similar results comparing the kinetics of nitrazepam after overnight fasting and after light food intake. Only t_{max} was delayed about 1 hour in feed condition, whereas C_{max} and AUC were not affected.

Biotransformation: Nitrazepam is mainly transformed by hepatic nitroreduction leading to 7-aminonitrazepam (Kangas & Breimer, 1981; Greenblatt et al. 1985). Acetylation of the amino derivative forms 7-acetamidonitrazepam. After a single oral dose of 5 mg nitrazepam, only about 1% of the unchanged drug was detected in the urine. A large interindividual variation of total excreted metabolites was observed (17-99% of the dose during 7 days). The conjugated metabolites of this amount made up 57% (Kangas 1979).

Interaction: Mild to moderate renal insufficiency had no influence on pharmacokinetic parameters after correction for individual values (Ochs et al. 1992). After pretreatment with rifampin, a potent inducer of the liver microsomal enzyme system, for seven days, the total body clearance of nitrazepam increased by 83% (that of antipyrine by 87%), the mean elimination half-life was shortened from 32.7 to 19.9 hr (Brockmeyer et al. 1990). Probenecid decreases the tubularsecretion of many drugs and its metabolites and is supposed to have an inhibition effect on phase II hepatic metabolism. Brockmeyer et al. (1990) observed a 25% reduction of total body clearance of nitrazepam (antipyrine 22%) after coadministration of probenecid. In both drugs, nitrazepam and antipyrine, the extent of the influence of rifampin and probenecid was similar, suggesting that the same isoenzyme of cytochrome P450 might be involved in the metabolism of these drugs.

Interaction of erythromycin, a strong inhibitor of CYP3A4, and nitrazepam was observed by Luurila et al. (1995) after pretreatment of 10 volunteers with erythromycin (500 mg x 3) or placebo for 6 days. The area under the nitrazepam plasma concentration-time curve was reduced by 25% and the peak concentration by 30%. The authors concluded that the interaction between erythromycin and nitrazepam is of minor clinical significance.

Evaluation of studies: Table 69 demonstrates that after administration of 5 or 10 mg nitrazepam, a rapid absorption takes place with a peak level at 1.22 ± 0.44 hr. Cp0 and t½β values show a low scattering of about 10%. That may be caused by comparatively slight individual differences in the hepatic biotransformation rate including first-pass metabolism. Peak levels deviate much more than Cp0 values caused by different participation of the distribution process. Calculation of V% results in a high standard deviation of 34.5%. This value is too high to be compatible with the scattering of C_{max}. Thus it was taken a value of 20%.

Table 69: 10 mg Nitrazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Breimer et al. 1977	(10M)		5	-	-	-	30(3)	-	-
Rieder et al. 1973. Graß 1989	(6M)	24.7±4.1	10	62.2(2)	0.495(2)	0.900(2)	26.7(2)	0.190(2)	17.0(2)
Jochemsen et al. 1983e	+(elderly)+(liver cirrhosis) intravenous (8M/1F)	22-49	5.24	-	-	-	25.5(2)	-	-
Jochemsen et al. 1982	luteal phase (6F)	19-28	5	53.9(2!)	0.241(2!)	0.559(2!)	30.5(2)	0.025(2!)	17.3(2!)
„	follicular phase (6F)	19-28	5	53.6(2!)	0.372(2!)	0.643(2!)	28.0(2!)	0.617(2!)	36.9(2!)
Abernethy et al. 1986	+(obesity effects) (1M)	32	10	94.3(2!)	0.197(2!)	0.298(2!)	17.7(2!)	0.489(2!)	9.08(2!)
“	and nonsmokers (7M/7F)	19-42	10	65.7(2)	-	-	23.9(2)	-	-
Ochs et al. 1992	+ (renal insufficiency) (3M/6F)	30-87	5	50.3(2!)	0.301(2!)	2.21(2!)	20.3(2!)	0.054(2!)	96.5(2!)
De Boer et al. 1978	bioavailability (1M)	20-23	5	62.9(1!)	0.666(2!)	1.74(2!)	28.4(2!)	0.167(2!)	39.9(2!)
“	studies (1M)	20-23	5	53.2(1!)	0.077(2!)	0.644(2!)	28.1(2!)	0.192(2!)	65.1(2!)
“	Mogadon® (7M)	20-23	5	-	-	-	28(2)	-	-
“	Sameko® (7M)	20-23	5	-	-	-	27(2)	-	-
Brockmeyer et al.1990	before rifampin (8)	21-33	5	-	0.220(2)	-	32.7(2)	-	-
	before rifampin/probenecid (8)	21-33	5	-	0.296(2)	-	29.8(2)	-	-
	before probenecid (8)	21-33	5	-	0.268(2)	-	28.9(2)	-	-
	Mean ± SD			**59.2 ±6.4**	**0.307 ±0.100**	**1.17 ±0.72**	**27.2 ±3.4**	**0.211 ±0.225**	**47 ±34.5**
	Number of trials			8	10	7	15	7	7
	Number of observations			44	54	30	101	30	30

Continuation of Table 69: 10 mg Nitrazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Breimer et al. 1977	(10M)	82.7(2)	1.35(2)	-	78±8.4			-
Rieder et al. 1973. Graß 1989	(6M)	76.2(2)	1.59(2)	2352(2!)	63.0±5-3	78±16		
Jochemsen et al. 1983e	+(elderly)+(liver cirrhosis) intravenous (8M/1F)	-	-		73±7			1.89(3)
Jochemsen et al. 1982	luteal phase (6F)	119.6(2)	0.66(2)	2420(2!)	61±3.5			
„	follicular phase (6F)	112.8(2)	1.2(2)	2205(2!)	61±3.5			
Abernethy et al. 1986	+(obesity effects) (1M)	195(2)	1(2)	2429(2!)	70.5			
„	(7M/7F)	107.1(3)	1.59(2)	-	63±3		137	2.22
Ochs et al. 1992	+ (renal insufficiency) (3M/6F)	47.4(2!)	2.0(2!)	1448(2!)	64±4		228	
De Boer et al. 1978	bioavailability (1M)	91.7(1!)	1.75(2!)	2672(1!)	64-86			
“	studies (1M)	77.5(1!)	0.75(2!)	2154(1!)	64-86			
“	Mogadon® (7M)	-	1.47(2)	2194(1)	64-86			
“	Sameko® (7M)	-	0.63(2)	2230(1)	64-86			
		158(2)	0.75(2)	-	72.4±6.8		118.7	
		163(2)	0.88(2)	-	72.4±6.8		121.6	
		168(2)	0.76(2)	-	72.4±6.8		94.3	
	Mean ± SD	**114.2 ±40.4**	**1-22 ±0.44**	**2089 ±384**		**78 ±16**	**141.4 ±44.7**	**2.09 ±0.12**
	Number of trials	12	14	9			5	2
	Number of observations	78	92	44			47	23

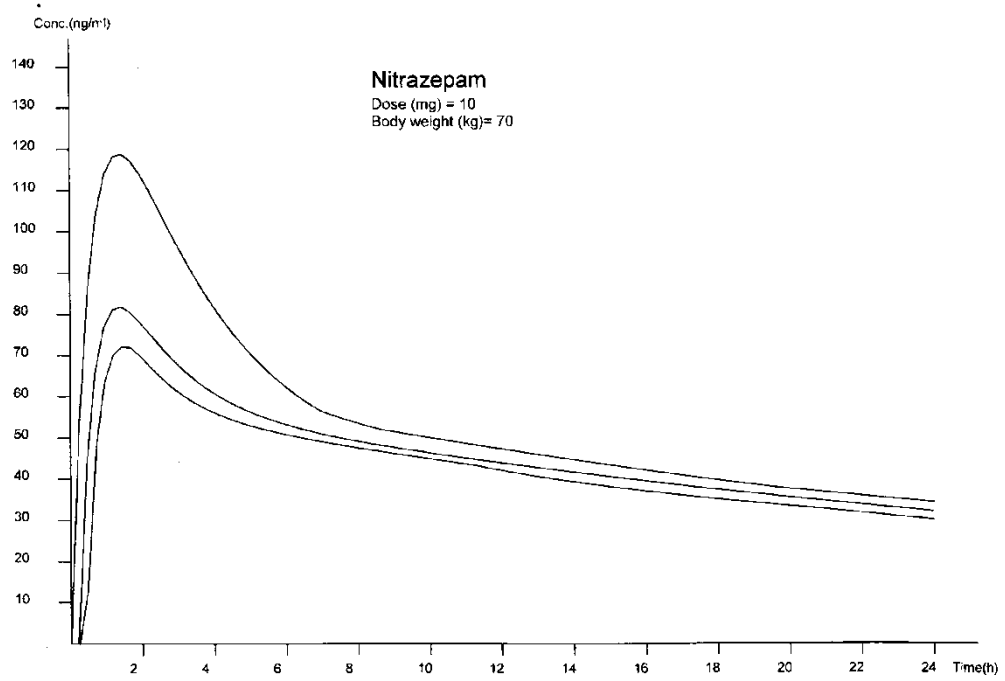


Figure 73: Plasma concentration-time curve of nitrazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	59.1	±	6.4	ng/mL
Ka:	2.26	±	0.56	h^{-1}
α:	0.592	±	0.23	h^{-1}
β:	0.0255	±	0.0028	h^{-1}
t_0:	0.211	±	0.211	h
V%:	47.0	±	20.0	%
B:	78	±	16	%

				derived from time-course of plasma concentrations
C_{max}:	114.2	±	40.4 ng/mL	81.7 (72.1-118.7) ng/mL
t_{max}:	1.22	±	0.44 h	1.41 (1.41-1.44) h
AUC_{o-oo} :	2089	±	384 ng*h/mL	2371 (2091-2830) ng*h/mL
V_β/B	:141.4	±	44.7 L	178 ± 20.6 L
V_β/G	:2.09	±	0.16L/kg	1.91 ±0.23 L/kg

7.2.1.3.2 Flunitrazepam

Application: Greenblatt et al. (1981) define the intermediate to short-acting benzodiazepines by half-lives ranging from 5 to 24 hr. Flunitrazepam is effective in low doses of 0.5 to 2 mg as hypnotic and is used as an intravenous anesthetic agent too. Further ways of incorporation are sublingual (Hüttel et al. (1986) and snorting administration ((Bond et al. 1994). Flunitrazepam is considered to be about 10 times as potent as diazepam (Stovner et al. 1973), caused by high affinity to the GABA receptors of the brain. As other benzodiazepines, beside the sedative/hypnotic effect flunitrazepam has anxiolytic, anticonvulsant, and muscle relaxant properties. A single dose of 0.5 mg is supposed to have effective hypnotic activity free from residual effects. By this manner the long distribution phase is used for the sleep inducing influence (Jochemsen & Breimer 1984). The pharmacokinetics after oral intake is influenced by the circumstances of the administration, fasting or after a standard diner. Absorption half-life and time of peak level, but not elimination was prolonged (Bareggi et al. (1988). Flunitrazepam has a potential for abuse, alone or in combination with alcohol or other drugs.

Biotransformation: Nitro-reduction and demethylation are the primary degradation steps of flunitrazepam yielding 7-amino-flunitrazepam and N-desmethyl-flunitrazepam. 68 and 22% of the administered dose were recovered as those metabolites (Wendt 1976). Only N-desmethyl-flunitrazepam appeared to be pharmacologically active (Cano 1983). Further metabolism steps are glucuronidation of 7-amino-flunitrazepam, which represents the main excretion product in urine, nitro-reduction of N-desmethyl-flunitrazepam to 7-amino-N-desmethyl-flunitrazepam, and hydroxylation to 3-hydroxy derivatives, which are glucuronidated too. In plasma in addition to the parent drug, the metabolites N-desmethyl-flunitrazepam, 7-amino-flunitrazepam, and in lower concentration 7-amino-N-desmethyl-flunitrazepam are detected. But above all, the unaltered drug is responsible for the sleep inducing effect (Wendt 1976). In a study of Wickstrøm et al. (1980), flunitrazepam was administered once daily for 28 consecutive days. There was no evidence of systematic change in elimination rate during the study. Only slight accumulation of flunitrazepam and its metabolites in plasma was observed (Wickstrøm et al. 1980).

Interaction: Kanto et al. (1981) found no statistically significant influence of age on the kinetics of flunitrazepam, but the sedative effect was clearly increased in the group over 60 years. Drouet-Coassolo et al. (1990) compared three groups of male subjects, 6 healthy volunteers (22-43 yr), 6 patients with acute viral hepatitis (21-24 yr) and 6 patients with alcoholic cirrhosis (48-53 yr). They observed no relevant prolongation of the elimination half-

life or alteration of other pharmacokinetic parameters of flunitrazepam. Only the plasma levels of N-desmethyl- flunitrazepam were statistically significant lower in the hepatic group than in the other subjects. A pharmacological competition between flunitrazepam and diazepam caused by affecting the same receptor site was demonstrated by Richard et al. (1981). There was a blocking action or a reduction in the pharmacological action of flunitrazepam by the previous administration of a clinical dose of diazepam. Drug-alcohol interaction on psychomotor skills was shown, when 2 mg flunitrazepam was given in the evening at 23:00 h and 0.5 g/kg body weight alcohol the following morning. Statistically significant impairments of standing steadiness, tracking, and relative skills were observed (Seppälä et al. /1983). Combination with erythromycin led to increases of C_{max}, $t_{½}\beta$, and AUC of flunitrazepam, but these alterations seemed to be of limited clinical significance (Luurilla et al. 1996).

Evaluation of studies: Pharmacokinetic studies have been performed with 2 or 1 mg doses. Even after normalization to a dose of 1 mg and a body weight of 70 kg, the values Cp0, C_{max}, and AUC show large deviations, which may be caused by different activity of oxidizing liver enzymes.

7.2.1.3.3 Flurazepam

Application: The benzodiazepine derivative flurazepam is widely used for short-term treatment of patients with insomnia. The relative contribution of the parent substance and the numerous metabolites to the clinical effects remain uncertain. The rapid absorption of flurazepam and the fast formation of active metabolites may be result in the falling asleep effect, whereas the long-time sedative influence can be attributed to the the metabolite desalkylflurazepam. The residual effects after nighttime administration of flurazepam, such as sleepiness and impaired psychomotor and cognitive functions are caused by the very slow elimination of desalkylflurazepam.

Biotransformation: Flurazepam is extensively metabolized, predominantly by oxidative pathways to form active metabolites. First steps are desethylation of the parent drug to desethyl- and didesethyl-flurazepam. Oxidative desamination leads to flurazepamaldehyde, which is dehydrogenated to the important metabolite hydroxyethylflurazepam. Finally a very stable product is formed, desalkylflurazepam, a fluorine substituted desmethyldiazepam. Detectable in blood predominantly are hydroxyethylflurazepam and desalkylflurazepam, whereas into the urine above all glucuronidated metabolites are excreted. The main product of those is hydroxyethylflurazepam glucuronide (Aderjan et al. 1980). Because of the long

elimination half-life of desalkylflurazepam (about 3 days), an accumulation occurs during chronic administration of flurazepam. That results in daytime carry-over effects of flurazepam: somnolence, lethargy or drowsiness.

Interaction: The influence of gender and age on the kinetics and clinical effect in healthy subjects of 19 to 85 years of age was studied by Greenblatt et al. (1981). The elimination half-life of desalkylflurazepam was prolonged in elderly men by a factor of about 2, in elderly women by 50%. But there was no evidence of increased sensitivity to flurazepam in the elderly. During coadministration of cimetidine, an inhibitor of oxidative hepatic metabolism, the average elimination half-life of desalkylflurazepam was prolonged from 94 to 141 hours (Greenblatt et al. 1984a).

Evaluation of studies: Flurazepam is absorbed very fast with a mean absorption half-life of about 16 minutes and time of peak level at less than 1 hour (Table 71). But the ranges of the peak concentrations and of the elimination half-lives are large. This may be caused by a different extent of the first-pass metabolism in the evaluated studies. More important for the pharmacological activity are the contributions of hydroxyethylflurazepam and desalkylflurazepam, which according to results of animal studies, are more active than the parent drug (Randall et al., 1973) The course of the hydroxyethylflurazepam concentration-time curve is very different in evaluated studies. For describing the course as conformably as possible, low concentrations at time above 8 hours after drug intake in the studies of Cooper et al. (1984) and Salama et al. (1988) were not used for calculations of the pharmacokinetic parameters, which are analogues to those of the parent drug. But a quite different course is that of desalkylflurazepam with a peak level at about 10 hours after drug administration and an average elimination half-life of 78 hours.

Table 70: 1 mg Flunitrazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Boxenbaum et al. 1978	single (1M)	23	2	3,9 (2)	0.0090(3)	1.76(3)	9,45(3)	0,125(3)	-
"	and (1M)	23	2	2,7 (2)	0,954(3)	5.58(3)	24,6(3)	0,077(3)	-
"	multiple (1M)	21	2	4,4 (2)	0.607(3)	0.478(3)	10,1(3)	0,151(3)	-
„	doses (1M)	22	2	3,8 (2)	0.305(3)	1.85(3)	12,8(3)	0,225(3)	
„	to healthy (1M)	20	2	3,1 (3)	0.0311(3)	2.22(3)	15,0(3)	0,41(3)	42(3)
„	human subjects (1M)	20	2	3,0 (3)	0.324(3)	1.49(3)	12,2(3)	0,198(3)	30(3)
„	(1M)	22	2	2,4 (3)	1.22(3)	1.32(3)	15,5(3)	0,432(3)	8(3)
„	(1M)	21	2	2,1 (3)	0.154(3)	2.04(3)	17,8(3)	0,446(3)	25(3)
Clarke et al. 1980	subj. Effects (5M)	35	2	-	-	-	12.2(2)	-	-
Wickstrøm et al. 1992	+(prolonged administration) (6M/2F)	36±21	2	2,9 (2)	0,745(2)	1.22(2)	15,65(2)	0,244 (2)	18,2(2)
Drouet-Coassolo	+(liver) (1M)	22	2	2,50(2)	-	-	16,2(3)	-	-
"	(desease)(1M)	24	2	3.08(2)	-	-	21.0(3)	-	-
"	(patients) (1M)	43	2	1.99(2)	-	-	28.1(3)	-	-
"	(1M)	36	2	1.97(2)	-	-	28.0(3)		-
"	(1M)	27	2	2.77(3!)	0.749(3!)	1.59(3!)	17.3(3!)	0.838(3!)	16.4(3!)
"	(1M)	40	2	3.18(2)	-	-	21.1(3)	-	-
Bareggi et al. 1988	+(after diner) (8)	22-25	2	3.16(1!)	0.408(2!)	0,753(2!)	25,0(2!)	0,228(2!)	21,7(2!)
Seppälä et al. 1993	+(midazolam) (1M/4F)	66-74	1	2,3(1!)	0.159(2!)	0.89(2)	10.6(2)	0,181(2!)	21,2(2!)
Grahnen et al. 1991	sedation effect (11M/9F)		1	4,57(1!)	0.559(2!)	1.54(2!)	26.3(2!)	0.100(2!)	18.8(2!)
„	2 brands (11M/9F)		1	4.29(1!)	0.559(2!)	1.99(2!)	23.0(2!)	0.102(2!)	24.8(2!)
Gafni et al. 2003	CYP2C19 activity (7M/7F)	18-65	1	2.65(2!)	0.283(2!)	1.24(2!)	15.2(2!)	0.189(2!)	17.6(2!)
Cano et al. 1977	bioavailability			-	-	-	-	-	-
	Mean ± SD			**3.32 ±0.84**	**0.484 ±0.215**	**1.53 ±0.68**	**19.9 ±5.7**	**0.178 ±0.120**	**20.9 ±4.6**
	Number of trials			8	8	8	9	8	8
	Number of observations			89	84	84	94	84	84

Continuation of Table 70: 1 mg Flunitrazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Boxenbaum et al. 1978	single (1M)				60.0			3.70
"	and (1M)				61.8			5.51
"	multiple (1M)				83.6			3.44
„	doses (1M)				70.9			3.87
„	to healthy (1M)	6,7 (3)	1,0 (3)	73,9(2)	69.1			4.25
„	human subjects (1M)	6,0 (3)	1,4 (3)	62,9(2)	74.1			4.08
„	(1M)	4,1 (3)	3,0 (3)	62,9(2)	63.6			5.35
„	(1M)	8,5 (3)	1,25 (3)	70,4(2)	59.1			5.31
Clarke et al. 1980	subj. Effects (5M)	7,4 (2)	1,0 (2)		66			
Wickstrøm et al. 1992	+(prolonged administration) (6M/2F)			68,7(2)	71.4±8.1			
Drouet-Coassolo	+(liver) (1M)	5,7(3)	0,5(3)	48,3(3)	58			6,9(3)
"	(desease)(1M)	5,3(3)	1,5(3)	85,7(3)	65			5,0(3)
"	(patients) (1M)	5,8(3)	0,5(3)	65,8(3)	57			8,8(3)
"	(1M)	4,6(3)	4,0(3)	66,5(3)	59			8,6(3)
"	(1M)	6,8(3)	2,0(3)	82,6(3!)	70			5,4(3)
"	(1M)	5,5(3)	1,8(3)	77,6(3)	56			5,6(3)
Bareggi et al. 1988	(8m) fastg.	5,4(2!)	1,0 (2!)	99,3(1!)				
Seppälä et al. 1993	+(midazolam) (1M/4F)	4,1(1!)	0,6 (2)	(14,9)				
Grahnen et al. 1991	sedation effect (11M/9F)	12.6(1!)	1.9(2!)	197.8(1!)				4,13 (1)
„	2 brands (11M/9F)	10.9(1!)	1.9(2!)	165.0(1!)				6,00 (1)
Gafni et al. 2003	CYP2C19 activity (7M/7F)	8.7(2!)	1.33(2!)	73.3(2!)	73±17			
Cano et al. 1977	bioavailability					80		
	Mean ±SD	**8.3 ±2.7**	**1.57 ±0.59**	**110.4 ±52.7**		**80**		**5.24 ±1.35**
	Number of trials	8	8	7				4
	Number of observations	82	82	80				54

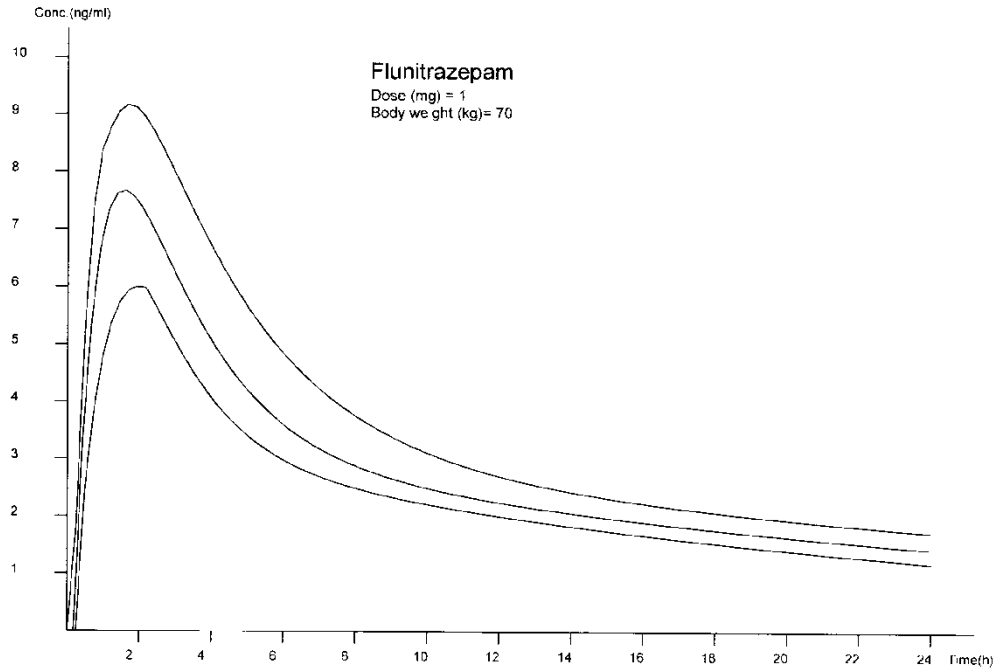


Figure 74: Plasma concentration-time curve of flunitrazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	3.32	±	0.84	ng/mL
Ka:	1.43	±	0.44	h^{-1}
α:	0.453	±	0.139	h^{-1}
β:	0.0348	±	0.0077	h^{-1}
t_0:	0.143	±	0.139	h
V%:	20.9	±	4.6	%
B:	80%			

				derived from time-course plasma concentration
C_{max}:	8.3	±	2.7 ng/mL	7.7 (6.0-9.2) ng/mL
t_{max}:	1.57	±	0.59 h	1.68 (1.68-1.92) h
AUC_{o-oo}:	110.4	±	52.7 ng*h/mL	111.9 (86.6-151.9) ng*h/mL
V_β/G	:5.24	±	1.35 L/kg	3.53±1.20 L/kg

Table 71: 30 mg Flurazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Miller et al. 1988	receptor binding (18M)	19-43	30	3.86(2!)	0.253(2!)	1.33(2!)	1.14(2!)	0.314(2!)	98.4(2!)
Selinger et al. 1989	analytical method (9M)	18-45	30	2.97(1!)	0.181(2!)	0.261(2!)	1.52(2!)	0.407(2!)	82.0(2!)
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	19-38	30	10.00(2!)	0.181(2!)	0.717(2!)	3.09(2!)	0.179(2!)	87.2(2!)
«	Dalmane® (10M/10F)	19-38	30	7.10(2!)	0.314(2!)	0.355(2!)	4.19(2!)	0.294(2!)	21.2(2!)
Salama et al. 1988	treatment A (28M)		60	3.48(1!)	0.346(2!)	1.47(2!)	1.75(2!)	0.086(2!)	86.1(2!)
«	treatment B (28M)		60	3.25(1!)	0.268(2!)	1.49(2!)	2.17(2!)	0.104(2!)	84.8(2!)
	Mean			**5.74**	**0.271**	**1.06**	**2.35**	**0.196**	**76.9**
	± SD			**±2.70**	**±0.060**	**±0.49**	**±1.00**	**±0.108**	**±25.0**
	Number of trials			6	6	6	6	6	6
	Number of observations			123	123	123	123	123	123

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Miller et al. 1988	receptor binding (18M)	2.52(2)	1.0(2)	5.03(2!)	73.5			
Selinger et al. 1989	analytical method (9M)	2.10(1)	1.0(2)	5.82(1!)	>60			
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	8.86(2!)	1.0(2!)	43.2(2!)	62.05			
«	Dalmane® (10M/10F)	6.28(2!)	1.0(2!)	41.4(2!)	62.05			
Salama et al. 1988	treatment A (28M)	2.37(1!)	1.0(2!)	7.95(1!)				
«	treatment B (28M)	2.80(1!)	0.75(2!)	8.95(1!)				
	Mean	**4.75**	**0.94**	**22.6**				
	± SD	**±2.66**	**±0.11**	**±17.6**				
	Number of trials	6	6	6				
	Number of observations	123	123	123				

Table 72: N-1-Hydroxyethylflurazepam from 30 mg Flurazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Miller et al. 1988	receptor binding (18M)	19-43	30	35.2(2!)	0.425(2!)	1.33(2!)	1.27(2!)	0.266(2!)	82.0(2!)
Greenblatt et al. 1989	+ (extended-release) (9M/4F)	31±2	15	(50.5)	0.428(2!)	0.425(2!)	0.816(2!)	0.287(2!)	18.5(2!)
Selinger et al. 1989	analytical method (9M)	18-45	30	31.7(1!)	0.317(2!)	0.468(2!)	1.59(2!)	0.416(2!)	84.8(2!)
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	19-38	30	13.0(2!)	0.293(2!)	0.660(2!)	2.67(2!)	0.182(2!)	46.5(2!)
«	Dalmane® (10M/10F)	19-38	30	15.9(2!)	0.315(2!)	0.603(2!)	2.26(2!)	0.296(2!)	74.7(2!)
Salama et al. 1988	treatment A (28M)		60	20.3(1!)	0.375(2!)	1.25(2!)	2.42(2!)	0.105(2!)	86.8(2!)
«	treatment B (28M)		60	19.0(1!)	0. 439(2!)	0.924(2!)	2.55(2!)	0.079(2!)	65.1(2!)
	Mean			**21.04**	**0.376**	**0.881**	**2.10**	**0.198**	**67.3**
	± SD			**±6.17**	**±0.056**	**±0.324**	**±0.62**	**±0.103**	**±20.7**
	Number of trials			6	7	7	7	7	7
	Number of observations			123	136	136	136	136	136

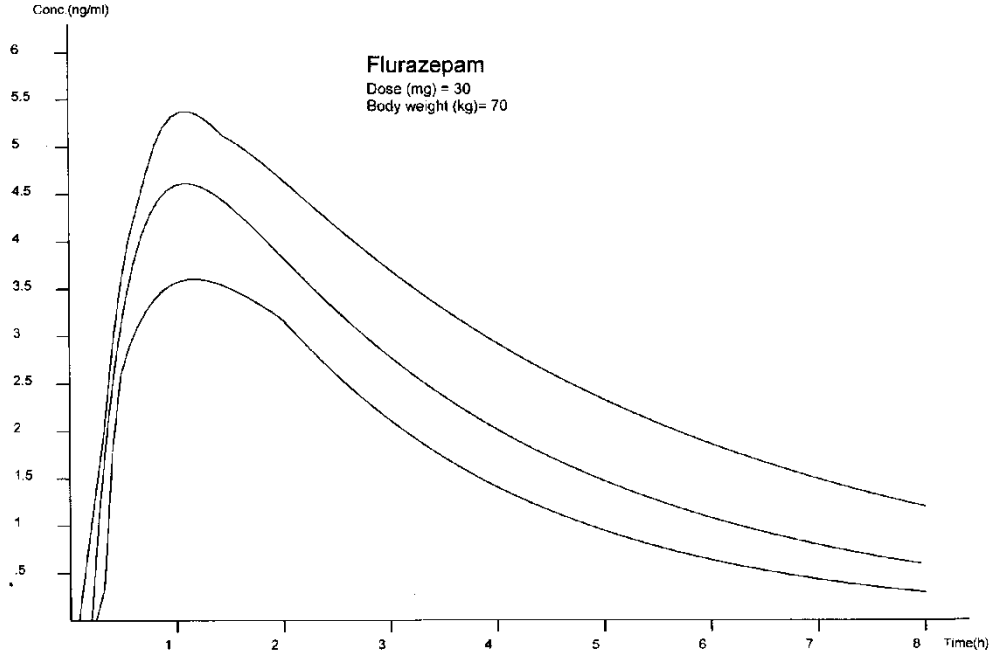
Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Miller et al. 1988	receptor binding (18M)	13.3(2)	1.0(2)	41.3(2!)	73.5			
Greenblatt et al. 1989	+ (extended-release) (9M/4F)	14.7(2)	1.0(2)	32.7(2!)	70±4			
Selinger et al. 1989	analytical method (9M)	17.5(1)	1.0(2)	56.7(1!)	>60			
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	13.0(2!)	1.0(2!)	52.7(2!)	62.05			
«	Dalmane® (10M/10F)	11.1(2!)	1.0(2!)	46.7(2!)	62.05			
Salama et al. 1988	treatment A (28M)	14.2(1!)	1.0(2!)	63.8(1!)				
«	treatment B (28M)	14.2(1!)	1.0(2!)	64.9(1!)				
	Mean	**13.4**	**1.0**	**50.4**				
	± SD	**±1.5**	**±0.0**	**±10.6**				
	Number of trials	7	7	7				
	Number of observations	136	136	136				

Table 73: Desalkyl-flurazepam from 30 mg Flurazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Miller et al. 1988	receptor binding (18M)	19-43	30	24.9(2!)	1.64(2!)	1.76(2!)	60.8(2!)	0.029(2!)	50.0(2!)
Selinger et al. 1989	analytical method (9M)	18-45	30	32.3(1!)	3.24(2!)	2.11(2!)	69.3(2)	0.059(2!)	96.9(2!)
Greenblatt et al. 1989	+(temazepam + triazolam) (9M/4F)	31±2	15	26.7(2!)	0.592(2)	1.58	-	0.109	99.2(2)
Greenblatt et al. 1981	young and (elderly (1F)	20	15	25.4(1!)	0.536(2)	1.20	48.1(2)	0.019	96.9(2)
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	19-38	30	23.5(2!)	1.30(2!)	1.22(2!)	82.5(2!)	0.028(2!)	75.0(2!)
«	Dalmane® (10M/10F)	19-38	30	20.3(2!)	1.42(2!)	1.81(2!)	84.5(2!)	0.037(2!)	73.5(2!)
Salama et al. 1988	treatment A (28M)		60	25.7(1!)	3.24(2!)	1.20(2!)	78.8(2!)	0.029(2!)	99.6(2!)
«	treatment B (28M)		60	24.0(1!)	2.65(2!)	1.09(2!)	82.5(2!)	0.017(2!)	99.2(2!)
Greenblatt et al. 1984a	+(cimetidine) (1M)		30	-	-	-	41.0	-	-
“	+(oxazepam + lorazepam) (6M)		30	-	-	-	94.0	-	-
	Mean ± SD			**24.3 ±2.7**	**2.09 ±0.92**	**1.44 ±0.33**	**78.1 ±9.4**	**0.037 ±0.025**	**84.9 ±17.7**
	Number of trials			8	8	8	9	8	8
	Number of observations			137	137	137	131	137	137

Continuation of Table 73: Desalkyl-flurazepam from 30 mg Flurazepam (absorption, distribution and elimination).

Data from comparative single dose studies	**Evaluated studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{o-oo} (ng_*h/mL)**	**G (kg)**	**B (%)**	**V_β/B (L)**	**V_β/G (L/kg)**
Miller et al. 1988	receptor binding (18M)	19.2(2)	6.0(2)	2112(2!)	73.5			
Selinger et al. 1989	analytical method (9M)	22.3(1)	8.0(2)	3068(1!)	>60			
Greenblatt et al. 1989	+(temazepam + triazolam) (9M/4F)	27.6(2!)	8.0(2)	-	70±4			
Greenblatt et al. 1981	young and (elderly (1F)	22.9(1)	12.0(2)	1729(1)				
Cooper et al. 1984	2 formulations Som-pam® (10M/10F)	18.7(2!)	7.0(2!)	2733(2!)	62.05			
«	Dalmane® (10M/10F)	16.9(2!)	7.0(2!)	2432(2!)	62.05			
Salama et al. 1988	treatment A (28M)	20.0(1!)	12(2!)	2800(1!)				
«	treatment B (28M)	19.5(1!)	12(2!)	2756(1!)				
Greenblatt et al. 1984a	+(cimetidine) (1M)	39.,0(1!)	2.0(2!)	1553(1!)				
“	+(oxazepam + lorazepam) (6M)	31,2(1!)	27.5(2!)	5450(1!)				
	Mean ± SD	**±**	**±**	**±**				
	Number of trials	10	10	9				
	Number of observations	144	144	131				

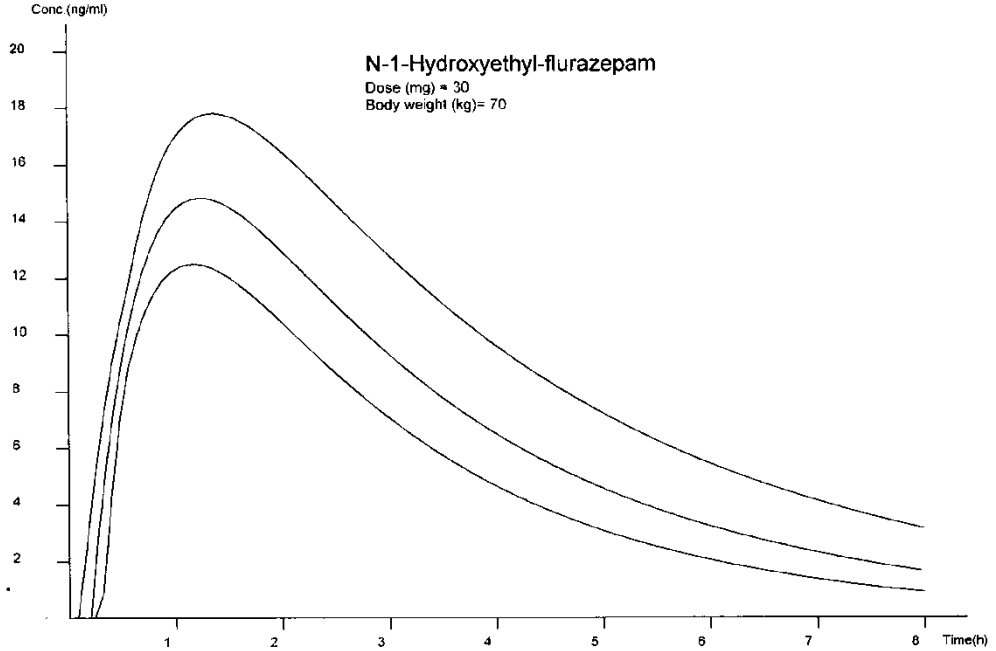


Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	5.74	±	2.66	ng/mL
Ka:	2.56	±	0.47	h^{-1}
α:	0.654	±	0.207	h^{-1}
β:	0.295	±	0.088	h^{-1}
t_0:	0.196	±	0.108	h
V%:	76.9	±	25.0	%
B:	5%			

				derived from time-course of plasma concentration
C_{max}:	4.75	±	2.66 ng/mL	4.61 (3.60-5.34) ng/mL
t_{max}:	0.94	±	0.11 h	1.10 (0.96-1.20) h
AUC_{o-oo}:	22.6	±	17.6 ng*h/mL	19.1 (13.3-29.0) ng*h/mL

Figure 75: Plasma concentration-time curve of flurazepam after oral administration.



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	21.04	±	6.17	ng/mL	
Ka:	1.84	±	0.24	h^{-1}	
α:	0.787	±	0.306	h^{-1}	
β:	0.3301	±	0.0753	h^{-1}	
t_0:	0.198	±	0.103	h	
V%:	67.3	±	20.7	%	
B:	100%				

				derived from time-course of plasma concentration
C_{max}:	13.4	±	1.5 ng/mL	14.8 (12.5-17.8) ng/mL
t_{max}:	1.0	±	0.0 h	1.24 (1.20-1.36) h
AUC_{o-oo}:	50.4	±	10.6 ng*h/mL	59.7 (43.7-87.6) ng*h/mL

Figure 76: Plasma concentration-time curve of N-1-hydroxyethyl-flurazepam after oral administration of 30 mg flurazepam.

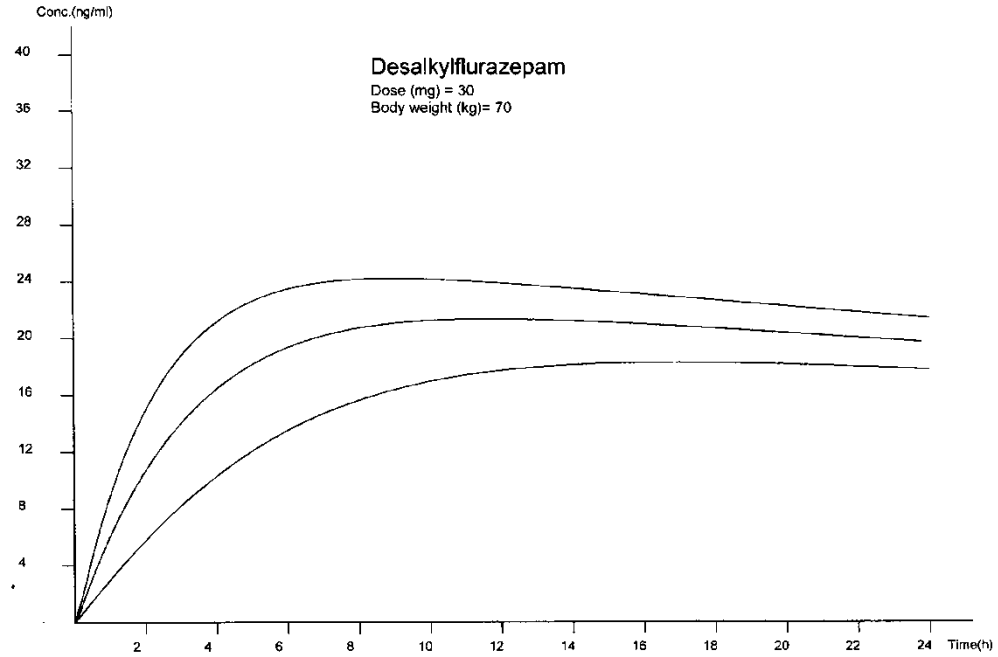


Figure 77: Plasma concentration-time curve of desalkylflurazepam after oral administration of 30 mg flurazepam.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	24.3	±	2.7	ng/mL
Ka:	0.332	±	0.102	h^{-1}
α:	0.481	±	0.00096	h^{-1}
β:	0.00888	±	0.088	h^{-1}
t_0:	0.037	±	0.025	h
V%:	84.9	±	17.7	%

				derived from time-course of plasma concentrations
C_{max}:	20.4	±	3.8 ng/mL	21.3 (18.2-24.2) ng/mL
t_{max}:	9.8	±	4.5 h	11.7 (8.9-16.8) h
AUC_{o-oo}:	2655	±	584ng*h/mL	2486 (2054-2611) ng*h/mL

7.2.2 Benzodiazepine related hypnotics/sedatives

The similarity of zopiclone, zolpidem, and zaleplon is not based on conformity in the chemical structure, but in pharmacological activity at the GABA receptor complex, yet they appear to have more selectivity for certain subunits of GABA receptor. The clinical profile is more efficient with fewer side-effects (Drover 2004). Common is to the three active agents that they contain bicyclic aromatic nitrogenous ring systems: zopiclone a pyrrolo-pyrazin, zolpidem an imidazo-pyridine, and zaleplon a pyrazolo-pyrimidine-ring. In addition several substituents are present. The complexity of the single chemical structures points at a manifold biotransformation of zopiclone, zolpidem, and zaleplon and a more rapid metabolization compared with benzodiazepines. Review articles, pointing out the common and special properties of the three drugs, are published among others by Goa and Heel (1986), Durand et al. (1992), Salva and Costa 1995, Noble et al. (1998), and Drover (2004).

7.2.2.1 Zopiclone

Application: Therapeutic oral doses of zopiclone between 3.75 and 15 mg led to areas under the plasma concentration-time curve proportional to the doses. No differences were seen between males and females (Gaillot et al 1983). Conversion of the peak concentrations to a uniform dose of 7.5 mg are in a good agreement (Table 74). Channer et al. (1984) studied the effect of posture at the time of administration on the central depressant effects. Standing position of the volunteers resulted in a more action of the hypnotic zopiclone as if it had been swallowed in the supine position. Bioavailability and elimination rate constants were not statistically significant affected. But lag time and time at peak concentration increased (Table 74).

Biotransformation: The main metabolites of zopiclone are formed in the liver by decarboxylation, N-demethylation, and N-oxidation. Only 5% of a dose was recovered in the urine as unchanged compound, 15% as desmethyl-zopiclone, and 11% as N-oxide. An autoinduction could not be stated, for the course of plasma concentration was changed not even after administration of 7.5 mg zopiclone for 15 days. Elderly subjects showed a prolongation of elimination half-lives (Gaillot et al 1983). A pronounced increase of C_{max} and AUC, caused by a diminished metabolic activity, was demonstrated at a group of 74-85 years old patients (Gaillot et al 1987).

Interaction: Rifampicin, a potent inducer of CYP3A4 and other CYP isoforms, showed strong interaction with zopiclone. After treatment of a group of young healthy volunteers with 600

mg Rifampicin for 5 days a dose of 10 mg zopiclone led to a plasma concentration-time curve with peak concentration of 30.9% relating to the placebo curve. The area under the curve was 11.1% and the elimination half-life 60.3% of that after the placebo (Villikka et al. 1997). After pretreatment of healthy volunteers with erythromycin three times a day for 6 days the peak concentration was increased by 40% and the total AUC by 80%. The interaction between erythromycin and zopiclone resulted in accelerated absorption of zopiclone, which may be caused by a diminished first-pass metabolization, yet elimination half-life was enhanced by 77% (Aranko et al. 1994). After daily intake of 200 mg itraconazole, which is an inhibitor of CYP3A4 like erythromycin, and a single oral administration of 7.5 mg zopiclone, C_{max} was increased from 49 to 63 ng/mL, the elimination half-life was prolonged from 5.0 to 7.0 h (Jalava et al. 1996). Gemfibrozil, an inhibitor of CYP2C8, another isoenzyme of cytochrome P450, had no statistically significant influence on the plasma concentration curve, whereas the concentrations of the mean metabolites desmethyl-zopiclone and the N-oxide were increased, pointing out participation of CYP2C8 in the further biotransformation of these primary metabolites (Tornio et al. 2006).

Evaluation of the studies: From the evaluation of 11 studies with 141 observations results (Table 74) the course of the plasma concentration-time curve can be described by a one compartment model. The value of V% was in most cases in the order of 90% so that differentiation between distribution and elimination was not appropriate.

7.2.2.2 Zolpidem

Application: Zolpidem is preferably used as hypnotic in a dose of 5 or 10 mg with a bioavailability of approximately 70%, which is not affected by dose or length of administration. The absorption parameters were independent of the pharmaceutical form (suspension, capsule, or tablet), and chronic administration did not modify the absorption or bioavailability. In the range of 2.5 to 40 mg linearity between doses on the one hand and peak concentrations and areas under the curve on the other hand were observed (Durand, 1992). This is evident in the Table 75 too. The parameters C_{max}, AUC_{∞}, and Cp0 of the studies published by Greenblatt et al. (1998) and Drover et al. (2000) show a good conformity, after the values have been related on 10 mg dosage and 70 kg body weight. Comparing the influence of gender on the pharmacokinetics of benzodiazepine agonists triazolam and zolpidem, Greenblatt et al. (2000) found a larger difference of the clearance with zolpidem than with triazolam. Weight-normalized clearance of triazolam was higher in women than in men, whereas zolpidem clearance was by a factor of 2 lower in women than in men. The

differences between male and female subjects are obvious in Table 75, also concerning the study of Olubodun et al. (2003). The elimination is accelerated in men and the areas under concentration-time curve diminished.

Biotransformation: Methyl oxidation on the phenyl moiety of the molecule leads to an alcohol and a carboxylic acid. This pathway corresponds to the main route of biotransformation and accounts for 52% of the administered dose. Another carboxylic acid is created by oxidation of the methyl group on the imidazopyrimidine group and accounts for 12%. By hydroxylation of the imidazopyrimidine moiety are formed further metabolites with a part of 10% excreted products (Durand et al., 1992). The amount of zolpidem excreted unchanged in the urine was less than 1% (Salvá and Costa, 1995). All the metabolites are pharmacologically inactive.

The P450 (CYP) isoenzymes are involved in the metabolism as follows: CYP3A4 (= 60%), CYP2C9 (= 22%), CYP1A2 (= 14%), CYP2D6 and CYP2C19 (both= 3%) (Holm and Goa 2000, von Moltke et al. 1999).

Interaction: Since various isoenzymes participate in the biotransformation of zolpidem, intake combined with other active agents does not lead to such serious interactions as for instance with triazolam that is inactivated by a single degradation step. The fungicide itraconazole led to 30% increase of the area under the plasma concentration curve (Luurila et al. 1998). The elimination half-life was elevated from 2.84 to 3.38 h. A comparative investigation of Greenblatt et al. 1998a) demonstrated that the fungicides itraconazole and fluconazole diminished the clearance from 422 to 320 resp. 338 mL/min. The elimination half-life rose from 1.9 to 2.4 h. Another fungicide, voriconazole, increased at combined administration with zolpidem Cmax 1.23-fold and AUC∞ 1.48-fold. The elimination half-life was prolonged from 3.2 to 4.1 h. All these modifications were not so strong that the pharmacodynamics was affected (Saari et al. 2006). A side-effect of treatment with antidepressants is insomnia. Therefore it is of interest if interactions of zolpidem and antidepressants occur. Combined administration of zolpidem and fluoxetine or sertraline revealed only little intensification of the hypnotic effect (Allard et al. 1998).

Evaluation of the studies: Evaluation of 15 studies with 233 observations resulted to values of V% ranging predominantly between 80 and 100% and pointing out that a one compartment model describes the plasma-concentration-time curve sufficiently. The course suggests that only little next-day effect may be expected, when zolpidem is administered at bedtime.

7.2.2.3 Zaleplon

Application: By three studies the relationship of dose, plasma concentration was evaluated. Greenblatt et al. (1998) and Drover et al. (2000) chose doses of 10 and 20 mg zaleplon. Beer et al. (1994) administrated 1, 5, 15, 30, and 60 mg. Related on a dose of 10 mg and on a body weight of 70 kg, so far as the body weights were given, showed the values of Cp0, Cmax, and AUC were in good accordance. Only the dose of 1 mg led to plasma concentrations, which were too low for curve fitting. Thus in the range of 5-60 mg linearity between oral dose and the named parameters, linearity is to be assumed.

Biotransformation: Table 76 and the plasma concentration-time curve (Figure 80) show that zaleplon is rapidly absorbed and eliminated. The elimination half-life is about one hour and therefore the efficacy is short. A special feature is the low bioavailability of 30% caused by a pronounced first-pass hepatic metabolism (Rosen et al. 1999). One metabolite, N-desethyl-zaleplon, was detectable in blood after zaleplon intake, but the concentration was low (Beer et al. (1994). This degradation product is formed enzymatically too by an NADPH dependent reaction with liver microsomes. This reaction is catalyzed by isoforms of CYP3A4 but not by other enzymes of the P450 complex (Renwick et al. 1998). Further but pharmacological inactive metabolites are 5-oxo-zaleplon and N-desethyl-3-oxo-zaleplon. Inhibition experiments with human liver cytosol preparations demonstrated that transformation of zaleplon to 5-oxo-zaleplon is catalyzed by aldehyde-oxidase (Lake et al. 2002)

Interaction: Interaction of drugs with zaleplon is similar as those with zopiclone or zolpidem. A comprehensive review is given by Hesse et al. (2003). Inductive effect by rifampicin is to be considered leading to a decrease of the hypnotic activity by enhanced elimination. On the other hand a large number of active agents inhibits the cytochrome P450 system as erythromycin, azoles (fungicides), histamine H(2) receptor antagonists (cimetidine and ranitidine) ritonavir, and some antidepressants. The inhibition is not so pronounced that the dosage must be diminished, because the metabolization of zaleplon is catalyzed by different enzymes of Cytochrome P450.

Evaluation of the studies: From the evaluation of 11 studies with 107 observations (Table 76) results the course of the plasma concentration-time curve which can be described by a one compartment model. The value of V% lays in most cases at 100% so that differentiation between distribution and elimination is not appropriate.

Table 74: 7.5 mg Zopiclone (absorption, distribution. and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Greenblatt et al. 1998	placebo + (rifampicin (8)	young	10	81.3(1!)	1.093(2!)	-	3.77(2!)	0.018(2!)	(84.8)
Tornio et al. 2006	placebo + (gemfibrozil) (7M/3F)	20-27	7.5	46.3(2!)	0.336(2!)	-	4.99(2!)	0.164(2!)	(69.8)
Aranko et al. 1994	placebo + (erythromycin) (3M/7F)	22-31	7.5	71.2(1!)	0.745(2!)	-	4.31(2!)	0.071(2!)	(72.4)
Parker et al. 1983	control (liver cirrhosis) (4M/4F)	20-23	7.5	56.0(1!)	0.513(2!)	-	5.30(2!)	0.190(2!)	(65.1)
Channer et al. 1984	intake standing (6M/3F)	20-24	7.5	71.9(1!)	0.149(2!)	-	4.49(2!)	0.140(2!)	(99.6)
„	intake lying (6M/3F)	20-24	7.5	69.4(1!)	0.284(2!)	-	4.47(2!)	0.310(2!)	(92.3)
Paul et al. 2003	comparison with zaleplon u.a. (9M/14F)	21-53	7.5	68.5(1!)	0.363(2!)	-	4.62(2!)	0.469(2!)	(99.2)
Allain et al. 1995	comparison with zolpidem u.a. (16M)	23±2	7.5	59.1(2!)	0.016(2!)	-	5.10(2!)	0.003(2!)	(96.5)
Gaillot et al. 1983	doses. (16)	young	3.75	65.4(1!)	0.492(2!)	-	5.00(2!)	0.229(2!)	(65.1)
„	between (12)	-	5	-	-	-	4.8±0.9(2)	-	-
„	3.75 and 15 mg (16)	-	7.5	69.4(1!)	0.608(2!)	-	4.73(2!)	0.164(2!)	(92.3)
„	and bioavailability (16)	-	15	69.1(1!)	0.661(2!)	-	4.52(2!)	0.183(2!)	(92.3)
	Mean ± SD			**64.3 ±8.7**	**0.455 ±0.264**	**-**	**4.70 ±0.34**	**0.201 ±0.145**	**(100)**
	Number of trials			11	11		12	11	11
	Number of observations			141	141		153	141	141

Continuation of Table 74: 7.5 mg Zopiclone (absorption, distribution. and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Villikka et al. 1997	placebo + (rifampicin (8)	57.7(1!)	3.0(2!)	373(1!)	-			
Tornio et al. 2006	placebo + (gemfibrozil) (7M/3F)	49.2(2!)	1.5(2!)	340(2!)	74			
Aranko et al. 1994	placebo + (erythromycin) (3M/7F)	53.0(1!)	2.0(2!)	390(1!)	50-76			
Parker et al. 1983	control (liver cirrhosis) (4M/4F)	64.4(1!)	0.93(2!)	418(1!)	-			
Channer et al. 1984	intake standing (6M/3F)	63.6(1!)	0.83(2!)	450(1!)	-			
„	intake lying (6M/3F)	58.9(1!)	1.33(2!)	428(1!)	-			
Paul et al. 2003	comparison with zaleplon (9M/14F)	52.5(1!)	1.75(2!)	409(1!)	-			
Allain et al. 1995	comparison with zolpidem (16M)	60.7(2!)	0.25(2!)	433(2!)	71.1			
Gaillot et al. 1983	doses. (16)	52.9(1!)	1.76(2!)	450(1!)	-	80		101.7
„	between (12)	-	-	480(1!)	-			-
„	3.75 and 15 mg (16)	45.4(1!)	2.2(2!)	416(1!)	-			104.6
„	and bioavailability (16)	43.3(1!)	2.33(2!)	359.6(1!)	-			99.6
	Mean ± SD	**53.9 ±6.5**	**1.64 ±0.71**	**411 ±39**		**80**		
	Number of trials	11	11	12				3
	Number of observations	141	141	153				48

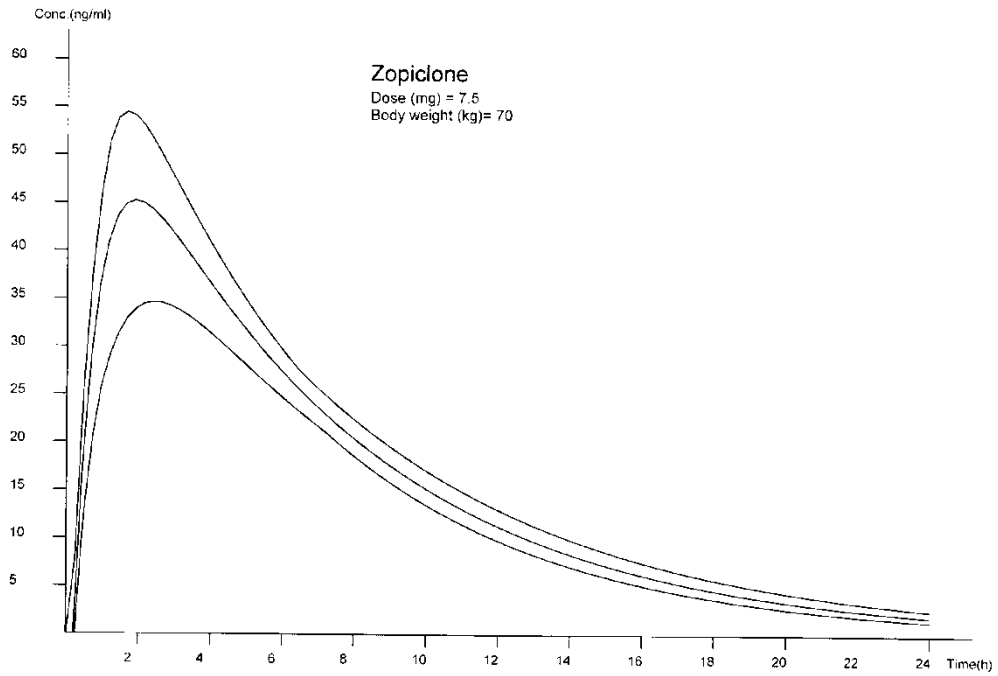


Figure 78: Plasma concentration-time curve of zopiclone after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	64.3	±	8.7	ng/mL
Ka:	1.52	±	0.56	h^{-1}
α:	0.5	±	0.0	h^{-1}
β:	0.147	±	0.012	h^{-1}
t_0:	0.201	±	0.145	h
V%:	100%			
B:	80%			

				derived from time-course of plasma concentrations
C_{max}:	53.9	±	6.5 ng/mL	45.2(37.4-54.5) ng/mL
t_{max}:	1.64	±	0.71 h	2.0(1.68-2.4) h
AUC_{o-oo}:	411	±	39ng*h/mL	394.2(327-460) ng*h/mL
V_β/G:	1.34	±	0.31 L/kg	

Table 75: 10 mg Zolpidem (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Greenblatt et al. 1998	comparison with zaleplon (10M)	21-44	10	178.7(1!)	0.542(2!)	-	2.19(2!)	0.360(2!)	(98.4)
„	2 dosages (10M)	21-44	20	199(1!)	0.488(2!)	-	2.14(2!)	0.127(2!)	(97)
Drover et al. 2000	comparison with Zaleplon (5M/5F)	23-31	10	188.0(2!)	0.188(2!)	-	2.16(2!)	0.009(2!)	(99.2)
„	2 dosages (5M/5F)	23-31	20	204.6(2!)	0.734(2!)	-	2.24(2!)	0.248(2!)	(70)
Greenblatt et al. 2000	comparison men (10M)	26±4.1	10	180.4(2!)	0.265(2!)	-	1.61 2!)	0.385(2!)	(99.6)
„	and women (8F)	28±5.6	10	193.5(2!)	0.582(2!)	-	2.49(2!)	0.0585(2!)	(86.1)
Olubodun et al. 2003	comparison men (8M)	23.4±5.5	5	114.8(2!)	0.225(2!)	-	1.69(2!)	0.10(2!)	(96.1)
«	and women + age (16F)	27.8±5.3	5	143.4(2!)	0.343(2!)	-	2.47(2!)	0.094(2!)	(86.8)
Luurila et al. 1998	placebo + (itraconazol) (4M/6F)	20-22	10	105.8(1!)	0.379(2!)	-	2.84(2!)	0.141(2!)	(43.1
Allard et al. 1998	placebo + (fluoxetine) (29F)	20-45	10	190.2(2!)	0.630(2!)	-	3.11(2)	0.093(2!)	(73.8)
Saari et al. 2006	placebo + (voriconazole) (10M)	19-29	10	91.0 (1!)	0.315(2!)	-	3.2(2)	0.03 (2!)	(69.2)
Allain et al. 1995	comparison with zopiclone (16M)	23±2	10	128.5(2!)	0.175(2!)	-	4.07(1!)	0.196(2!)	(99.6)
Allard et al. 1999	placebo + (sertraline) (28M)	20-44	10	224.1(1!)	0.718(2!)	-	3.077(2!)	0.125(2!)	(95.4)
	Mean ± SD			**170.7 ±37.1**	**0.468 ±0.201**	-	**2.67 ±0.54**	**0.144 ±0.099**	
	Number of trials			13	13		13	13	13
	Number of observations			175	175		175	175	175

Continuation of Table 75: 10 mg Zolpidem (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Greenblatt et al. 1998	comparison with zaleplon (10M)	125(1!)	1.7(2!)	408.0(1!)				
„	2 dosages (10M)	116(1!)	2.0(2!)	445.0(1!)				
Drover et al. 2000	comparison with zaleplon (5M/5F)	122.2(2!)	1.36(2!)	392.9(2!)	71.3		69.6	
«	2 dosages (5M/5F)	131.9(2!)	1.58(2!)	532.7(2)	71.3		63.3	
Greenblatt et al. 2000	comparison men (10M)	128.0(2!)	1.2(2!)	375.8(2!)	75.3			
„	and women (8F)	133.6(2!)	1.56(2!)	533.4(2!)	66.8			
Olubodun et al. 2003	comparison men (8M)	87.3(2!)	0.8(2!)	250.8(2!)	76.4			
„	und women + age (16F)	113.7(2!)	1.2(2!)	472.6(2!)	66.3			
Luurila et al. 1998	placebo + (itraconazol) (4M/6F)	163(1!)	1.0(2!)	588.5(1!)	52-83			
Allard et al. 1998	placebo + (fluoxetine) (29F)	145.3(2!)	1.8(2!)	885.8(2!)	62.2			
Saari et al. 2006	placebo + (voriconazole) (10M)	112(1!)	1.0 (2!)	563.0(1!)	67-100			
Allain et al. 1995	comparison with zopiclone (16M)	-	-	716.9(2!)	71.1			
Allard et al. 1999	placebo + (sertraline) (28M)	132.6(1!)	1.95(2!)	773(1!)				
	Mean ± SD	**128.5.2 ±16.6**	**1.53 ±0.38**	**601.8 ±199.0**		**70 %**		
	Number of trials	12	12	13				
	Number of observations	159	159	175				

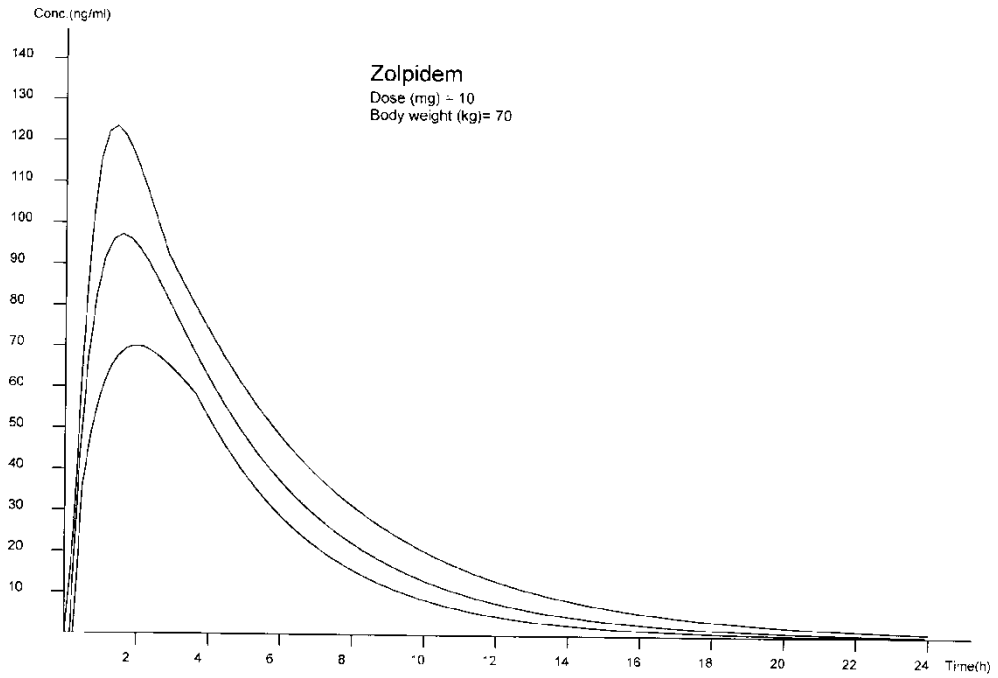


Figure 79: Plasma concentration-time curve of zolpidem after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	170.7	±	37.1	ng/mL	
Ka:	1.48	±	0.44	h^{-1}	
α:	0.5	±	0.0	h^{-1}	
β:	0.260	±	0.044	h^{-1}	
t_0:	0.144	±	0.099	h	
V%:	100%				
B:	70%				
					derived from time-course of plasmaconcentrations
C_{max}:	128.5	±	16.6 ng/mL		97.0(70.1-123.5) ng/mL
t_{max}:	1.53	±	0.38h		1.64(1.44-1.92)h
AUC_{o-oo}:	601.8	±	199.0 ng∗h/mL		539.6(397.2-710.6) ng∗h/mL
V_β/G:	0,711	±	0,197 L/kg		

Table 76: 10 mg Zaleplon (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Greenblatt et al. 1998	comparison with zolpidem (10M)	21-44	10	47.6(1!)	0.284(2!)	-	0.952(2!)	0.300(2!)	(100)
„	2 dosages (10M)	21-44	20	54.6(1!)	0.398(2!)	-	1.00(2!)	0.221(2!)	(100)
Drover et al. 2000	comparison with zolpidem (5M/5F)	23-31	10	40.4(2!)	0.333(2!)	-	1.21(2!)	0.215(2!)	(100)
„	2 dosages (5M/5F)	23-31	20	41.1(2!)	0.150(2!)	-	1.09(2!)	0.200(2!)	(70.3)
Beer et al. 1994	doses (5M)	18-32	1	(14.8)	(0.996)	-	-	(0.109)	(100)
«	between (4F)	18-32	5	47.4 (1!)	0.450(2!)	-	1.11 (2!)	0.224(2!)	(97)
«	1 and 60 mg (5M)	18-32	15	44.**7(1!)**	0.521(2!)	-	1.093 (2!)	0.111(2!)	(50)
«	(5M)	18-32	30	65.3(1!)	0.410(2!)	-	1.076 (2!)	0.186(2!)	(50)
«	(5M)	18-32	60	72.3(1!)	0.521(2!)	-	0.930 (2!)	0.157(2!)	(99.8)
Rosen et al. 1999	determination of the (10M)	19-32	10	42.6(2!)	0.204(2!)	-	0.992 (2!)	0.200 (2!)	(98.4)
«	bioavailability (10F)	19-32	10	46.0(2!)	0.257(2!)	-	1.324 (2!)	0.190 (2!)	(35.2)
Paul et al. 2003	comparison with zopiclone u.a. (9M/14F)	21-53	10	35.72(1!)	0.379(2!)	-	1.489(2!)	0.528(2!)	(100)
	Mean ± SD			**44.7 ±8.3**	**0.334 ±0.105**	**-**	**1.18 ±0.20**	**0.280 ±0.140**	**(100)**
	Number of trials			11	11		11	11	11
	Number of observations			107	107		107	107	107

Continuation of Table 76: 10 mg Zaleplon (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Greenblatt et al. 1998	comparison with zolpidem (10M)	26.0(1!)	1.1(2!)	39.9(1!)	-			
„	2 dosages (10M)	24.5(1!)	1.1(2!)	47.3(1!)	-			
Drover et al. 2000	comparison with Zolpidem (5M/5F)	27.6(2!)	1.41(2!)	51.2(2!)	71.3		285	
«	2 dosages (5M/5F)	31.1(2!)	0.93(2!)	57.1(2!)	«		295	
Beer et al. 1994	doses (5M)	31.0(1!)	0.9 (2!)	-	74.3			
„	between (4M)	20.0(1!)	1.0 (2!)	45.3 (1!)	„			
„	1 and 60 mg (5M)	39.6(1!)	1.2 (2!)	36.9 (1!)	„			
„	(5M)	57.3(1!)	0.9(2!)	62.6 (1!)	„			
„	(5M)	43.2(1!)	1.5(2!)	42.6 (1!)	„			
Rosen et al. 1999	determination of the (10M)	30.0(2!)	0.7(2!)	48.4 (2!)	72.3	31 ±11.1		1.18
„	bioavailability (10F)	29.7(2!)	0.85(2!)	70.8 (2!)	59.0	30.3 ±9.8		1.36
Paul et al. 2003	comparison with zopiclone u.a. (9M/14F)	20.34(1!)	1.75(2!)	61.54(1!)	-			
	Mean ± SD	**29.1 ±7.4**	**1.19 ±0.36**	**54.4 ±9.7**		**30 ±10**		**~1.3**
	Number of trials	12	12	11		2		2
	Number of observations	112	112	107		20		20

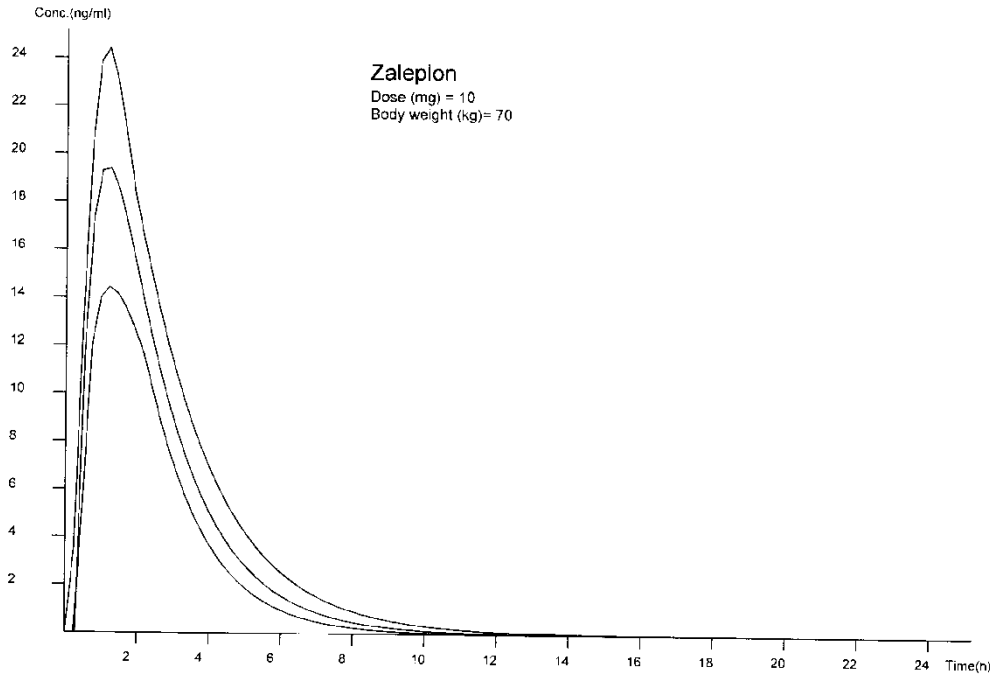


Figure 80: Plasma concentration-time curve of zaleplon after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	44.7	±	8.3	ng/mL	
Ka:	2.08	±	0.52	h^{-1}	
α:	0.5	±	0.0	h^{-1}	
β:	0.587	±	0.085	h^{-1}	
t_0:	0.280	±	0.140	h	
V%:	100%				
B:	30%				
					derived from time-course of plasma concentrations
C_{max}:	29.1	±	7.4 ng/mL		19.5(14.4-24.4) ng/mL
t_{max}:	1.19	±	0.36 h	1.18	(1.2-1.4) h
AUC_{o-oo}:	54.4	±	9.7 ng∗h/mL		54.2(40.5-71.6) ng∗h/mL
V_β/G:	1.3 L/kg		1.34	±	0.31 L/kg

7.3 Psychotropic substances

7.3.1 Antidepressants

7.3.1.1 Tricyclic non-selective antidepressants

7.3.1.1.1 Amitriptyline

Application: Amitriptyline is a tricyclic antidepressant with sedative effect. Typical dosages are 25 to 150 mg daily, half of this initially for elderly or adolescents. Further indications of treatment with amitriptyline are chronic pain, migraine, headache, tinnitus, and others. Lower dosages of 10 to 50 mg are required for pain treatment. The main biochemical mechanism of amitriptyline is the inhibition of reuptake of neurotransmitters, mainly serotonin and noradrenaline. In oral treatment of depression amitriptyline can be replaced by amitriptyline-N-oxide, a high degree of which is metabolized to amitriptyline.

Biotransformation: The steps of amitriptyline biotransformation are very similar to those of imipramine. N-Demethylation leads to nortriptyline, a pharmacological active agent, which is hydroxylated in the same way as the parent drug in 10-position of the ring system. 10-hydroxyamitriptyline and 10-hydroxynortriptyline are formed in two optical isomers yielding Z-10-hydroxyamitriptyline (cis-isomer) and E-10-hydroxyamitriptyline (trans-isomer) respectively Z-10-hydroxynortriptyline (cis-isomer) and E-10-hydroxynortriptyline. In vitro studies of Hyttel et al. (1980) showed an equal inhibitory effect of amitriptyline on uptake of serotonin as on noradrenaline, whereas nortriptyline was a more potent inhibitor of noradrenaline uptake than of serotonin uptake. The metabolites had a similar effect range as nortriptyline. All the metabolites had a less anticholinergic effect than amitriptyline and nortriptyline. After chronic treatment with 150 mg amitriptyline per day, steady-state plasma levels of 10-hydroxy nortriptyline were in the same order of magnitude as amitriptyline and nortriptyline concentrations (Robinson et al., 1985). Further metabolites are amitriptyline-N-oxide, desmethylnortriptyline, and trans-10, 11-dihydroxyamitriptyline. From urine of patients treated with amitriptyline, in addition to O-glucuronides of E- and Z-hydroxyamitriptyline, N-glucuronides are isolated. These quaternary ammonium glucuronnides are resistant to acid hydrolysis, but could be hydrolyzed enzymatically (Breyer-Pfaff et al., 1990).

Interaction: A prolongation of elimination time was associated with age as it has been demonstrated with a number of drugs, especially with those, which are metabolized by hepatic oxidative degradation. After intravenous administration, Schulz et al. (1983) found a mean $t_{½}\beta$ value of 21.7 in 62-81 aged men vs. 16.2 hr in 21-23 aged subjects. After oral intake, the values were 20.8 vs. 15.2 hr. Ogura et al. (1983) determined nearly duplicated half-lives and peak concentrations in elderly patients (65 to 74 yr), 27.2 vs. 14.7 hr, respectively 27.6 vs. 14.2 ng/mL. Still more increased was the area under the plasma concentration-time curve, 814.5 vs. 234.3 ng*mL^{-1}/h. Warrington et al. (1984) observed little pharmacodynamic effect after a single dose of 50 mg amitriptyline and 0.5 mL/kg ethanol, but Dorian et al. (1983) found enhanced AUC values of amitriptyline 104.2 vs. 75.1 ng*mL^{-1}/h in volunteers, who had received 25 mg amitriptyline and ethanol dosed to achieve and maintain blood ethanol concentration of 800 mg/L. The AUC value of nortriptyline was increased by a mean of 26%.

It is expected that inhibitors of N-demethylation and hydroxylation have influence on the pharmacokinetics of amitriptyline. Concomitant dosing of divaloproex led to a 42% higher mean area under the curve for the sum of amitriptyline and nortriptyline concentrations (Wong et al., 1996). Fluvoxamine inhibited the N-demethylation of amitriptyline (Härtter et al., 1993). A life threatening dextromethorphan intoxication was observed in a poor CYP2D6 metabolizer associated with amitriptyline intoxication (Forget et al., 2008). Coadministration of ketoconazole, a selective CYP3A inhibitor, had only a slight influence on amitriptyline clearance Venkatakrishnan et al., 2001). The interaction of fluoxetine was studied by el-Yazige et al. (1995), Schmider et al. (1999), Hambrecht (1995), and Bonin et al. (1996).

Evaluation of studies: Amitriptyline is absorbed slowly with comparatively large lag time of 0.7 hr, a t_{max} of 4.2 hr, and an absorption half-life of 1.34 hr (Table 77). Due to the slow absorption and the high distribution volume, the distribution phase is not pronounced. The concentration dependent pharmacokinetic parameters Cp0, C_{max}, and AUC derived from the study of Dorian et al. (1983) could not be used for averaging, because the values refer to free amitriptyline plasma concentrations. In addition to this, the observation period of 8 hours was too short for calculation an elimination half-life.

7.3.1.1.2 Imipramine

Application: Imipramine was introduced as the first tricycle antidepressant in the early 1960s. Its effects are manifold. Transmitter systems in the brain are influenced by inhibiting the reuptake into the presynaptic vesicles. Effects of biogenic amines, mainly noradrenalin serotonin, are enhanced by this. The dosage of ambulatory patients is 25 to 75 mg daily

increasing up to 200 mg daily. The absolute bioavailability of imipramine shows considerable variations after oral intake with values between 29 and 77% (Ullmann et al., 2001) because of a distinct first-pass metabolism, the extent of which is influenced by many factors.

Biotransformation: The main degradation step of imipramine is N-demethylation to its pharmacologically active metabolite desipramine. Hydroxylation occurs in 2- and 10-position of the aromatic ring system yielding 2-hydroxy and 10-hydroxy derivatives of imipramine and desipramine, which are partially conjugated to the glucuronides and excreted into the urine. Other minor pathways of imipramine are N-oxidation and didemethylation (Hermann et al., 1992). 2-Hydroxyimipramine and 2-hydroxydesipramine are detectable in plasma after administration of imipramine in addition to the parent drug as the main component and desipramine and influences of other drugs on the time courses of these substances have been investigated by Hermann et al. (1992). Antidepressant and cardiotoxic activity is also attributed to the hydroxylated metabolites of imipramine and desipramine and may be particularly relevant for the elderly and acute overdose (Sallee & Pollock,1990). The 2D6 isoenzyme of cytochrome P450, CYP2D6, mediates the hydroxylation step of imipramine and desipramine, whereas the demethylation is catalyzed by CYP2C8, the mephenytoin oxygenase. That was demonstrated by a pharmacokinetic study with poor and extensive metabolizers of mephenytoin by Skjelbo et al., 1991).

Interaction: Due to diminished activity of oxidative enzymes in the elderly, the mean elimination half-life after a single dose of imipramine in 75-83 aged subjects was high (26.4 hr) (Hrdina et al., 1988). Also comparing investigations of Abernethy et al. (1985) revealed marked prolongations of elimination half-lives in elderly vs. young males (28.6 vs. 16.5 hr) and females (30.2 vs. 17.8 hr). Peak plasma concentrations were higher in elderly volunteers, too (males: 40.2 vs. 19.5 ng/mL; females: 44.7 vs. 10.4 ng/mL). Abernethyl et al. (1984) found no influence of food on the bioavailability of imipramine after administration of 50 mg to volunteers after overnight fast and 30 min after eating a standardized breakfast. In chronic alcoholics, the elimination half-lives of imipramine were not changed vs. nonalcoholic patients, but after administration of 50 mg three times daily for at least 10 days, levels of imipramine and 2-hydroxyimipramine in alcoholics had only half the values of nonalcoholics (Ciraulo et al., 1982). After pretreatment of six healthy men with 300 mg cimetidine four times daily for two days, a decrease of clearance and an increase of bioavailability due to inhibition of oxidative metabolism were observed (Henauer & Hollister, 1984), A similar study of Abernethy et al. (1984a) showed inhibition of imipramine pharmacokinetics not only after oral but also after intravenous administration. The absolute bioavailability was increased

by the inhibition effect from 40.2 to 75.3%. The antibiotic troleandomycin, which has been shown to inhibit in vitro CYP3A isoenzymes in human liver microsomes, had in vivo effects on the pharmacokinetics of imipramine after pretreatment for two days (Wang et al., 1997). Olanzapine had no statistically significant influence on the time courses of imipramine and desipramine, but its plasma concentrations were diminished by imipramine (Callaghan et al., 1977). The cardiovascular agents verapamil, diltiazem, and lobetalol raised imipramine area under the plasma concentration-time curve (relative bioavailability) by 15%, 30%, and 53% respectively. Lobetalol diminished additionally the amounts of 2-hydroxyimipramine and 2-hydroxydesipramine (Hermann et al., 1992). The pharmacokinetics of imipramine was influenced in users of oral contraceptive steroids, the elimination half-live was prolonged after intravenous infusion of imipramine and the absolute bioavailability was elevated (Abernethy et al., 1984b).

Evaluation of studies: Absorption of imipramine after oral intake occurs slowly. The calculated lag time (Table 78) is 0.752 ± 0.348 hr and peak plasma level is reached after about 4 hours. The relatively high variations of peak plasma levels, Cp0, and AUC values are due to the variable absolute bioavailability of imipramine and the large distribution volume, which is dependent on individual factors.

Table 77: 50 mg Amitriptyline (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Warrington et al., 1984	+(ethanol) trazodone (2M/6F)	19-22	50	17.9(1!)	0.937(2!)	1.22(2!)	8.42(2!)	0.950(2!)	46.9(2!)
Gupta et al., 1999	+ (controlled release) (15M)	21-37	75	18.0(2!)	1.61(2!)	3.19 (2!)	17.3(2!)	0.339(2!)	48.1(2!)
Sticht et al., 1983	2 formulations: Saroten® (7M)	22-52	50	35.6(1!)	0.932(2!)	1.09(2!)	16.4(2!)	0.954(2!)	24.8(2!)
-	Tranxipress® (7M)	.	50	38.9(1!)	0.835(2!)	1.69(2!)	15.1(2)	957(2!)	84.8(2!)
Rogers et al., 1978	pharmacokinetic (12)	30±7	25	16.6(2!)	1.73(2!)	2.82(2!)	24.5(2!)	0.617(2!)	35.2(2!)
Kuss et al., 1985	+ (amitriptylinoxide (5M/6F)	22-40	50	29.9(2)	1.61(2)	-	11.0(2)	0.400(2)	-
Schulz et al., 1983	+ (elderly) oral (7M)	21-23	80-100	-	-	-	18.5(2)	-	-
“	intravenous (7M)	21-23	40-60	-	-	-	16.2(2)	-	-
Ogura et al., 1983	+(elderly) + dithiepin (7)	21-25	25	29.5(2!)	1.25(2!)	1.67(2!)	11.4(2!)	0.785(2!)	42.4(2!)
Dorian et al., 1983	+(ethanol) free amitrip. (2M/3F)	26±3	25	(2.11)	0.541(2!)	1.56(2!)	(4.4)	0.855(2!)	32.8(2!)
Garland & Min 1978, Graß, 1989	(8M)	young	75	11.5(2)	1.65(2)	3.40(2)	21.2(2)	1.10(2)	10.43(2)
	Mean			**23.3**	**1.34**	**2.28**	**16.3**	**0.705**	**41.0**
	± SD			**±7.8**	**±0.386**	**±0.875**	**±4.8**	**±0.272**	**±18.9**
	Number of trials								
	Number of observations								

Continuation of Table 77: 50 mg Amitriptyline (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Warrington et al., 1984	+(ethanol) trazodone (2M/6F)	16.7(2)	3.91(2)	200.5(1!)	61-82			
Gupta et al., 1999	+ (controlled release) (15M)	17.9(2)	6.3(2)	451(2!)	77.4			
Sticht et al., 19	2 formulations: Saroten® (7M)	28.7(2)	3.0(2)	453.9(2!)	-			
-	Tranxipress® (7M)	31.7(2)	3.0(2)	472.3(2!)	-			
Rogers et al., 1978	pharmacokinetic (12)	23.2(2)	4.0(2)	336.4(2!)	63±10			
Kuss et al., 1985	+ (amitriptylinoxide (5M/6F)	22.9(2)	4.85(2)	397(2)				
Schulz et al., 1983	+ (elderly) oral (7M)	-	1.8	-		47.7±11		
"	Intravenous (7M)	-	-	-				
Ogura et al., 1983	+(elderly) + dithiepin (7)	25.0(2)	4.0(2)	455.2(2!)	63.9			
Dorian et al., 1983	+(ethanol) free amitriptyline (2M/3F)	(1.45)	3.0(2!)	(6.32)	62.5±8			
Garland & Min 1978, Graß 1989	(8M)	20.3(1)	5.5(2)	596.8(1)	75-102			
	Mean	**22.2**	**4.2**	**413**		**47.7**		
	± SD	**±4.0**	**±1.3**	**±86**		**±11**		
	Number of trials							
	Number of observations							

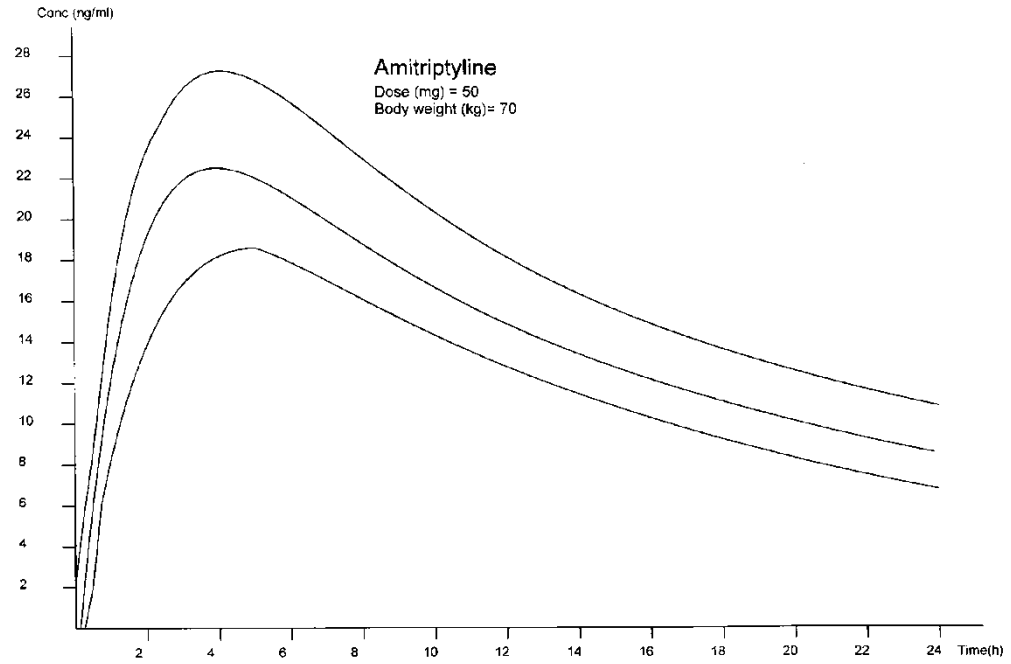


Figure 81: Plasma concentration-time curve of amitriptyline after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	23.3	±	7.8	ng/mL
Ka:	0.518	±	0.116	h^{-1}
α:	0.303	±	0.084	h^{-1}
β:	0.0425	±	0.0096	h^{-1}
t_0:	0.705	±	0.272	h
V%:	41.0	±	18.9	%
B:	47.7	±	11.0	%

				derived from time-course of plasma concentrations
C_{max}:	22.2	±	4.0 ng/mL	22.5 (18.6-27.2) ng/mL
t_{max}:	4.2	±	1.3 h	4.6 (4.6-5.5) h
AUC_{o-oo}:	413	±	86 ng*h/mL	549 (417-755) ng*h/mL

Table 78: 75 mg Imipramine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Wang et al., 1997	+(troleandomycin) (9M)		100	30.6(1!)	1.46(2!)	2.14(2!)	27.6(2!)	0.495(2!)	10.9(2!)
Callaghan et al., 1997	control (9M)	32-54	75	19.8(2!)	1.16(2!)	2.01(2!)	17.3(2!)	1.62(2!)	38.7(2!)
«	+ olanzapine (9M)	32-54	75	24.3(2!)	1.95(2!)	2.32(2!)	15.7(2!)	1.23(2!)	32.3(2!)
Abernethyl et al., 1984	intravenous (12)	22-78	12.5	-	-	-	21.2(2!)	-	-
«	bioavailability(12) fasting	22-78	50	27.7(1!)	1.22(2!)	1.40(2!)	20.5(2!)	0.751(2!)	4.1(2!)
«	(12) with food	22-78	50	21.4(1!)	0.782(2!)	1.58(2!)	23.7(2!)	0.703(2!)	11.7(2!)
Gagnon et al., 1980	2 formulations: syrup (14M)	19-37	75	35.3(2!)	0.999(2!)	1.57(2!)	9.87(2!)	0.589(2!)	34.6(2!)
«	tablet (14M)	19-37	75	32.7(2!)	1.15(2!)	2.00(2!)	10.5(2!)	0.623(2!)	43.4(2!)
Henauer & Hollister, 1984	+(cimetidine) (6M)	20-33	100	34.6(1!)	0.753(2!)	2.21(2!)	14.4(2!)	0.611(2!)	34.6(2!)
Hermann et al., 1992	+(verapamil, diltiazem & labetalol) (12M)	20-36	100	40.0(1!)	0.596(2!)	1.99(2!)	10.9(2!)	0.398(2!)	64.6(2!)
Ullmann et al., 2001	solution (18M)	19-39	25	-	-	-	12.7(2)	-	-
«	Tofranil (18M)	19-39	25	-	-	-	12.0(2)	-	-
«	Tofranil mite (18M)	19-39	10	-	-	-	11,5(2)	-	-
Abernethy et al., 1984a	+(cimetidine) (6)	24-35	50	-	-	-	15.3(2)	-	-
Abernethy et al., 1984b	+(contraceptive steroids) (8F)	52-77	50	-	-	-	19.1(2)	-	-
	Mean			**29.7**	**1.10**	**1.87**	**15.4**	**0.752**	**30.9**
	± SD			**±6.3**	**±0.37**	**±0.30**	**±5.1**	**±0.348**	**±18.6**
	Number of trials			9	9	9	15	9	9
	Number of observations			97	97	97	177	97	97

Continuation of Table 78: 75 mg Imipramine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Wang et al., 1997	+(troleandomycin) (9M))	58.3(1)	4.0(2)	1392(1!)	-	-	-	-
Callaghan et al., 1997	control (9M)	20.1(2)	5.6(2)	489 (2!)	68.8±2.4	-	-	-
«	+ olanzapine (9M)	20.2 (2)	5.9(2)	509(2!)	68.8±2.4	-	-	-
Abernethyl et al., 1984	Intravenous (12)	-	-	-	-	-	-	-
«	bioavailability(12) fasting	53.0(1)	2.8(2)	934(1!)	-	43.6(2)	-	-
«	(12) with food	45.5(1)	3.2(2)	882(1!)	-	44.1(2)	-	-
Gagnon et al., 1980	2 formulations: syrup (14M)	31.1(2)	3.16(2)	507(2!)	68.0±1.57	-	-	-
«	tablet (14M)	29.1(2)	3.52(2)	491(2!)	68.0±1.57	-	-	-
Henauer & Hollister, 1984	+(cimetidine) (6M)	60.5(1)	2.0(2)	810(1!)	65-75			
Hermann et al., 1992	+(verapamil, diltiazem and labetalol) (12M)	48.8(1)	2.3(2)	848(!)				
Ullmann et al., 2001	solution (18M)	24.3(1)	4.0(2)	325(1)				
«	Tofranil (18M)	23.5(1)	4.0(2)	316(1)				
«	Tofranil mite (18M)	23.0(1)	4.0(2)	263(1)				
Abernethy et al., 1984a	+(cimetidine) (6)	29.0(1)	3.8(2)	459(1)	59-82	40.2(2)		
Abernethy et al., 1984b	+(contraceptive steroids) (8F)	-	-	278(2)	64±2.6	27.1(2)		
	Mean ± SD	**32.1 ±12.4**	**3.72 ±0.94**	**542 ±269**	-	**39.7 ±6.7**		
	Number of trials	13	13	14		4		
	Number of observations	157	157	165		38		

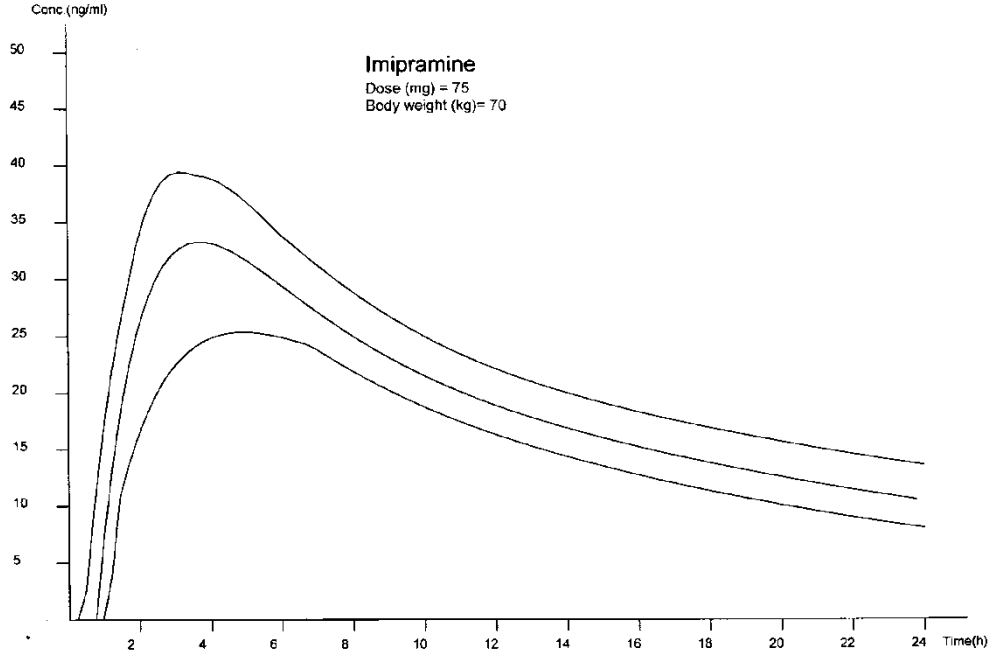


Figure 82: Plasma concentration-time curve of imipramine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	29.7	±	6.3	ng/mL
Ka:	0.630	±	0.158	h^{-1}
α:	0.370	±	0.052	h^{-1}
β:	0.0450	±	0.0112	h^{-1}
t_0:	0.752	±	0.348	h
V%:	30.9	±	18.6	%
B:	39.7	±	6.7%	

				derived from time-course of plasma concentrations
C_{max}:	32.1	±	12.4 ng/mL	33.3 (25.3-39.4) ng/mL
t_{max}:	3.72	±	0.94 h	3.75 (3.12-4.80) h
AUC_{o-oo}:	542	±	269 ng_*h/mL	686 (509-951) ng_*h/mL

7.3.1.1.3 Trazodone

Application: Trazodone was introduced as antidepressant in the eighties and is not related to the tricyclic antidepressants amitriptyline and imipramine. The main biochemical effect is inhibition of serotonin reuptake. It has antidepressant, sedative, and analgesic properties. Treatment with trazodone should be started with a daily dose of 25-50 mg in divided doses and the dosage may be increased up to 300 mg per day in ambulatory patients. Different formulations were tested for relative bioavailability. Ankier et al. (1981) compared two different capsules and found corresponding time-courses of trazodone plasma levels. Gammans et al. (1984) administered 50 mg trazodone in form of a one third-fragment of a dividose tablet, a film-sealed tablet, or a 1% solution to six healthy male volunteers. Comparing a liquid formulation and Molipaxin capsules, Harcus et al. (1983) revealed no statistically significant differences of the bioavailabilities.

Orally administered trazodone is absorbed more rapidly than amitriptyline and imipramine. The mean time for reaching peak level is 1-1.5 hours. It is to be considered that the duration of action is marked shorter as that of amitriptyline or imipramine.

Biotransformation: The first step of trazodone biotransformation leads to a pharmacologically active substance, which is also formed by degradation of some other psychiatric drugs, m-chlorophenylpiperazine (mCPP). The N-dealkylation reaction is mediated by the isoenzyme CYP3A4 of human liver cytochrome P450 system. This was proved by in vitro experiments with 16 different human liver microsomal preparations characterized for activities of 7 different P450 isoforms (Rotzinger et al., 1998). This was confirmed by the inhibitory effect of ketoconazole on the formation of mCPP. Further steps of trazodone biotransformation are hydroxylation and N-oxidation. m-CPP is transformed to p-hydroxy-mCPP by a CYP2D6 dependent reaction. Other isoforms of cytochrome P450 were not active in this trial with human liver microsomes. Moreover a specific inhibitor of CYP2D6, quinidine, caused after preincubation a concentration dependent decrease of p-hydroxy-mCPP formation (Rotzinger et al., 1998a). Trazodone is excreted into the urine only in minute amounts. Nilsen & Dale (1992) found 0.13% of an oral dose as unchanged parent drug in urine. Predominantly conjugates of hydroxylated compounds and a carboxylic acid were detected in urine after administration of ^{14}C-labelled trazodone (Jauch et al., 1976).

Interaction: Greenblatt et al. (1987) studied the influence of age, gender, and obesity on the pharmacokinetics of trazodone. Due to the similar degradation steps as those of amitriptyline and imipramine, elimination half-life of trazodone was prolonged in elderly in the same way

(men: 8.2 vs. 4.7; women: 7.6 vs. 5.9). Distribution volumes were also increased in elderly, but absolute bioavailability showed no relation to age and sex. $t_{½}\beta$ was enhanced in obese subjects (13.3 vs. 5.9 hr), and the distribution volume was enlarged (1.43 vs. 1.04 L/kg). Bayer et al. (1983) found nearly two-fold prolongation of half-life and statistically significant increased plasma concentrations of trazodone in elderly compared with young healthy volunteers. Coadministration of 100 mg trazodone and 0.5 mL/kg ethanol had no influence on blood ethanol concentration and the pharmacokinetics of trazodone except for a prolongation of t_{max}. The absolute bioavailability was statistically significant altered after oral intake of 100 mg trazodone-HCl with food in comparison with fasting (65 vs. 63%), but the mean peak concentration was decreased from 1.88 to 1.47 µg/mL and the time for reaching this level was increased from 1.3 to 2.0 hr (Nilsen & Dale, 1992). In vitro (Zalma et al., 2000) and in vivo studies (Greenblatt et al., 2003) revealed drug interactions of trazodone with viral protease inhibitors. A prolonged elimination half-life from 6.7 to 14.9 hr and an increased peak plasma concentration was determined after concomitant administration of 50 mg trazodone and 4 doses of 200 mg ritonavir in 10 healthy volunteers. In vitro inhibitions were observed with ketoconazole and indinavir, too. The involvement of the isoenzyme CYP2D6 in the metabolism of trazodone was confirmed by investigations of Yasui et al. (1995), who coadministrated thioridazine, an inhibitor of this isoform of cytochrome P450, anc trazodone. Plasma concentrations of trazodone and of the active metabolite mCPP were increased (969 vs. 713 ng/mL resp. 94 vs. 61 ng/mL).

Evaluation of studies: The pharmacokinetic parameters C_{max}, t_{max}, and AUC_{∞} (Table 79) show comparatively slight deviations. Absorptions occurs rapidly after oral administration with a half-life of a half hour and a lag time of 10 minutes. In comparison to amitriptyline and imipramine, the distribution phase is expressed more distinctly.

Table 79: 50 mg Trazodone (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Warrington et al., 1984	control (2M/4F)	19-22	100	586(1!)	0.405(2!)	1.50(2!)	4.87(2!)	0.035(2!)	49.4(2!)
«	+ ethanol (2M/4F)	19-22	100	620(1!)	0.459(2!)	3.30(2!)	4.95(2!)	0.190(2!)	65.4(2!)
Gammans et al., 1984	formulation A (6M)	22-27	50	464.3(2!)	0.924(2!)	1.07(2!)	6.97(2!)	0.190(2!)	6.05(2!)
«	formulation B (6M)	22-27	50	315.1(2!)	0.401(2!)	1.44(2!)	9.21(2!)	0.160(2!)	21.9(2!)
«	solution (6M)	22-27	50	384.9(2!)	0.341(2!)	0.906(2!)	8.49(2!)	0.075(2!)	21.9(2!)
Bayer et al., 1983	+(elderly) control 7(4M/7F)	23-30	100	475(2!)	0.710(3!)	1.59(2!)	7.34 (2!)	0.163(2!)	32.8(2!)
«	+ milk 4(4M/7F)	23-30	100	322(2!)	0.450(3!)	1.66(2!)	8.58 (2!)	0.218(2!)	35.2(2!)
Greenblatt et al., 2003	+(ritonavir) (9M/1F)	20-46	50	536(1!)	0.664(2!)	0.735(2!)	7.00(2!)	0.317(2!)	5.86(2!)
Ankier et al., 1981	capsule A (6M/7F)	20-46	50	748(2!) ±243	0.333(2!) ±0.395	1.04(2!) ±0.49	5.82(2!) ±2.03	0.206(2!) ±0.129	48.2(2!) ±18.7
«	capsule B (6M/7F)	20-46	50	713(2!) ±306	0.432(2!) ±0.380	0.973(2!) ±0.394	6.04(2!) ±2.30	0.211(2!) ±0.150	31.44(2!) ±24.0
Munday et al., 1975	effect of mood and arousal (5M/5F)	20-30	1 mg/kg	344.6(2!)	0.234(2!)	1.32(2!)	9.69(2!)	0.000(2!)	46.5(2!)
Nilsen & Dale, 1992	fasting (8)		100						
«	with food (8)		100						
	Mean ± SD			**531 ±156**	**0.470 ±0.186**	**1.31 ±0.61**	**7.05 ±1.55**	**0.167 ±0.091**	**33.5 ±12.3**
	Number of trials			11	11	11	11	11	11
	Number of observations			87	87	87	87	87	87

Continuation of Table 79: 50 mg Trazodone (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Warrington et al., 1984	control (2M/4F)	830(1)	1.22(2)	4702(1!)	61-82			
«	+ ethanol (2M/4F)	800(1)	1.92(2)	5360(1!)	61-82			
Gammans et al., 1984	formulation A (6M)	790(2)	0.7(2)	5305(2!)	70±6			
«	formulation B (6M)	944(2)	1.2(2)	5324(2!)	70±6			
«	solution (6M)	840(2)	1.3(2)	5572(2!)	70±6			
Bayer et al., 1983	+(elderly) control 7(4M/7F)	800(2)	2.0(2)	5761(2!)	62.9±9.2			
«	+ milk 4(4M/7F)	650(2)	1.5(2)	4788(2!)	62.9±9.2			
Greenblatt et al., 2003	+(ritonavir) (9M/1F)	842(1)	1.93(2)	5763(1!)				
Ankier et al., 1981	capsule A (6M/7F)	1040(2) ±87	1.3(2) ±0.3	6180(2!) ±1810	67.9			
«	capsule B (6M/7F)	1020(2) ±120	1.3(2) ±0.3	5920(2!) ±1370	67.9			
Munday et al., 1975	effect of mood and arousal (5M/5F)	421(2)	2.0(2)	5294(2!)	(70)			
Nilsen & Dale, 1992	fasting (8)						63	
«	with food (8)						65	
	Mean ±SD	**839 ±197**	**1.51 ±0.39**	**5604 ±418**			**65**	**±**
	Number of trials	11	11	11			2	
	Number of observations	87	87	87			16	

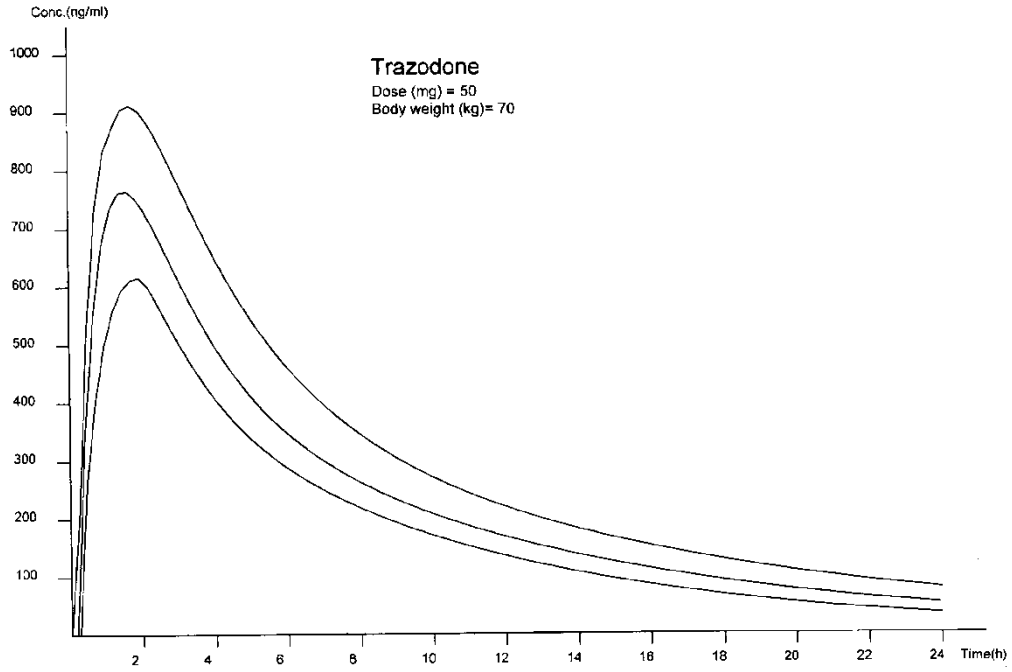


Figure 83: Plasma concentration-time curve of trazodone after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	531	±	156	ng/mL
Ka:	1.48	±	0.42	h^{-1}
α:	0.53	±	0.17	h^{-1}
β:	0.0983	±	0.0177	h^{-1}
t_0:	0.167	±	0.091	h
V%:	33.5	±	12.3	%
B:	64%			

				derived from time-course of plasma concentrations
C_{max}:	839	±	197 ng/mL	762 (616-913) ng/mL
t_{max}:	1.51	±	0.39 h	1.67 (1.68-1.92) h
$AUC_{o\text{-}oo}$:	5604	±	418 ng*h/mL	6306 (4876-8503) ng*h/mL

7.3.1.2 Selective antidepressants

7.3.1.2.1 Citalopram

Application: Escitalopram is a selective serotonin reuptake inhibitor (SSRI) causing increased serotonin neurotransmission (Hyttel, 1977). Only the S(+)-enantiomer of citalopram has this pharmacological effect (Hyttel et al., 1992). Comparing racemic citalopram and the S-enantiomere, containing the same amount of S-entantiomer, to placebo, escitalopram showed a better effect in clinical and non-clinical studies. These differences are supposed to be due to an inhibitory effect of the R(-)-enantiomer, possibly by an allosteric interaction with the serotonin transporter (Sanchez et al., 2004; Chen et al., 2005). Steady-state plasma levels in 70 patients ranged from 95 to 720 nM (31-239 ng/mL) at 30 to 60 mg daily. At the standard dose of 40 mg daily, the mean level was 245 nM (80 ng/mL) (Overø, 1982).

Biotransformation: Escitalopram is transformed to the pharmacologically active metabolite S-desmethylcitalopram and to S-didesmethylcitalopram. These reactions were studied in vitro in human liver microsomes by von Moltke et al. (2001). The isoforms of cytochrome P450, CYP2C19, CYP2D6, and CYP3A4, contribute to the metabolism steps. Inhibition of enzymatic demethylation by ketoconazole or quinidine confirmed these findings. A conclusion of these investigations is that escitalopram and S-desmethylcitalopram are unlikely to cause clinically important interactions. After a single oral dose of 40 mg citalopram or 20 mg escitalopram, the mean peak level of S-desmethylcitalopram was about 19% of that of the parent drug. Due to the slow elimination of the active metabolite ($t_{½}\beta$ = 50-60 hr), the peak level is reached roughly after 14 hours (Søgaard et al., 2005). Multiple dose studies resulted in a steady-state after 7-10 days and an average concentration ratio between escitalopram and its active metabolite of 2.7. The levels of the didemethylated compound were negligible (Overø, 1982).

The excretion of escitalopram and S-desmethylcitalopram into the urine was 8% resp. 10% of the dose (Søgaard et al., 2005). Kragh-Sørensen et al. (1981) determined 1/7 of the dose as unchanged drug in urine.

Interaction: Leinonen et al. (1996) investigated the influence of age and concomitant treatment with other psychoactive drugs using a nonenantioselective HPLC method. Even during monotherapy, the variability of dose- and weight related serum citalopram and desmethylcitalopram concentrations was large (10.6-fold resp. 7.2-fold). Citalopram but not desmethylcitalopram concentration increased with aging. No sex-related differences were

observed, and an effect of a single neuroleptic alone could not be detected. But the concentrations of citalopram and its active metabolite increased by 121% resp. 88%, when neuroleptics were pooled. The steady-state citalopram concentrations in elderly patients (72-90 yr) were up to four times higher than expected from data in younger patients (Overø et al., 1985). It is suggested that daily doses of 5-20 mg citalopram give approximately the same steady-state levels in elderly as a dose of 40 mg in younger subjects. Coadministrated triazolam caused no alterations of pharmacokinetics of both drugs (Nolting & Abramowitz, 2000). Concomitant administration of escitalopram and cimetidine or omeprazole led to moderate increases of AUC values and small increases of $t_{½}\beta$ values (Malling et al., 2005). Sproule et al. (1997) have given a review concerning interactions of selective serotonin reuptake inhibitors and central nervous system drugs.

Evaluation of studies: The dose in the evaluated single oral dose studies (Table 80) was 20 mg. Despite failing body weights the mean fictive initial concentrations, peak levels, and areas under the concentration-time curves are in good conformance. The comparatively high standard deviation of V% (19%) was not used for calculation of the maximal curve of citalopram. Otherwise Cmax of the curve would have exceeded that from table 80 by far. Citalopram is comparatively rapidly absorbed with a concentration maximum at about 3 hours after drug intake. The elimination occurs slowly and therefore one dose daily is sufficient.

7.3.1.2.2 Fluoxetine

Application: Fluoxetine is the selective serotonin reuptake inhibitor (SSRI) with the longest duration of staying in the body, predominantly that of its active metabolite N-desmethylfluoxetine. A 3- to 4-fold interindividual variation in C_{max} was seen after administration of single doses of fluoxetine (Aronoff et al., 1984). Thus a nonlinear pharmacokinetic profile of fluoxetine was supposed (Altamura et al., 1994). Such high deviations of C_{max}, Cp0, and AUC were found in the evaluated studies (Table 81), too. Causes for these findings are assumed to be a large volume of distribution (20-40 L/kg), a high plasma protein binding (95%), extensive first-pass metabolism, and genetic polymorphism (poor and extensive metabolizers). The pharmacological effect of desmethylfluoxetine must be taken into the account, because this metabolite is supposed to be as potent as the parent drug in inhibiting serotonin uptake and for the very long elimination period. Due to a minor variation of the plasma concentrations, pharmacodynamics can be related to fluoxetine plus desmethylfluoxetine levels. Caused by the slow elimination of fluoxetine and particularly

desmethylfluoxetine, the attainment of steady-state plasma concentrations requires several weeks of therapy. Similarly large is the wash-out phase (Keller et al., 2005).

Biotransformation: The N-demethylation product is as specific for inhibition of serotonin reuptake as the parent drug. In healthy individuals approximately 60% of an oral dose was excreted into the urine within 35 days, with only 2.5% as unchanged drug and 5.2% as its glucuronide. The excretion of the main metabolite was higher, 10% desmethylfluoxetine and 9.5% of its glucuronide. Most of the incorporated drug (72.8%) was excreted in form of unidentified metabolites (Altamura et al., 1994). In vitro experiments with human liver microsomes using (R)-, (S)-, and racemic fluoxetine as substrates, showed that the isoenzymes of cytochrome P450, CYP2D6, CYP3A4, and CYP2C19, are involved in the oxidative metabolism of fluoxetine and desmethylfluoxetine (Stresser et al., 2009).

Interaction: Reduced hepatic capability is supposed to impair the metabolism of fluoxetine, whereas other antidepressants, age, food, obesity, or renal impairment did not affect fluoxetine pharmacokinetics (Altamura et al., 1994). Fluoxetine, taken over 8 days, did not affect the elimination of warfarin, diazepam, tolbutamide, chrlorothiazide, or ethanol (Lemberger et al., 1985). Orlistat, a lipase inhibitor, led not to statistically significant alterations of fluoxetine pharmacokinetics (Zhi et al., 2003). Fluoxetine and desmethylfluoxetine are potent inhibitors of cytochrome P4502D6 (CYP2D6). This was demonstrated by an in vivo experiment with 12 CYP2D6 extensive metabolizers. The dextromethorphan/dextrorphan urinary ratio was statistically significant lower (0.017 vs. 0.313) after administration of fluoxetine (Alfaro et al., 2000). Comparable inhibition was observed by Cai et al. (1999) and additionally the CYP2D6 mediated metabolism of propaphenone enantiomers was impaired after concomitant fluoxetine administration. Moclobemide concentrations were enhanced after coadministration of fluoxetine, but the influence was not of clinical relevance (Dingemanse et al., 1998). An effect of CYP2D6 genotypes on steady-state fluoxetine and desmethylfluoxetine was proved by Llerena et al. (2004), whereas the influence ofCYP2C9 could not be cleared by this study.

Evaluation of studies: The study of Saletu& Grünberger (1985) was not suitable for calculating the elimination half-life because of too short observation period. The large variation of pharmacokinetic parameters of fluoxetine is obvious in the time course of the plasma concentrations (Figure 85) and in the table of pharmacokinetic parameters (Table 81). For the same reason as in the case of citalopram, the standard deviation of V% was not used. Notable are the very slow absorption and elimination of fluoxetine and its active metabolite.

7.3.1.2.3 Paroxetine

Application: Paroxetine is a very potent selective serotonin reuptake inhibitor (SSRI) and is applied orally at single daily doses of 20 to 50 mg. The absorption occurs not rapidly. Peak level is reached at 4 to 6 hours after administration with an absolute bioavailability of 30-60% depending on the saturation of first-pass metabolism (Hiemke, 1994).

Biotransformation: Paroxetine is a p-fluorophenylpiperidine derivative, the degradation of which occurs in the methoxy-3-benzodioxole (methylendioxyphenyl-oxymethyl) side group. By oxidative ring opening, two isomer methoxy-hydroxyphenyl derivatives are formed, which are eliminated into the urine as glucuronides and sulphates (Haddock et al., 1989). Furthermore the whole side group is split yielding hydroxymethyl-p-fluorophenylpiperidine, which is glucuronidated, too. All the metabolites are regarded as pharmacologically inactive. The oxidative degradation is mediated by distinct isoenzymes of cytochrome P450, CYP2D6 andCYP1A2 (Ozdemir et al., 1998). Drug elimination by way of this isoenzyme is characterized by genetic polymorphism (sparteine/debrisoquine). In poor metabolizers, the mean elimination half-life of paroxetine was in comparison to that of extensive metabolizers from 16 to 41 hours prolonged and the area under the concentration-time curve from 550 to 3910 nmol*hr/L increased (Sindrup et al., 1992). In white population about 7% are poor metabolizers and the remainder are extensive metabolizers (Alvan et al., 1990).

Interaction: In elderly subjects there were interindividual variations in single dose and steady-state pharmacokinetic parameters with higher plasma concentrations and slower elimination than in younger subjects. After single doses of 15 and 30 mg paroxetine, in elderly depressed patients elimination half-lives of 25.7 (20.7-34.1 hr) resp. 28.3 (15.1-44.1 hr) were determined (Ghose, 1989). Renal impairment led to increased plasma concentrations and AUC values. The elimination half-life was statistically significant enhanced only in patients with severe renal impairment at creatine clearance of less than 30 mL/min (Doyle et al., 1989). Greb et al. (1989a) concluded from studies with different conditions during paroxetine intake that it is not necessary to give special instructions for drug intake, such as fasting or non-fasting, low or high-fat diet, with milk or water, or with aludrox or without aludrox. Because paroxetine is a substrate of CYP2D6, a pretreatment with terbinafine, an inhibitor of CYP2D6, for 6 days and concomitant administration of paroxetine on the 6. day led to a 1.9 fold increase of the mean peak plasma level, a prolongation of elimination half-life from 15.3 to 22.7 hours, and a 2.5 fold increase of the AUC (0-48 hr) (Yasui-Furukori et al., 2008). Coadministration of perphenazine after pretreatment with a standard therapeutic dose of paroxetine led to an increase of plasma concentration and statistically significant enhancement of central nervous

side effects of perphenazine (Ozdemir et al., 1997). Only slight and not statistically significant alterations of the paroxetine pharmacokinetics were observed after pretreatment with cimetidine, an inhibitor of distinct microsomal oxidative enzymes, or with phenobarbitone, which is an inductor of hepatic oxidative enzymes (Greb et al., 1989). The inhibitory effect of itraconazole on the pharmacokinetics of paroxetine was supposed to be due to the influence in the intestinal absorption by P-glucoprotein interaction and not by CYP3A4 inhibition (Yasui-Furukori., 2007).

Evaluation of studies: The dose and body weight dependent pharmacokinetic parameters show only slight deviations, but it is to take into account that results from studies with poor metabolizers were not used for averaging. The interindividual variation in the pharmacokinetics is wide and is not reflected by the curve in Figure 87.

Table 80: 20 mg Escitalopram (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Søgaard et al., 2005	bioavailability (12M) oral	18-45	20	15.9(1!)	0.900(2!)	3.47(2!)	29.5(2!)	0.110(2!)	65.1(2!)
„	(12M) intravenous	18-45	10	-	-	-	26.6(2)	-	-
„	fed (10M/7F) oral	18-45	20	-	-	-	-	-	-
„	fasted (10M/7F) oral	18-45	20	-	-	-	-	-	-
Malling et al., 2005	placebo (12M/4F)	18-45	20	16.5(1!)	1.04(2!)	3.01(2!)	24.6(2!)	0.717(2!)	43.6(2!)
“	+ cimetidine (12M/4F)	18-45	20	24.9(1!)	1.26(2!)	1.33(2!)	29.0(2!)	0.481(2!)	8.79(2!)
“	placebo (8M/8F)	18-45	20	16.1(1!)	1.74(2!)	2.39(2!)	30.3(2!)	0.690(2!)	21.5(2!)
“	+ omeprazole (8M/8F)	18-45	20	17.6(1!)	1.42(2!)	1.81(2!)	37.7(2!)	1.21(2!)	17.6(2!)
Sidhu et al., 1997	enantiomers (4M/6F)	23-32	20	23.5(1!)	0.858(2!)	1.32(2!)	27.2(2!)	0.486(2!)	46.1(2!)
	Mean			**18.9**	**1.24**	**2.27**	**29.5**	**0.648**	**31.5**
	± SD			**±3.7**	**±0.31**	**±0.78**	**±4.1**	**±0.331**	**±19.0**
	Number of trials			6	6	6	7	6	6
	Number of observations			86	86	86	98	86	86

Continuation of Table 80: 20 mg Escitalopram (absorption, distribution and elimination).

Evaluated studies	**Data from comparative single dose studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{o-oo} (ng_*h/mL)**	**G (kg)**	**B (%)**	**V_β/B (L)**	**V_β/G (L/kg)**
Søgaard et al., 2005	bioavailability (12M) oral	18.8(1!)	0.99(2!)	677.9(2!)	-			
„	(12M) intravenous	-	-	-	-	80		
„	fed (10M/7F) oral	23.3(1)	-	663.4(1)	-			
„	fasted (10M/7F) oral	21.1(1)	-	622.2(1)	-			
Malling et al., 2005	placebo (12M/4F)	20.1(1!)	3.5(2!)	619(1!)	-			
“	+ cimetidine (12M/4F)	24.5(1!)	3.0(2!)	1017(1!)	-			
“	placebo (12M) (8M/8F)	15.6(1!)	4.0(2!)	708(1!)	-			
“	+ omeprazole (8M/8F)	21.3(1!)	4.0(2!)	955(1!)	-			
Sidhu et al., 1997	enantiomers (4M/6F)	27.0(1!)	3.3(2!)	909(1!)	51-74			
	Mean ± SD	**21.3 ±5.1**	**3.2 ±1.0**	**766 ±154**		**80**		
	Number of trials	8	6	8				
	Number of observations	120	86	120				

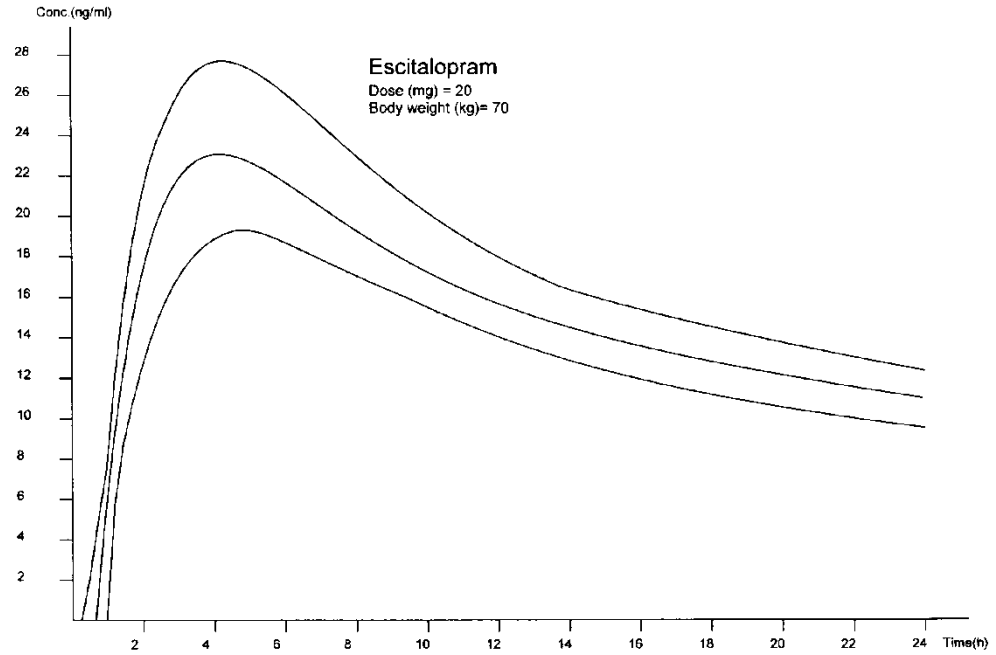


Figure 84: Plasma concentration-time curve of escitalopram after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	18.9	±	3.7	ng/mL
Ka:	0.559	±	0.112	h^{-1}
α:	0.305	±	0.078	h^{-1}
β:	0.0235	±	0.0029	h^{-1}
t_0:	0.648	±	0.331	h
V%:	31.5			%
B:	80%			

				derived from time-course of plasma concentrations
C_{max}:	21.3	±	5.1 ng/mL	23.1 (19.3-27.7) ng/mL
t_{max}:	3.2	±	1.0h	4.2 (4.2-4.8) h
AUC_{o-oo}:	766	±	154 ng*h/mL	831 (693-993) ng*h/mL

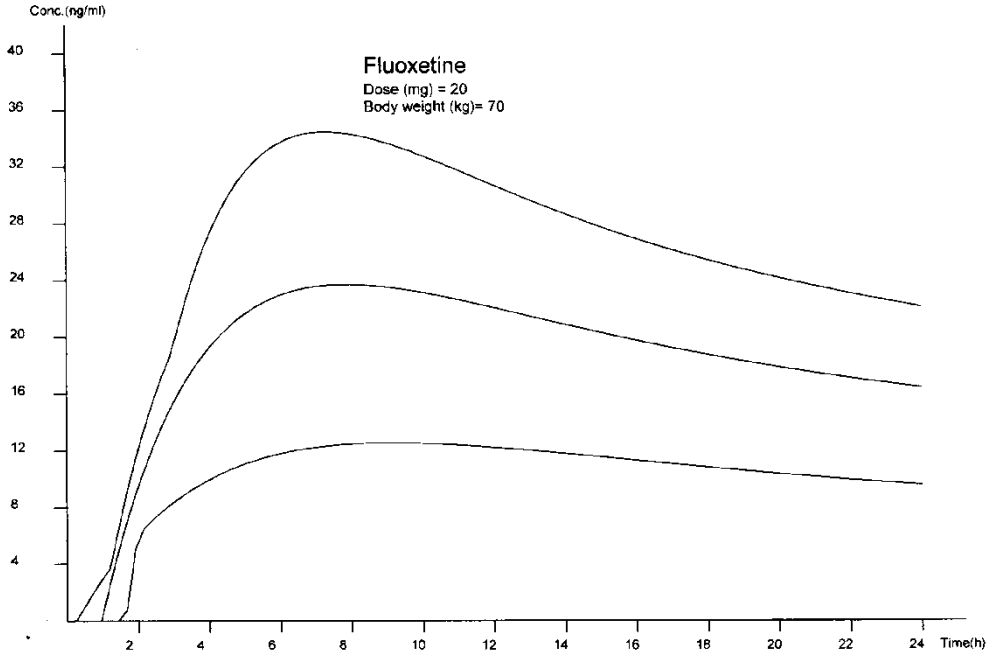


Figure 85: Plasma concentration-time curve of fluoxetine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	20.3	±	10.0	ng/mL	
Ka:	1.32	±	0.50	h^{-1}	
α:	0.551	±	0.164	h^{-1}	
β:	0.0116	±	0.0038	h^{-1}	
t_0:	0.95	±	0.69	h	
V%:	36.1			%	
					derived from time-course of plasma concentrations
C_{max}:	25.9	±	16.0 ng/mL		23.7 (12.5-34.4) ng/mL
t_{max}:	6.7	±	1.6 h		7.9 (7.2-9.1) h
AUC_{o-oo}:	1598	±	2476 ng*h/mL		1734 (996-2455) ng*h/mL

Table 81: 20 mg Fluoxetine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Zhi et al., 2003	+ Placebo (12M/12F)	18-53	40	14.1(2!)	1.77(2!)	3.09(2!)	30.2(2!)	1.55(2!)	36.9(2!)
«	+ Orlistat (12M/12F)	18-53	40	14.9(2!)	2.17(2!)	2.45(2!)	30.0(2!)	1.52(2!)	10.8(2!)
Keller et al., 2005	reference tablet (34M)	18-50	20	5.40(1!)	2.54(2!)	4.20(2!)	82.5(2!)	0.568(2!)	10.8(2!)
«	test tablet (34M)	18-50	20	4.61(1!)	2.75(2!)	4.05(2!)	85.6(2!)	0.479(2!)	6.25(2!)
Saletu & Grünberger, 1985	pharmaco-EEG (4M/4F)	21-27	30	27.8(1!)	0.701(2!)	0.892(2!)	(13.9)	1.81	87.5(2!)
«	psychometric (4M/4F)	21-27	60	30.1(1!)	1.33(2!)	2.09(2!)	(17.0)	1.58	49.6(2!)
«	analyses (4M/4F)	21-27	75	31.9(1!)	1.44(2!)	2.75(2!)	(13.9)	0.517	65.4(2!)
Zaid et al., 2006	Fluoxicare® (24M)	18-28	20	44.74(1!)	2.00(2!)	5.42(2!)	102(2!)	0.017(2!)	48.4(2!)
«	Prozac® (24M)	18-28	20	44.74(1!)	1.74(2!)	4.75(2!)	102(2!)	0.016(2!)	46.1(2!)
Moraes et al., 1999	Psiquial® (12M/12F)	18-43	20	5.71(2!)	2.08(2!)	5.29(2!)	44.7(2!)	1.93(2!)	21.3(2!)
«	Prozac® (12M/12F)	18-33	20	5.71(2!)	2.31(2!)	4.62 (2!)	44.7(2!)	2.02(2!)	27.2(2!)
Jovanoviç et al., 2006	tablet fluoxetine (13M/11F)	22-50	20	32.3(2!)	2.97(2!)	4.41(2!)	28.1(2!)	0.875(2!)	74.7(2!)
«	capsule Prozac® (13M/11F)	22-50	20	34.4(2!)	3.57(2!)	7.97(2!)	27.2(2!)	0.517(2!)	70.0(2!)
	Mean ± SD			**20.3 ±14.2**	**2.30 ±0.62**	**4.36 ±1.52**	**59.7 ±29.7**	**0.95 ±0.69**	**36.1 ±24.7**
	Number of trials			13	13	13	13	13	13
	Number of observations			284	284	284	284	284	284

Continuation of Table 81: 20 mg Fluoxetine (absorption, distribution and elimination).

Data from comparative single dose studies	Evaluated studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Zhi et al., 2003	(12M/12F) + Placebo	15.5(2)	6.0(2)	640(2!)	63.3±10.3			
«	+ Placebo (12M/12F)	16.3(2)	5.7(2)	684(2!)	63.3±10.3			
Keller et al., 2005	reference tablet (34M)	13.6(1)	5.4(2)	688(1!)				
«	test tablet (34M)	14.3(1)	5.4(2)	635(1!)				
Saletu & Grünberger, 1985	pharmaco-EEG (4M/4F)	23.6(1)	4.0(1)	529(1!)	63.3			
«	psychometric (4M/4F)	28.0(1)	4.0(1)	716(1!)	63.3			
«	analyses (4M/4F)	32.46(1)	6.0(1)	606(1!)	63.3			
Zaid et al., 2006	Fluoxicare® (24M)	61.2(2)	8.25(2)	6682(1!)				
«	Prozac® (24M)	44.7(2)	7.33(2)	6690(1!)				
Moraes et al., 1999	Prozac® (12M/12F)	10.15(2)	6.0(2)	445(2)	62.9±2.1			
«	Psiquial® (12M/12F)	11.6(2)	6.0(2)	451(2)	62.9±2.1			
Jovanoviç et al., 2006	tablet fluoxetine (13M/11F)	30.0(2!)	9.2(2!)	1184(2!)	74.6±18.6			
«	capsule Prozac® (13M/11F)	33.3(2!)	9.7(2!)	1260(2!)	74.6±18.6			
	Mean ± SD	**25.9 ±16.0**	**6.7 ±1.6**	**1598 ±2476**				
	Number of trials	13	13	13				
	Number of observations	284	284	284				

Table 82: Desmethylfluoxetine from 20 mg Fluoxetine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Zhi et al., 2003	+ Placebo (12M/12F)	18-53	40	14.2(2!)	10.1(2!)	6.42(2!)	129(2!)	0.070(2!)	98.5(2!)
«	+ Orlistat (12M/12F)	18-53	40	14.2(2!)	9.24(2!)	6.66 (2!)	124(2!)	0.067(2!)	96.9(2!)
Keller et al., 2005	reference tablet (34M)	18-50	20	15.8(1!)	10.7(2!)	2.97(2!)	136(2!)	0.134(2!)	99.2(2!)
«	test tablet (34M)	18-50	20	15.9(1!)	10.5(2!)	3.21(2!)	136(2!)	0.077(2!)	99.2(2!)
Moraes et al., 1999	Psiquial® (12M/12F)	18-43	20	25.8(2!)	13.3(2!)	24.8(2!)	87.7(2!)	0.119 (2!)	96.9(2!)
«	Prozac® (12M/12F)	18-33	20	25.8(2!)	13.6(2!)	19.8 (2!)	87.7(2!)	0.112(2!)	87.5(2!)
Jovanoviç et al., 2006	tablet fluoxetine (13M/11F)	22-50	20	17.5(2!)	5.68(2!)	7.79(2!)	33.7(2!)	1.42(2!)	65.6(2!)
«	capsule Prozac® (13M/11F)	22-50	20	23.4(2!)	7.00(2!)	10.8(2!)	28.9(2!)	1.37(2!)	68.1(2!)
	Mean ± SD			**19.3 ±4.8**	**10.1 ±2.6**	**9.6 ±7.4**	**99.2 ±41.0**	**0.391 ±0.544**	**90.0 ±13.0**
	Number of trials			8	8	8	8	8	8
	Number of observations			212	212	212	212	212	212

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Zhi et al., 2003	(12M/12F) + Placebo	10.2(2)	55.0(2)	1764(2!)	63.3±10.3
«	+ Placebo (12M/12F)	10.6(2)	52.7(2)	1757(2!)	63.3±10.3
Keller et al., 2005	reference tablet (34M)	10.2(1)	71.5(2)	2846(1!)	
«	test tablet (34M)	10.6(1)	79.9(2)	2864(1!)	
Moraes et al., 1999	Psiquial® (12M/12F)	11.6(2)	48.0(2)	3088(2)	62.9±2.1
«	Prozac® (12M/12F)	12.1(2)	48.0(2)	3098(2)	62.9±2.1
Jovanoviç et al., 2006	tablet fluoxetine (13M/11F)	13.6(2!)	19.1(2!)	733(2!)	74.6±18.6
«	capsule Prozac® (13M/11F)	14.4(2!)	19.3(2!)	749(2!)	74.6±18.6
	Mean ± SD	**11.8 ±1.5**	**51.7 ±20.9**	**2054 ±951**	
	Number of trials	8	8	8	
	Number of observations	212	212	212	

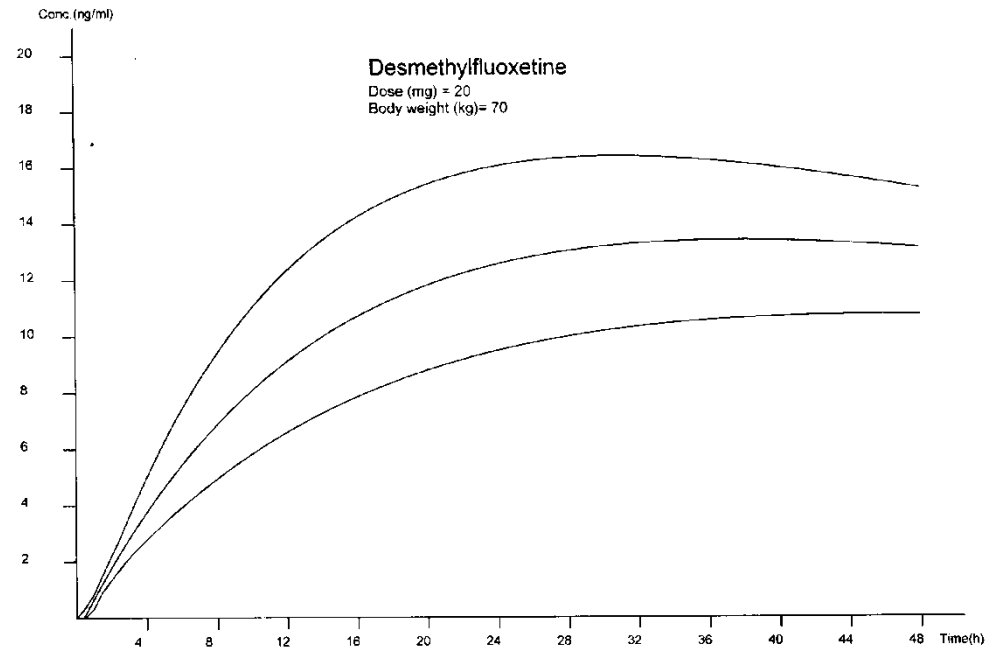


Figure 86: Plasma concentration-time curve of desmethylfluoxetine after oral administration of fluoxetine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	19.3	±	4.8	ng/mL
Ka:	0.069	±	0.014	h^{-1}
α:	0.072	±	0.031	h^{-1}
β:	0.0070	±	0.0021	h^{-1}
t_0:	0.391	±	0.391	h
V%:	90.0	±	13.0%	

				derived from time-course of plasma concentrations
C_{max}:	11.8	±	1.5 ng/mL	13.4 (10.7-16.4) ng/mL
t_{max}:	51.7	±	20.9 h	37.3 (30.7-45.6) h
AUC_{o-oo}:	2054	±	951 ng*h/mL	2137 (1719-3383) ng*h/mL

Table 83: 20mg Paroxetine (absorption, distribution and elimination.

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Yasui-Furukori et al., 2007	+(itraconazol) (10M/3F)	21-35	20	5.48(2!)	0.999(2!)	0.603(2!)	19.9(2!)	1.59(2!)	87.5(2!)
Yasui-Furukori et al., 2007b	+(terbinafine) (9M/3F)	22-35	20	6.42(2!)	1.63(2!)	1.41(2!)	15.7(2!)	0.933(2!)	75.0(2!)
McClelland & Raptopoulos, 1984	(5M)	22-44	70	7.21 (2!)	0.670(2!)	0.403(2!)	22.9(2!)	0.558(2!)	36.3(2!)
Greb et al., 1989	Control + (cimetidine) (10M)	20-28	30	-	-	-	11.4(2)	-	-
«	Control + (phenobarbitone (10M)	20-28	30	-	-	-	29.8(2)	-	-
Greb et al., 1989a	fasting (10M)	-	30	-	-	-	10.6(2)	-	-
«	non-fasting (10M)	-	30	-	-	-	13.6(2)	-	-
«	low-fat diet (10M)	-	30	-	-	-	13.0(2)	-	-
«	high-fat diet (10M)	-	30	-	-	-	12.2(2)	-	-
«	with milk (10M)	-	30	-	-	-	12.9(2)	-	-
«	with water (10M)	-	30	-	-	-	16.2(2)	-	-
«	without aldudrox (10M)	-	30	-	-	-	25.1(2)	-	-
«	with aldudrox (10M)	-	30	-	-	-	22.0(2)	-	-
Jhee et al., 2007	(24) reference	19-27	20	6.51(2!)	0.760(2!)	0.592(2!)	15.2(2!)	0.611(2!)	23.4(2!)
«	(24) test	19-27	20	6.56(2!)	0.801(2!)	0.654(2!)	15.2(2!)	0.556(2!)	21.9(2!)
Doyle et al., 1989	control + (renal impairment) (6)	19-65	30	-	-	-	17.3(2)	-	-
Sindrup et al., 1992	extensive + (poor) metabolizer (9)	20-30	30	6.68(2!)	0.758(2!)	1.51(2!)	12.6(2!)	0.081(2!)	74.7(2!)
	Mean ± SD			**6.42 ±0.43**	**0.922 ±0.30**	**0.81 ±0.37**	**16.5 ±4.8**	**0.73 ±0.42**	**45.7 ±27,7**
	Number of trials			6	6	6	17	6	6
	Number of observations			87	87	87	193	87	87

Continuation of Table 83: 20mg Paroxetine (absorption, distribution and elimination.

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Yasui-Furukori et al., 2007	+(itraconazol) (10M/3F)	5.48(2)	5.0(2)	148.4(2!)	57.3±7.2	-	-	- -
Yasui-Furukori et al., 2007b	+(terbinafine) (9M/3F)	5.41(2)	5.0(2)	129.8(2!)	58.3±8.5	-	-	-
McClelland, Raptopoulos, 1984	(5M)	7.57(1)	6.0(2)	226.3(1!)	-	-	-	-
Greb et al., 1989	control + (cimetidine) (10M)	5.6(1)	4.8(2)	130.4(1)	-	-	-	-
«	control + (phenobarbitone)(10M)	9.6(1)	6.4(2)	404(1)	-	-	-	-
Greb et al., 1989a	fasting (10M)	5.8(1)	5.8(2)	106.5(1)	-	-	-	-
«	non-fasting (10M)	6.5(1)	5.4(2)	125.7(1)	-	-	-	-
«	low-fat diet (10M)	7.6(1)	4.8(2)	181.4(1)	-	-	-	-
«	high-fat diet (10M)	6.3(1)	6.3(2)	180.1(1)	-	-	-	-
«	with milk (10M)	9.9(1)	4.1(2)	167.4(1)	-	-	-	-
«	with water (10M)	9.7(1)	4.9(2)	289.8(1)	-	-	-	-
«	without aldudrox (10M)	7.7(1)	4.2(2)	283.5(1)	-	-	-	-
«	with aldudrox (10M)	9.0(1)	5.0(2)	316.9(1)	-	-	-	-
Jhee et al., 2007	(24) reference	7.68(2)	5.0(2)	130.1(2!)	69.8	-	-	-
«	(24) test	7.40(2)	5.0(2)	131.6(2!)	69.8	-	-	-
Doyle et al., 1989	control + (renal impairment)	13.2(1)	4.3(2)	383(1)	-	-	-	-
Sindrup et al., 1992	extensive + (poor) metabolizer (9)	5.65(2)	4.0(2)	116.8(2!)	73.2			
	Mean	**7.24**	**5.0**	**170.6**				
	± SD	**±1.61**	**±0.6**	**±77.6**				
	Number of trials	17	17	17				
	Number of observations	193	193	193				

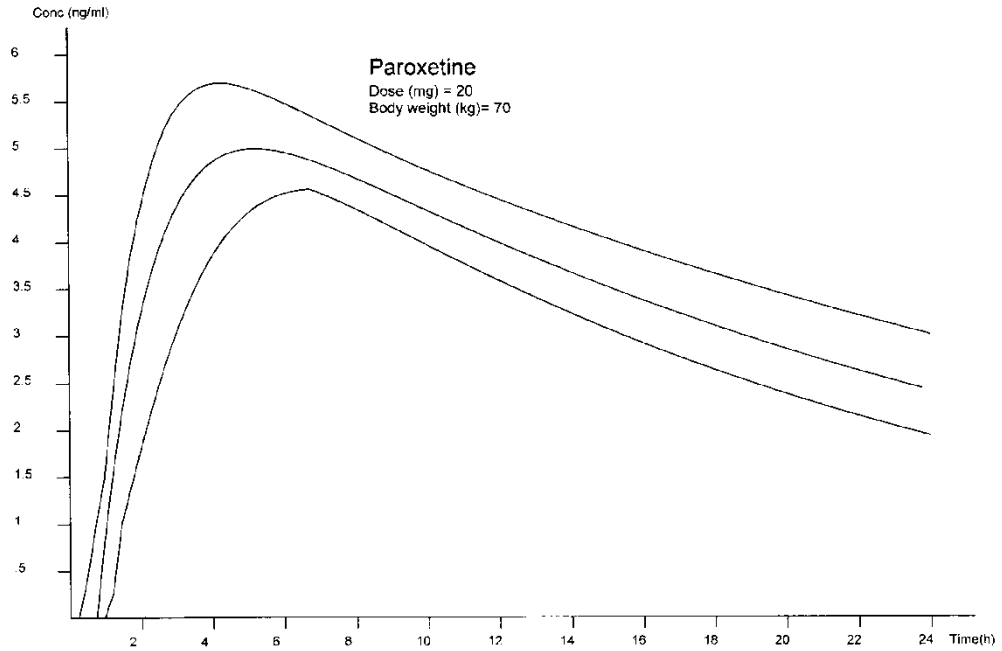


Figure 87: Plasma concentration-time curve of paroxetine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	6.42	±	0.43	ng/mL	
Ka:	0.752	±	0.185	h^{-1}	
α:	0.856	±	0.269	h^{-1}	
β:	0.0420	±	0.0095	h^{-1}	
t_0:	0.73	±	0.42	h	
V%:	45.7	±	27.7%		
B:	30-60%				
					derived from time-course of plasma concentrations
C_{max}:	7.24	±	3.8ng/mL		5.00 (4.6-5.7) ng/mL
t_{max}:	5.0	±	0.6 h		5.3 (4.3-6.7) h
AUC_{o-oo}:	170.6	±	77.6ng*h/mL		143.0 (110.1-192.2) ng*h/mL
V_β/G:	21.2	±	1.5 L/kg		

7.3.1.3 Other antidepressants

7.3.1.3.1 Mianserin

Application: Mianserin is a tetracyclic antidepressant, the clinical efficacy of which is similar to that of tricyclic antidepressants, but it causes statistically significant fewer anticholinergic side effects than imipramine or amitriptyline. It seems to be less likely that these drugs generate serious cardiotoxicity on overdosage (Brogden et al., (1978). Hopman (1980) reported on experiences with 192 out-patients treated with daily doses of 10-130 mg mianserin depending on their individual response. A marked improvement after 1-2 weeks of treatment was observed in about 80% of those with different forms of depression.

Mianserin is administered as racemate, even though the S(+)-enantiomer is reported to be a more potent antidepressant than the R(-)-enantiomer, but both enantiomers appear to have similar sedative properties (Pinder & Van Delft, 1983). In the majority of depressed Japanese patients, treated with mianserin, the more active S(+)-enantiomer possessed higher plasma concentrations than the R(-)-enantiomer with a mean S/R ratio of 1.9 ± 0.9 (Tybring et al., 1995). Eap et al. (1994) found in mianserin treated patients S/R-ratios from 1.0 to 4.06 for mianserin and 0.19 to 0.64 for desmethylmianserin.

Biotransformation: The three main metabolites of mianserin, N-desmethylmianserin, 8-hydroxymianserin, and mianserin-N-oxide were detected in urine and plasma of mianserin treated patients (Eap et al., 1994). N-desmethylmianserin and 8-hydroxymianserin have antidepressant activity, but they were less active than mianserin in tests indicative for sedation, while mianserin-N-oxide appered to be relatively inactive (Pinder & Van Delft, 1983). Concentrations of desmethylmianserin in plasma after single or multiple dosages were in the order of magnitude of one third of mianserin concentration. The active metabolites were supposed to contribute to the antidepressant effects of mianserin (Pinder & Van Delft, 1983). Lambert et al. (1989) studied the mechanism of mianserin biotransformation by in vitro trials using different enzyme inhibitors of hepatic cytochrome isoforms. Koyama et al. (1996) concluded from in vitro experiments using human liver microsomes, that CYP2D6 mediates the hydroxylation of both enantiomers of mianserin to 8-hydroxymianserin, whereas the N-demethylation and the N-oxidation of the S(+)-enantiomer are catalyzed by CYP1A2. The authors suggested, that CYP3A isoenzymes are involved to a certain extent in each of the stereoselective mianserin metabolic pathways.

Interaction: The plasma concentrations of mianserinin in depressed patients receiving 30 mg mianserin at bedtime increased with advancing age, while those of mianserin plus desmethylmianserin remained unchanged. Sex, smoking, and coadministration of benzodiazepines did not affect the metabolism of mianserin (Otani et al., 1993). The terminal half-life of mianserin was statistically significant prolonged in elderly patients (mean age 76) to 27 ± 13.1 hr from that of young subjects with $\beta = 9.6 \pm 1.9$ hr (Shami et al., 1983).

Evaluation of studies: Large variations of mianserin exist in Table 84 and Figure 88, predominantly concerning the absorption and the distribution phases due to a high distribution volume and to pronounced distribution of mianserine during the absorption.

Table 84: 30 mg Mianserin (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (mg/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Shami et al., 1983	(1M)	19-31	30	25.2(2!)	0.372(2!)	1.59(2!)	5.64(2)	0.236(2)	32.6(2!)
«	(1M)	19-31	30	20.9(2!)	1.72(2!)	1.97(2!)	12.1(2)	0.163(2!)	2.93(2!)
«	(1M)	19-31	30	39.0(2!)	1.69(2!)	2.38(2!)	16.0(2!)	0.126(2!)	8.79(2!)
«	(1F)	19-31	30	9.23(2!)	1.75(2!)	2.52(2!)	17.5(2!)	0.990(2!)	5.30(2!)
«	(1F)	19-31	30	6.80(2!)	0.724(2!)	0.798(2!)	17.2(2!)	0.032(2!)	1.57(2!)
«	(1F)	19-31	30	28.6(1!)	1.14(2!)	2.57(2!)	20.9(2!)	0.451(2!)	21.5(2!)
Altamura et al., 1982	+(elderly) (3M/2F)	21-43	30	19.2(2!)	0.972(2!)	0.911(2!)	8.02(2!)	0.468(2!)	10.4(2!)
«	(1)	26	30	10.9(2)	0.980(2)	1.15(2)	13.5(2)	-	
«	(1)	25	30	13.5(2)	0.900(2)	1.07(2)	17.3(2)	-	-
«	(1)	21	30	26.3(2)	0.950(2)	1.00(2)	10.7(2)	-	-
«	(1)	27	30	11.2(2)	-	-	10.7(2)	-	-
«	(1)	41	30	14.2(2)	0.350(2!)	2.17(2)	12.0(2)	-	-
Xu et al., 2008	bioequivalence (12M) Vick		60	23.4(1!)	0.619(2!)	0.666(2!)	(30.1)	0.248(2!)	4.39(2!)
«	study (12M) Tolvon		60	16.7(1!)	0.506(2!)	1.44(2!)	(36.5)	0.190(2!)	21.5(2!)
Maguire et al., 1982	(8M)	20-30	60	14.4(2!)	0.478(2!)	3.73(2!)	21.9(2!)	0.829(2!)	24.6(2!)
«	comparison (1M)		60	-	1.5(2)	1.6(2)	12(2)	0.97(2)	-
«	of blood and (1M)		60	-	0.1(2)	3.1(2)	19(2)	0.64(2)	-
«	plasma levels (1M)		60	-	2.6(2)	2.7(2)	20(2)	1.40(2)	-
«	(1M)		60	-	1.7(2)	1.8(2)	28(2)	0.89(2)	-
«	(1M)		60	-	2.8(2)	2.9(2)	14(2)	1.20(2)	-
«	(1M)		60	-	1.0(2)	1.0(2)	22(2)	0.73(2)	-
«	(1M)		60	-	0.3(2)	3.3(2)	21(2)	0.68(2)	-
«	(1M)		60	-	0.5(2)	2.0(2) (2)	29(2)	0.98(2)	-
	Mean			**18.3**	**0.787**	**1.73**	**16.7**	**0.455**	**14.7**
	± SD			**±6.1**	**±0.523**	**±1.06**	**±6.3**	**±0.330**	**±9.1**
	Number of trials			5	5	5	5	5	5
	Number of observations			48	55	55	56	51	43

Continuation of Table 84: 30 mg Mianserin (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (mg/L)	t_{max} (h)	AUC_{o-oo} (mg*h/L)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Shami et al., 1983	(1M)	41.9(2)	1.5 (2)	282(2!)	95.2	60		
«	(1M)	58.7(2)	3.4(2)	555 (2!)	88.5	120		
“	(1M)	29.2(2)	4.0(2)	439(2!)	73.3	140		
“	(1F)	31.4(2)	4.0(2)	394(2!)	69.7	30		
“	(1F)	23.5(2)	0.75(2)	205(2!)	64.2	50		
“	(1F)	60.4(1)	3.0(2)	1027(1!)	-	-		
Altamura et al., 1983	+(elderly) (3M/2F)	29.3(2)	2.0(2)	254(2!)	64.9±11.4			
«	(1)	22.0(2)	2.0(2)	246(2)	81.1			33.8
«	(1)	28.3(2)	2.0(2)	330(2)	68.2			32.5
«	(1)	35.7(2)	2.0(2)	291(2)	50.0			22.8
«	(1)	21.4(2)	2.0(2)	161(2)	65.2			40.94
«	(1)	31.7(2)	2.0(2)	211(2)	60.0			35.2
Xu et al., 2008	bioequivalence (12M) Vick	51.2(1)	1.6(2)	(1020)				
«	study (12M) Tolvon	48.6(1)	1.8(2)	(935)				
Maguire et al., 1982	/8M)	51.0(2)	3.0(2)	645(2)	71(63-83)			
«	(1M)	26.0(1)	2.0(2)	281(1)				
«	(1M)	46.5(1)	1.5(2)	536(1)				
«	(1M)	46.5(1)	5.0(2)	639(1)				
«	(1M)	69.0(1)	4.0(2)	1178(1)				
«	(1M)	40.0(1)	4.0(2)	444(1)				
«	(1M)	54.5(1)	2.0(2)	879(1)				
«	(1M)	58.0(1)	2.0(2)	805(1)				
«	(1M)	67.5(1)	2.0(2)	664(1)				
	Mean ± SD	**43.5 ±11.9**	**2.21 ±0.83**	**464 ±233**		**82**		**33.0 ±6.6**
	Number of trials	5	5	3		1		1
	Number of observations	56	56	32		5		5

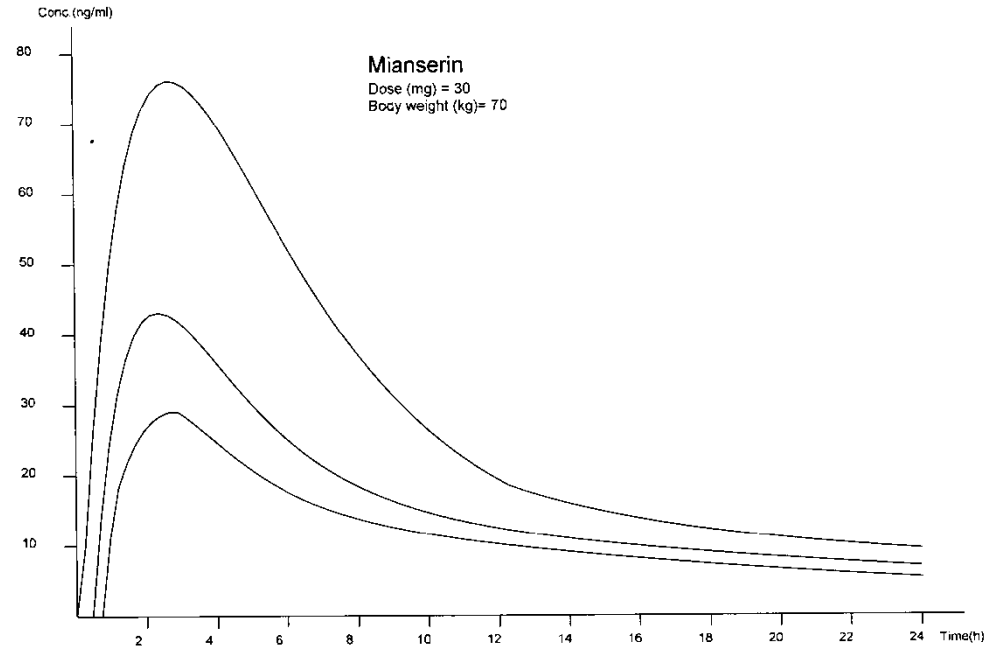


Figure 88: Plasma concentration-time curve of mianserin after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	18.3	±	6.1	ng/mL
Ka:	0.881	±	0.258	h^{-1}
α:	0.401	±	0.153	h^{-1}
β:	0.0478	±	0.0068	h^{-1}
t_0:	0.0415	±	0.0114	h
V%:	14.7	±	9.1	%
B:	80%			

				derived from time-course of plasma concentrations
C_{max}:	43.5	±	11.9 ng/mL	43.1 (29.1-76.1) ng/mL
t_{max}:	2.21	±	0.83 h	2.26 (2.26-2.88) h
AUC_{o-oo}:	464	±	233 ng*h/mL	564 (386-1011) ng*h/mL
$V_\beta/G*B$:	33.0	±	6.6 L/kg	19.7 ± 9.8L/kg

7.3.2 Neuroleptics

7.3.2.1 Highly potent neuroleptics

7.3.2.1.1 Haloperidol

Application: Haloperidol, a dopamine D2-receptor antagonist, is one of the most prescribed antipsychotic drugs worldwide. The treatment is indicated in the therapy of acute and chronic schizophrenia. Further indications are among others Tourette`s disorder, hyperactivity, and acute delirium. Methods of haloperidol incorporations are intravenous, intramuscular, and oral administrations. Beside the intravenous, the intramuscular administration has the advantages of rapid absorption and high bioavailability. Schaffer et al. (1982) compared the intramuscular and oral treatment of 8 schizophrenic patients with 10 mg resp. 20 mg haloperidol. The time required to reach peak plasma levels for intramuscular administration was only about half an hour vs. 101 min after oral intake. The relative bioavailability of oral administration, derived from the areas under plasma concentration-time curves, was only 38.3%.

Because of large variability in the pharmacokinetic of haloperidol, attempts have been made to predict a steady-state level, which is required for a therapeutic response after a single test dose (Khot et al., 1993). Javaid et al. (1996) evolved from results after administration of haloperidol in drug-free schizophrenic and schizoactive patients a nomogram, which can help to predict the maintenance dose for achieving the desired therapeutic steady-state level in the range from 5 to 20 ng/mL plasma.

Biotransformation: Haloperidol undergoes four main degradation steps. Oxidative dealkylation leads to an irreversible split of the molecule to p-fluoro-benzoyl-propionic acid and 4-(4-chlorophenyl)-4-hydroxypiperidine (CPHP). Fang et al. (1997) postulated that the two isoforms CYP3A4 and CYP2D6 are involved in the dealkylation reaction of haloperidol. Pan et al. (1997) demonstrated using human liver microsomes that CYP3A4 moderates the N-dealkylation. The formation of CPHP correlated with dextromethorphan (DM) N-demethylase activity and not with O-demethylase (CYP2D6), phenacetin O-deethylase (CYP1A2) or tolbutamide hydroxylase activity (CYP2C9). This could be confirmed with specific inhibitors of the cytochrome isoenzymes.

A NADPH dependent reductase, which catalyzes the conversion of haloperidol into the reduced form (oxo- into hydroxy derivative), was detected in the cytosol fraction of human and guinea pig liver homogenate (Inaba & Kovacs, 1989). The reaction was proved to be

stereospecific and leads to the S(-)-enatiomer (Eyles & Pond, 1992). Midha et al. (1989) found reduced haloperidol concentrations in plasma being generally much lower than those of the parent drug. The back oxidation to haloperidol was proved enzymatically in human liver microsomes and CYP2D6 is supposed as mediating enzyme (Tyndale et al., 1991). Kudo & Odomi (1998) and Pan et al. (1998) concluded from in vitro experiments with different CYP isoforms and specific inhibitors that CYP3A4 catalyzes the back oxidation to haloperidol.

In haloperidol treated psychotic patients, the plasma concentration of haloperidol glucuronide was the highest among the metabolites, followed by haloperidol, reduced haloperidol, and reduced haloperidol glucuronide (Someya et al., 1992). The authors supposed that glucuronidation is a major contributing factor in the interindividual variability of haloperidol biotransformation. A potentially neurotoxic pyridinium metabolite of haloperidol was first identified in urine samples of schizophrenic patients (Subramanyam et al., 1991) and then in plasma (Avent et al., 1997). Following results of in vitro investigations (Usuki et al., (1996), the conversion of haloperidol to the pyridinium metabolite is mediated by CYP3A4. The daily urinary excretion of the pyridinium metabolites of haloperidol and reduced haloperidol accounted to 0.4 resp 2.3% of the haloperidol dose (Eyles et al., 1994), while 1% is excreted as unchanged parent drug.

Interaction: Caused by participation of several isoenzymes of cytochrome P450, the biotransformation of haloperidol is influenced by enzyme inducing substances and drugs, the metabolism of which is mediated by those enzymes. Plasma haloperidol concentrations were decreased by about 60% after coadministration of carbamazepine for 2-3 weeks (Jann et al., 1985; Arana et al., 1986; Kidron et al., 1985). In similar way, the steady-state concentration of haloperidol was decreased by about 50%, caused by the inducing effect of rifampicin on CYP isoforms (CYP3A4, 2C9, and 2C19) in schizophrenic patients taking antituberculosis drugs, and the elimination half-life was shortened (4.9 hr) compared with the control group (9.4 hr) (Takeda et al., 1986). Pretreatment with the anticonvulants phenobarbitone and (or) phenytoin showed a decrease of the plasma haloperidol levels by 40-72% (Linnoila et al., 1980).

Concomitant administration of itraconazole, a potent inhibitor of CYP3A4, led to increased plasma concentrations of haloperidol and reduced haloperidol (16.9 ± 11.2 and 6.1 ± 6.6 ng/mL vs. 13.0 ± 7.9 and 4.9 ± 5.1) (Yasui et al., 1999). Further drugs increasing haloperidol levels are quinidine (Young et al., 1993), fluvoxamine (Daniel et al., 1994), and fluoxetine (Vandel et al., 1995). A comprehensive and detailed update of haloperidol pharmacokinetics is given by Kudo & Ishizaki (1999).

Evaluation of studies: The large variability of haloperidol plasma levels becomes apparent having a look at the dose and body weight normalized Cp0, Cmax, and AUC values in Table 85. The calculated standard deviation of Cp0 (1.20 ± 0.81) is so high, that it is not compatible with the formula for calculation of the plasma minimal and maximal concentration-time curves. A value of 0.5 was chosen, which leads to minimal and maximal curves being conformable with the C_{max} and AUC values so far as possible.

Table 85: 5 mg Haloperidol (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Yun et al., 2005	Myung In tablets (24)	23.3±1.65	5	0.587(2!)	1.33(2!)	1.61(2!)	24.4(2!)	0.648 (2)	43.8(2!)
«	Peridol® (24)	23.3±1.65	5	0.548(2!)	1.38(2!)	1.52(2!)	26.5(2!)	0.252(2!)	18.2(2!)
Park et al., 2006	CYP2D6*1 +(itraconazol) (8M)	24.5±2.2	5	1.12(2!)	1.72(2!)	2.30(2!)	17.8(2!)	0.848(2!)	18.5(2!)
«	CYP2D6*10 +(itraconazol) (7M)	24.5±2.2	5	1.50(2!)	1.51(2!)	2.57(2!)	18.0(2!)	0.666(2!)	36.3(2!)
Desai et al., 2003	extensive (8M)	32.1±4.0	10	-	-	-	13.1(2)	-	-
«	+ poor metabolizers (8F)	26.9±8.0	10	-	-	-	15.1(2)	-	-
Llerena et al., 1992	extensive (3M/3F)	27-58	4	0.979(2!)	1.08(2!)	1.23(2!)	18.9(2!)	0.688(2!)	6.25(2!)
«	and poor metabolizers (2M/4F)	26-47	4	1.88(2!)	0.942(2!)	0.967(2!)	23.0(2!)	1.31(2!)	3.13(2!)
Khot et al., 1993	+(steady-state) withdrawal (23)	19-45	14	3.09(1!)	3.09(2!)	2.16(2!)	18.4(2!)	0.469(2!)	43.1(2!)
Midha et al., 1989	intersubject variation (28M)	18-50	5	0.983(1!)	2.37(2!)	5.06(2!)	29.4(2!)	0.513(2!)	35.2(2!)
Holley et al., 1983	absolute bioavailability (1M)	31	34.65	2.37(2!)	0.266(2!)	1.68(2!)	21.1(2!)	0.195(2!)	32.8(2!)
«	(9M)	19-37	35.2	-	0.37(2!)	0.96(2!)	14.5(2!)	0.820(2!)	-
Isawa et al., 1999	+(carteolol, biperiden) (8M)	23-32	2	1.96(2!)	3.43(2!)	4.62(2!)	13.6(2!)	0.905(2!)	24.2(2!)
Schaffer et al., 1982	schizophrenic patients (5M/3F)	18-32	20	-	-	-	-	-	-
Magliozzi et al., 1985	schizophrenic patients	24-58	35	-	-	-	17.5(2)	-	-
	Mean			**1.20**	**1.87**	**2.52**	**21.5**	**0.590**	**31.2**
	± SD			**±0.81**	**±0.86**	**±1.47**	**±5.3**	**±0.243**	**±12.7**
	Number of trials			10	10	10	13	10	10
	Number of observations			135	144	144	166	144	144

Continuation of Table 85: 5 mg Haloperidol (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Yun et al., 2005	Myung In tablets (24)	0.790(2)	6.13(2)	19.8(2!)	63.6±8.65			
«	Peridol® (24)	0.772(2)	4.92(2)	20.3(2!)	63.6±8.65			
Park et al., 2006	CYP2D6*1 +(itraconazol) (8M)	1.38(2)	4.60(2)	30.1(2!)	74.1±8.5			
«	CYP2D6*10 +(itraconazol) (7F)	1.59(2)	4.60(2)	39.7(2!)	74.1±8.5			
Desai et al., 2003	poor and extensive (8M)	4.48(2)	2.9(2)	63.1(2)	62.3±6.7			
«	metabolizers (8F)	4.48(2)	2.9(2)	58.8(2)	82.5±14.2	65±14(2)		
Llerena et al., 1992	extensive (3M/3F)	1.36(2)	4.0(2)	29.7(2!)	77±12			
«	and poor metabolizers (2M/4F)	1.99(2)	4.0(2)	62.0(2!)	70±14			
Khot et al., 1993	+(steady-state) withdrawal (23)	3.75(1)	4.5(2)	83.2(1!)	-			
Midha et al., 1989	intersubject variation (28M)	1.41(1)	6.1(2)	45.3(1!)	-			
Holley et al., 1983	absolute bioavailability (1M)	5.42(2)	1.0(2)	80.65(2!)	69.1			
«	(9M)	-	-	-	70.8			
Isawa et al., 1999	+(carteolol, biperiden) (8M)	1.98(2)	5.6(2)	39.3(2!)	60.5			
Schaffer et al., 1982	schizophrenic patients (5M/3F)	2.30(2)	1.69(2)	-		38.3(2)		
Magliozzi et al., 1985	schizophrenic patients(6M)	-	-	-	(70)	64±23(2)		
	Mean ± SD	**1.90 ±1.31**	**4.79 ±1.27**	**39.8 ±20.8**		**55.0 ±12.8**		
	Number of trials	13	13	12		3		
	Number of observations	159	159	151		22		

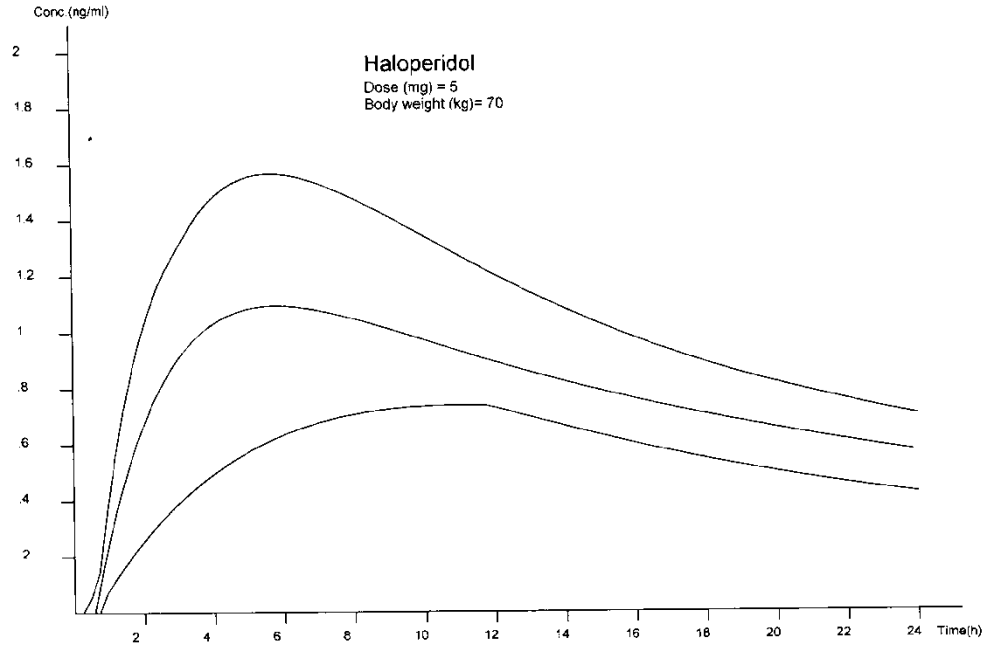


Figure 89: Plasma concentration-time curve of haloperidol after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	1.20	±	0.50	ng/mL	
Ka:	0.372	±	0.18	h^{-1}	
α:	0.275	±	0.101	h^{-1}	
β:	0.0322	±	0.0063	h^{-1}	
t_0:	0.590	±	0.243	h	
V%:	31.2	±	12.7%		
B:	55	±	12.8%		
					derived from time-course of plasma concentrations
C_{max}:	1.90	±	1.31 ng/mL		1.09 (0.74-1.56) ng/mL
t_{max}:	4.79	±	1.27 h		5.69 (5.69-11.0) h
AUC_{o-oo}:	39.8	±	20.8ng*h/mL		36.5 (25.0-51.2) ng*h/mL

7.3.2.2 Low potent neuroleptics

7.3.2.2.1 Promethazine

Application: Promethazine is a member of the phenothiazine group, widely used as antihistaminic, sedative, hypnotic, and antiemetic drug. The different routes of administration, intravenous, intramuscular, oral, and rectal have been compared in several studies relating to pharmacokinetic parameters. Oral intake of promethazine containing syrup showed similar relative bioavailability as rectal administration of different formulations of suppositories, however, the polyethylene glycol additive in the suppositories had the advantage to cacao butter-white wax of shorter time to peak serum concentration and statistically higher peak levels (Stavchansky et al., 1987). On an average, absorption was more rapid and peak levels higher for the syrup than for the suppositories. The time of C_{max} was statistically significant shorter for the syrup. (Mean 4.4 hr) than for the suppositories (6.7-8.6 hr). All the formulations were comparable in terms of dose normalized AUC and C_{max} values. No statistically significant differences in pharmacokinetics, on the base of sex or race, were observed (Strenkoski-Nix et al., 2000). After intramuscular administration of 25 mg promethazine, the blood concentration was four times higher than after oral intake. From the mean parotid saliva to whole blood ratio, a percentage of free drug in blood of 20-24% was determined (DiGregorio & Ruch, 1980). Similar results were obtained by Schwinghammer et al. (1984) at their comparison of oral, rectal, and intramuscular dosing.

Biotransformation: The low bioavailability of promethazine is due to a high first-pass metabolism. Investigations of Dahl (1976) have suggested that the sulphoxide, the main metabolite of promethazine in analogy to methotrimeprazine, is found following oral intake and not after intramuscular administration. The authors suggested from this finding that S-oxidation is limited to the gut wall and only occurs during the absorption process. But the study of Taylor et al. (1983) revealed that the area under the blood concentration-time curve was not dependent on the administration route, so that the S-oxidation is proved to occur in the liver and not in the gut wall. Maximum blood concentration of promethazine sulphoxide was attained between 4 and 10 hours after intravenous administration, earlier than after oral dosing. Peak and post-peak promethazine sulphoxide concentrations exceeded those of the parent drug, independently of the administration route. The excretion into the urine accounted for an average of 10%, that of the parent drug less than 1%. Low concentrations of monodesmethylpromethazine were detected in most of the subjects. The peak level was up to

1 ng/mL, in few cases 1 ng/mL was exceeded (Taylor et al., 1983). In postmortem human material, additionally didesmethylpromethazine was detected (Allender & Archer, 1984). Ring-hydroxylated and N-oxygenenated metabolites are identified in vitro with rabbit liver homogenate (Clement & Beckett, 1981).

Interaction: Interaction of carbamazepine and promethazine was revealed in rabbits after coadministration of both drugs. Plasma level of carbamazepine was suppressed by induction and the character of the promethazine curve was influenced by carbamazepine (Rukhadze et al., 2003). Induction of hepatic enzymes in man by phenothiazines (chlorpromazine) was demonstrated, too (Galanopoulou et al., 1990; Rivera-Calimlim, 1982).

Evaluation of studies: Pharmacokinetic studies, used for calculation of the average pharmacokinetic parameters, have been performed with single oral doses of 25 and 50 mg. Dose normalized values of C_{max}, AUC, and Cp0 are in good accordance, so that dose proportionality in the range of 25 to 50 mg dose just as bioequivalence of promethazine solution and tablet formulations is to be assumed (Zaman et al., 1986).

Table 86: 25mg Promethazine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Taylor et al., 1983	intravenous (7M)	24-29	12.5	-	-	-	12.2(2)	-	-
«	intravenous (1M)	30	12.5	-	-	-	10.7(2!)		-
«	oral (1M)	30	25	3,06(1!)	1.18(2!)	1.27(2!)	9.87(2!)	0.884(2!)	2.73(2!)
Zaman et al., 1986	bioequivalency (15M) solution	18-32	50	5.81(1!)	0.510(2!)	0.536(2!)	9.14(2!)	0.372(2!)	32.8(2!)
«	(15M) cord tablet	18-32	50	6.23(1!)	0.660(2!)	0.495(2!)	8.25(2!)	0.423(2!)	34.9(2!)
«	(15M) Wyeth tablet	18-32	50	5.62(1!)	1.32(2!)	0.493(2!)	8.71(2!)	0.522(2!)	4.69(2!)
«	(15M) Wyeth tablet	18-32	25	7.92(1!)	0.913(2!)	0.598(2!)	6.72(2!)	0.509(2!)	24.6(2!)
Schwinghammer et al., 1984	solution (24M)	20-31	50	5.54(1!)	1.26(2!)	0.500(2!)	6.69(2!)	0.326(2!)	4.39(2!)
Gandia et al., 2006	(12M) ambulatory	29±6	50	6.90(2!)	1.01(2!)	1.99(2!)	16.6(2!)	432(2!)	24.6(2!)
«	+ (intramuscular) (12M) bed rest	29±6	50	10.8(2!)	1.41(2!)	1.48(2!)	13.0(2!)	144(2!)	4.10(2!)
Koytchev et al., 1994	bioavailability (6M/6F)	21-40	75	8.54	1.20	1.36	16.0	0.050	11.5
«	+(promazine + chlorpromazine) (6M/6F)	21-40	50	-	-	-	15.6	-	-
	Mean ± SD			**7.29 ±1.78**	**1.04 ±0.30**	**1.42 ±0.21**	**10.4 ±3.5**	**0.360 ±0.154**	**16.9 ±12.5**
	Number of trials			9	9	9	12	9	9
	Number of observations			121	121	121	141	121	121

Continuation of Table 86: 25mg Promethazine (absorption, distribution and elimination).

Evaluated studies	**Data from comparative single dose studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{o-oo} (ng*h/mL)**	**G (kg)**	**B (%)**	**V_β/B (L)**	**V_β/G (L/kg)**
Taylor et al., 1983	intravenous (7M)	-	-	-	72.4	25		
"	intravenous (1M)	-	-	-	-	20.5		
"	oral (1M)	5.14(1)	3.0(2)	52.2(1!)	-	-		
Zaman et al., 1986	bioequivalency (15M) solution	9.16(1)	1.8(2)	85.6(1!)	62.1-90.1	-		
«	(15M) cord tablet	8.44 (1)	2.4(2)	80.5(1!)		-		
«	(15M) Wyeth tablet	7.00(1)	3.0(2)	74.3(1!)		-		
«	(15M) Wyeth tablet	7.91(1)	3.1(2)	74.9(1!)		-		
Schwinghammer et al., 1984	solution (24M)	8.65(2)	2.3(2)	88.3(2!)	78	28.72		
Gandia et al., 2006	(12M) ambulatory	11.5(2)	2.9(2)	185(2!)	71.5±9.0	-		
«	+ (intramuscular) (12M) bed rest	15.9(2)	3.2(2)	207(2!)	71.5±9.0	-		
Koytchev et al., 1994	bioavailability (6M/6F)	10.1(2)	3.4(2)	197(2)	69	20.1		
«	+(promazine + chlorpromazine) (6M/6F) i.v.	-	-	-	69	«		
	Mean ± SD	**9.99 ±2.63**	**2.8 ±0.5**	**127 ±56**		**25.6 ±3.8**		
	Number of trials	9	9	9		4		
	Number of observations	121	121	121		40		

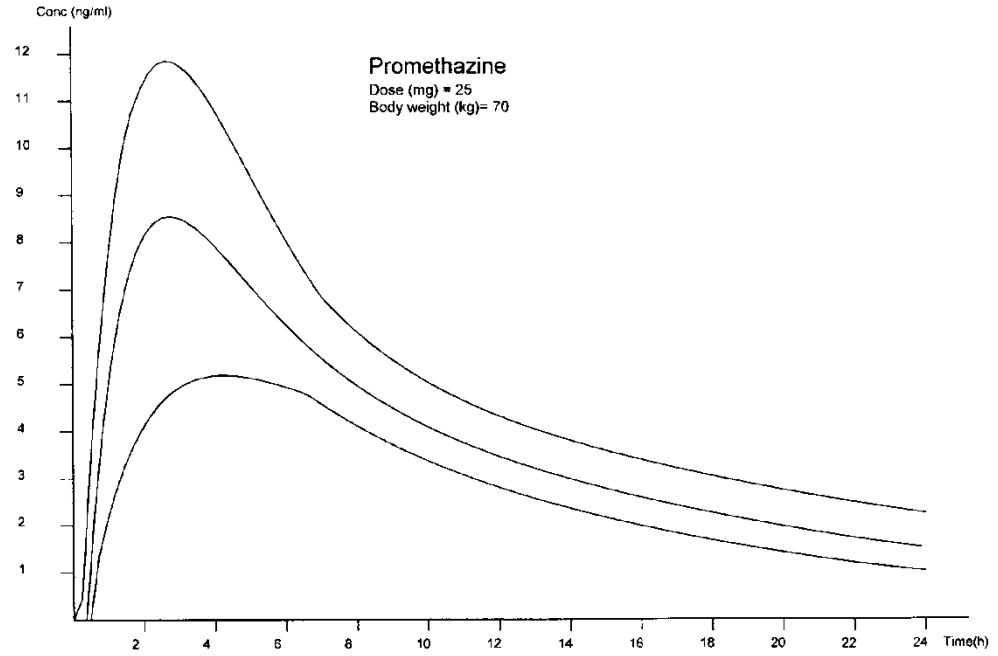


Figure 90: Plasma concentration-time curve of promethazine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	7.29	±	1.78	ng/mL	
Ka:	0.666	±	0.149	h^{-1}	
α:	0.490	±	0.065	h^{-1}	
β:	0.0666	±	0.0167	h^{-1}	
t_0:	0.360	±	0.154	h	
V%:	16.9	±	12.5	%	
B:	5.6	±	3.8	%	
					derived from time-course of plasma concentrations
C_{max}:	9.99	±	2.63 ng/mL		8.55 (5.18-11.9) ng/mL
t_{max}:	2.8	±	0.5 h		2.76 (2.64-4.32) h
$AUC_{o\text{-}oo}$:	127.6	±	56 ng*h/mL		117.7 (79.8-171.9) ng*h/mL

7.3.2.2.2 Sulpiride

Application: Sulpiride is an antipsychotic drug predominantly used for treatment of schizophrenia and depression. The biochemical effect is inhibition of dopamine D2 receptors. Because of relatively fast elimination, the daily dose is to be divided in two or three single doses; steady-state will be reached within 2-3 days (Wiesel et al., 1980). A linear relationship between dose and AUC resp. bioavailability in the range from 200 to 400 mg was demonstrated by Bressolle et al. (1992). After intramuscular administration in the range of 50 to 200 mg, pharmacokinetics was proven to be linear and independent of the dose (Bressolle et al., 1984). The absolute bioavailability after oral intake shows a large individual variability in comparison to intravenous or intramuscular administration. The average derived from serum concentrations was 35.5 ± 21.3%, that from urine excretion 23.3 ± 8.3%. Combined from plasma and urine data a value of 26.9 ± 8.8% was determined (Wiesel et al., 1980). The authors supposed an incomplete absorption as cause for the low bioavailability and not a first-pass metabolism. Sulpiride is metabolized in man if at all to a very small degree. That results from the high excretion rates of the drug after intravenous and intramuscular administration in the range from 90 to 95%.

Biotransformation: Metabolites of sulpiride (SP) could be identified in animal experiments. In rats a demethylation product, O-desmethyl-SP, a deethylation product, N-desethyl-SP, and oxo-derivatives, 5-oxo-pyrrolidine-SP and N-desethyl-5-oxo-pyrrolidine-SP were detected by Dross (1978). Into urine of rhesus monkeys, 60-80% of a sulpiride dose was excreted as unchanged drug and 10-30% as 5-oxo-pyrrolidine-SP, whereas in man the amount of unchanged drug was 95%. No metabolites were identified (Imondi et al., 1978; Brennan et al., 1982).

Interaction: The lack of hepatic metabolism makes metabolic interactions with substances acting as substrates of cytochrome P450 very unlikely (Corazza & Tonini, 2000). The absorption profile is complex. Rietbrock et al. (1995) assumed a pronounced lag time and different absorption rates along the gastrointestinal tract. The bioavailability, calculated from the cumulative amount of sulpiride excreted unchanged into the urine over 48 hours was dependent on the acid content of the stomach. After concomitant intake of 1 g sodium bicarbonate or during cimetidine dosing (200 mg three times a day), the absorbed amount from AEA® film-coated tablets in high bioavailability subjects was markedly reduced. In low bioavailability subjects, a coadministration of orange juice or hydrochloric acid led to an increase of sulpiride absorption (Shinkuma et al., 1989). Under the fasting state of cimetidine

induced achlorhydric subjects, the bioavailability from AEA® film-coated tablets was very poor, but it increased 6-fold with food intake (Shinkuma et al., 1991). In patients with impaired renal function, the elimination half-life was prolonged and the amount of unchanged sulpiride was statistically significant reduced. A 35-70% reduction of the dosage was suggested in renal impaired patients (Bressolle et al., 1989).

Evaluation of studies: From Table 87 it is observable, that the elimination half-life shows a relatively low variability, whereas the deviations of Cp0, C_{max}, and AUC are higher. Wiesel et al. (1980) determined a distribution factor of 2.72 ± 0.66 L/kg during the terminal slope of sulpiride. The average derived from 4 studies and 28 observations (Figure 91) was 2.88 ± 1.03 L/kg and in good accordance to the published value.

Table 87: 100 mg Sulpiride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Wiesel et al., 1980	Intravenous and oral (1)	25-34	100	98.0(2!)	0.433(2!)	2.61(2!)	10.6 (2!)	0.892(2!)	65.1(2!)
«	sulpiride (1)	25-34	100	-	-	-	6.2(2)	-	-
«	in healthy (1)	25-34	100	-	-	-	7.5(2)	-	-
«	human subjects (1)	25-34	100	138.4(2!)	1.30(2!)	5.46(2!)	10.6 (2!)	0.360(2!)	65.1(2!)
«	(1)	25-34	100	-	-	-	15.4(2)	-	-
«	(1)	25-34	100	-	-	-	12.1(2)	-	-
Rietbrock et al., 1995	absorption behaviour capsule (6M/6F)	25-30	100	-	-	-	-	-	-
«	tablet (6M/6F)	25-30	100	-	-	-	-	-	-
Cho et al., 2004	bioequivalence reference (12M)	25-30	25	195.7(2!)	0.924(2!)	3.87(2!)	9.07(2!)	0.266(2!)	86.1(2!)
«	tablet (12M)	25-30	25	217.3(2!)	0.701(2!)	4.42(2!)	8.77(2!)	0.312(2!)	98.4(2!)
Brès & Bressolle, 1991	intravenous (8M))	19-30	100	-	-	-	6.27(2)	-	-
«	+ (red blood cells) (7F)	19-29	100	-	-	-	6.70(2)	-	-
Chen et al., 1989	before washout period (6M)	27.6±4.7	400	-	-	-	8.37(2)	-	-
«	after washout period (6M)	27.6±4.7	400	-	-	-	8.01(2)	-	-
Bressolle et al., 1992	bioavailability solution (6M/6F)	27±3	200	-	-	-	6.73(2)	-	-
«	solution (1M)	27±3	200	531(1!)	0.592(2!)	0.967(2!)	6.82(2!)	0.122(2!)	16.4(2!)
«	solution (1M)	27±3	200	106.4(1!)	0.385(2!)	3.48(2!)	7.33(2!)	0.164(2!)	84.8(2!)
	Mean ± SD			**204.1 ±53.8**	**0.793 ±0.181**	**4.00 ±0.76**	**7.98 ±1.54**	**0.264 ±0.104**	**87.3 ±16.5**
	Number of trials			4	4	4	8	4	4
	Number of observations			28	28	28	65	28	28

Continuation of Table 87: 100 mg Sulpiride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Wiesel et al., 1980	Intravenous and oral (1)	118(2)	3.00(2)	1600(2!)	78	23.8(2)		
«	sulpiride (1)	-	-	2468(2)	94	59.2(2)		
«	in healthy (1)	-	-	686(2)	72	13.8(2)		
«	human subjects (1)	138(2)	6.00(2)	2213(2!)	69	62.9(2)		
«	(1)	-	-	1134(2)	53	29.6(2)		
«	(1)	-	-	522(2)	58	14.6(2)		
Rietbrock et al., 1995	absorption behaviour capsule (6M/6F)	246(2)	3.40(2)	2641(2)	67±12	39(2)		
«	tablet (6M/6F)	259(2)	3.20(2)	2707(2)	67±12	40(2)		
Cho et al., 2004	bioequivalence reference (12M)	168.1(2)	3.00(2)	2431(1!)	65.9±8.30	-		
«	tablet (12M)	195.6(2)	3.00(2)	2443(1!)	65.9±8.30	-		
Brès & Bressolle, 1991	intravenous (8M))	-	-	-		-		
«	+ (red blood cells) (7F)	-	-	-		-		
Chen et al., 1989	before washout period (6M)	391(2)	1.50(2)	3613(2)	74.6±7.7	-		
«	after washout period (6M)	392(2)	1.25(2)	2634(2)	74.6±7.7	-		
Bressolle et al., 1992	bioavailability solution (6M/6F)	334(2)	1.47(2)	1004(2)	66±7			
«	solution (1M)	605(1)	1.50(2)	6082(1!)		30(2		
«	solution (1M)	124(1)	1.00(2)	1148(1!)		-		
	Mean **± SD**	**263** **±84**	**2.59** **±0.93**	**2335** **±801**		**37.0** **±9.0**		
	Number of trials	8	8	8		4		
	Number of observations	76	76	77		36		

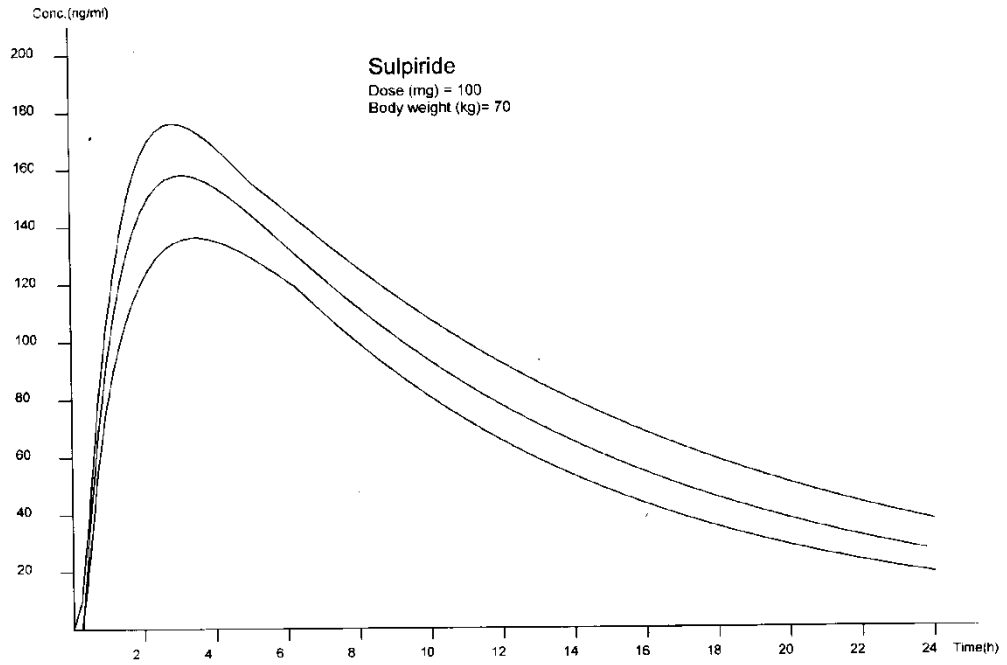


Figure 91: Plasma concentration-time curve of sulpiride after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	204.1	±	53.8	ng/mL
Ka:	0.874	±	0.162	h^{-1}
α:	0.173	±	0.027	h^{-1}
β:	0.0869	±	0.0141	h^{-1}
t_0:	0.264	±	0.104	h
V%:	87.3	±	16.5%	
B:	37.0	±	9.0%	

				derived from time-course of plasma concentrations
C_{max}:	263	±	84ng/mL	158 (136-176) ng/mL
t_{max}:	2.59	±	0.93 h	2.96 (2.88-3.60) h
AUC_{o-oo}:	2335	±	801 ng*h/mL	2251 (1836-2782) ng*h/mL
Vd=	2.88	±	1.03 L/kg	

7.3.2.3 Atypical neuroleptics

7.3.2.3.1 Olanzapine

Application: Olanzapine has been shown to be effective in treatment of patients with schizophrenia and psychosis of a schizoaffective nature. Affinity exists to serotoninergic and dopaminergic receptors. Furthermore anticholinergic and histaminergic activities occur with lower appearance of extrapyramidal symptoms than with conventional antipsychotic agents. Following single doses of 2.5 to 15 mg olanzapine, dose-proportional concentrations were observed.

The influence of age on the pharmacokinetics of olanzapine was demonstrated in a study with a group of young people (20-41 yr) and elderly (65-79 yr). The mean elimination half-life was prolonged by 53%, in similar manner the area under the curve was elevated (Callaghan et al. 1999).

Biotransformation: Olanzapine is metabolized in manifold way. Oxidation on the allylic methyl group results in 2-hydroxymethyl and carboxylic acid derivatives. N-oxide formation, N-desmethylation, and glucuronidation are further steps of biotransformation (Kassahun et al. 1997). The in vitro formation kinetics was studied in vitro by Ring et al. (1996). These experiments suggest that the isoenzyme of Cytochrome P450, CYP1A2, catalyzes N-desmethyl-olanzapine and 7-hydroxy-olanzapine formation, whereas CYP2D6 mediates hydroxylation of olanzapine to 2-hydroxymethyl-olanzapine, and a flavine-containing monooxygenase an N-oxididation to the N-oxide.

Interaction: The plasma clearance of olanzapine is elevated still more pronounced in smoking subjects compared to non-smokers than in male volunteers compared with females (Kassahun et al. 1997). A collective of male smoking schizophrenic patients with up to 4 cigarettes per day showed compared with that of non-smokers an 45.1% decrease of AUC, that of heavy smokers an decrease of 67.6%. A daily consumption of 5 cigarettes seems to be sufficient for an induction of olanzapine metabolism (Wu et al. 2008). Similar as nicotine carbamazepine induces liver microsomal enzymes, above others the P450 system that catalyzes the oxidative metabolism of olanzapine (Moreland et al. 1982; Parker et al. 1998). Thus an administration of 200 mg carbamazepine twice daily for two weeks and a single dose of 10 mg olanzapine led to an about 20% reduction of peak concentrations and elimination half-lives (Lucas et. al.1998).

Statistically significant changes of pharmacokinetic parameters have been observed after combined administration of olanzapine and inhibitors of Cytrochrome P450 enzymes. Fluvoxamine was recognized as inhibitor of CYP1A2 (Brøsen et al. 1993). In a placebo-controlled study Mäenpää et al. (1997) observed that concomitant treatment with fluvoxamine led to elevated olanzapine serum levels and decreased serum concentrations of N-desmethylolanzapine. Prolonged elimination, markedly increased peak concentrations, and areas under plasma level curves occurred after a concomitant administration of olanzapine and fluvoxamine (Chiu et al. 2004). Similarly, in a single patient, de Jong et al. (2001) demonstrated that the combined intake of fluvosamine (150 mg/day) and olanzapine (15 mg/day) for several months resulted in an olanzapine concentration of 120 ng/mL and a fluvoxamine level of 70 ng/mL. Fluvoxamine was replaced by paroxetine (20 mg/day) and the olanzapine dosage reduced to 5 mg/day. This resulted in concentrations of 27 ng/mL paroxetine and 22 ng/mL olanzapine. A doubling of the serum olanzapine level was observed after combination of the CYP1A2 inhibitor ciprofloxacin and olanzapine. The elevation of olanzapine level reversed, when the antibiotic was discontinued (Markowitz & DeVane, 1999).

The antidepressant imipramine is metabolized in similar way as olanzapine by oxidative reactions catalyzed by cytochrom P450 isoenzymes. But in vivo interaction study by Callaghan et al (1997) showed only a low elevation of olanzapine levels whereas the course of imipramine concentrations was not statistically significant affected. Similarly light effects occur after concomitant administration of olanzapine and fluoxetine (Gossen et al 2002). C_{max} was increased by 18% and the clearance decreased by 15%, whereas the elimination and t_{max} were not altered. No interactions of following substances have been stated: alcohol, aminophylline, Mylanta®, an antacid on the base of aluminium hydroxide und magnesium hydroxide, biperiden, cimetidine, diazepam, lithium und warfarin (Callaghan et al 1999).

Evaluation of studies: Results of pharmacokinetic and pharmacodynamic studies have been referred in the review article of Callaghan et al. (1999). In Table 88 (first line) median elimination half-lives and fictive initial concentrations, calculated from the given distribution volumes, the body weight of 70 kg, and 10 mg dose, are listed basing on a heterogenic collective of 279 subjects and 470 observations. Statistically significant differences between ethnic groups (Caucasians, Chinese, and Japanese) were not observed (Callaghan et al. 1999, Sathirakul et al. 2003). Further factors such as smoking and gender both seem to affect the pharmacokinetics more than the ethnic origin. The large part of smokers and male subjects in the collective of more than 470 observations is held responsible for a 30% increase of

distribution volumes (Sathirakul et al. 2003). Thus this value was not taken for averaging Cp0. Against that the elimination half-life of 33.1 h is in good accordance with those of the remaining studies.

Further results in Table 88 originate from studies with graphs newly evaluated. At this placebo experiments were used for calculating the mean values. Because in the range of therapeutic dosage peak concentrations and areas under the plasma concentration-time curves were proved as proportional to the doses, the parameters dependent on the dose could be standardized (70 kg body weight and 10 mg dose). The calculated standard deviation of V% is only slightly lower than the mean value. Therefore it is not compatible with the formula for computing the maximal plasma concentration-time curve and was not used.

Table 88: 10 mg Olanzapine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	Evaluated studies
Callaghan et al. 1999	healthy volunt. (165M/28F) n = 479-491	19-79	2,5 - 15	8,97±2,34 (1)	-	-	33,1±10,3 (1)	-	-
Callaghan et al. 1997	pla. (imipramine) (9M)	32-54	5	8,77 (2!)	1,72(2!)	2,40(2!)	22,7 (2!)	0,76 (2!)	49,2 (2!)
Callaghan et al. 1999 Ref. 39	pla. (antacid, Cimetidin, charcoal)(8)	?	7,5	11,2(1!)	1,83(2!)	1,85(2!)	26,6(2!)	1,4(2!)	1,5(2!)
Callaghan et al. 1999 Ref. 9	(12-16)	?	5	9,66(1!)	2,97(2!)	3,77(2!)	34,7(2!)	0,38(2!)	17,3(2!)
„	(12-16)	?	10	9,28(1!)	2,39(2!)	2,48(2!)	31,7(2!)	0,63(2!)	2,34(2!)
„	(12-16)	?	15	11,3(1!)	1,57(2!)	2,71(2!)	30,4(2!)	0,66(2!)	32,8(2!)
Callaghan et al. 1999 Ref. 17	Caucasians (Japaneses, Chineses) (6)		2,5	17,7(1!)	1,52(2!)	1,33(2!)	23,2(2!)	1,05(2!))	87,5(2!)
„	(6)		5	14,5(1!)	1,15(2!)	1,34(2!)	331,8(2!)	0,96(2!)	17,6(2!)
„	(6)		10	11,8(1!)	1,41(2!)	2,82(2!)	33,7(2!)	0,95(2!)	35,2(2!)
„	(6)		15	17,6(1!)	1,37(2!)	1,44(2!)	27,6 (2)	1,78(2!)	8,2(2!)
Gossen et al. 2002	placebo (fluoxetine) (11M/4F)	32 ± 5	5	15,4±6,0(2)	-	-	32,2±19,8(2)	-	-
Sathirakul et al 2003	Caucasian (12 M)	21-31	2,5	15,3(2)	-	-	30,0(2)	-	-
„	Caucasian (12 M)	**„**	5	15,3(2)	**-**	-	29,1(2)	-	-
„	Caucasian (12 M)	„	10	15,9(2)	**-**	-	28,7(2)	-	-
„	Chinese (12M)	21-32	2,5	14,0(2)	-	-	29,5(2)	-	-
„	Chinese (12M)	„	5	12,7(2)	**-**	**-**	31,2(2)	-	-
„	Chinese (12M)	„	10	13,3(2)	**-**	**-**	29,6(2)	**-**	**-**
	Mean ± SD			**13,5 ± 2,5**	**1,53 ± 0,59**	**2,4 ± 0,78**	**32,3 ± 8,4**	**0,84 ± 0,39**	**25,1 ± 23,3**
	Number of trials			16	9	9	16	9	9
	Number of observations			170	83	83	170+491	83	83

Continuation of Table 88: 10 mg Olanzapine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Callaghan et al. 1999	healthy volunteers (165M/28F) n = 479-491	-	-	-	-		1148±360	-
Callaghan et al. 1997	placebo (imipramine) (9M)	7,63(1!)	6(2!)	272,8(1!)	68,8 ± 2,4	-	-	(1,53)
Callaghan et al. 1999 Ref. 39	placebo (antacid, Cimetidin, charcoal) (8)	11,3(1!)	6(2!)	416(1!)	-	-		
Callaghan et al. 1999 Ref. 9	(12-16)	10,64(1!)	7(2!)	494(1!)	-	-		
„	(12-16)	11,19(1!)	5(2!)	443(1!)	-	-		
„	(12-16)	12,53(1!)	4(2!)	506(1!)	-	-		
Callaghan et al. 1999 Ref. 17	Caucasians (Japaneses, Chineses) (6)	13,6(1!)	5(2!)	535(1!)	-	-	-	-
„	(6)	15,5(1!)	4(2!)	605(1!)	-	-	-	-
„	(6)	14,1(1!)	5(2!)	543(1!)	-	-	-	-
„	(6)	15,6(1!)	10(2!)	683(1!)	-	-	-	-
Gossen et al. 2002	placebo (fluoxetine) (11M/4F)	15,4±6,0 (2)	3(2)	552±230 (2)	71±13(2)	-	-	-
Sathirakul et al 2003	Caucasian (12 M)	15,7(2)	8(2)	668(2)	71,3±6,8	-	727(2)	10,1(2)
„	Caucasian (12 M)	14,1(2)	6(2)	655(2)	„	-	805(2)	11,2(2)
„	Caucasian (12 M)	15,6(2)	7(2)	664(2)	„	-	765(2)	10,7(2)
„	Chinese (12M)	16,8(2)	6(2)	595(2)	65,3±6,7	-	611(2)	9,32(2)
„	Chinese (12M)	15,0(2)	6(2)	597(2)	**„**	-	608(2)	9,32(2)
„	Chinese (12M)	16,1(2)	4(2)	589(2)	**„**	-	587(2)	8,89(2)
Kassahun et al. 1997	Wiederfindung von ^{14}C (6M)	-	-	-	**-**	87%	**-**	**-**
	Mean ± SD	**14,4 ±2,2**	**5,6 ± 1,6**	**573 ± 91**		**87%**	**684 ±89**	**9,92 ±0,86**
	Number of trials	16	16	16				
	Number of observations	170	170	170				

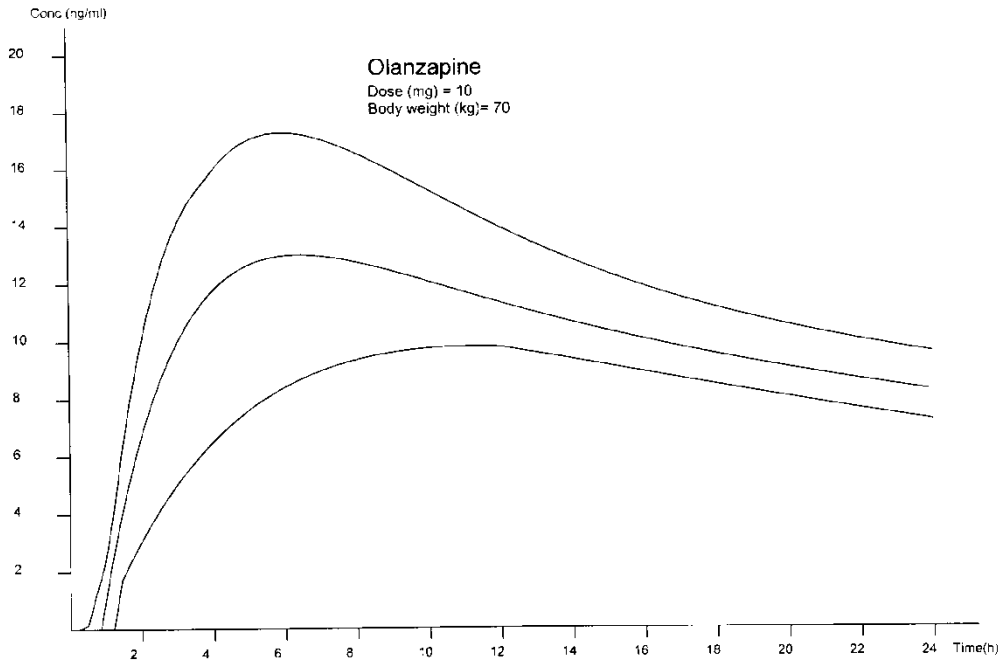


Figure 92: Plasma concentration-time curve of olanzapine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	13,5	±	2,5	ng/mL
Ka:	0,359	±	0,084	h^{-1}
α:	0,283	±	0,068	h^{-1}
β:	0,0215	±	0,0055	h^{-1}
t_0:	0,84	±	0,39	h
V%:	25,1 %			
B:	87 %			

				derived from time-course of plasma concentrations
C_{max}:	13,5	±	2,2 ng/mL	13,8 (9,84-17,27) ng/mL
t_{max}:	5,6	±	1,6 h	6,54 (6-11,52) h
AUC_{o-oo}:	573	±	91 ng_*h/mL	619,3 (452,1-865,0) ng_*h/mL
V_β/G:	9,92	±	0,86 L/kg	9,79 ± 2,23 L/kg

7.3.3 Tranquillizers

7.3.3.1 Medium-length acting tranquillizers

7.3.3.1.1 Bromazepam

Application: Bromazepam is a benzodiazepine introduced primarily as an anxiolytic agent. An antianxiety therapy with a mediate acting drug ($t_{½}\beta$ = 10-20 hr) requires at least 2 divided daily doses. Comparing the pharmacokinetic properties of bromazepam with those of other benzodiazepines, they are regular and easy to survey. Elimination half-lives and distribution volumes vary in a comparatively slight range of variation.

Biotransformation: The major metabolic pathway is the oxidative hydroxylation of bromazepam yielding 3-hydroxybromazepam (Schwartz et al., 1973), which is supposed to have some pharmacological activity (Jochemsen & Breimer 1984). But conjugation with glucuronic acid leads to an inactive metabolite, which is rapidly excreted into the urine. A second pathway is cleavage of the diazepine ring yielding 2-amino-5-bromo-benzylpyridine, which is hydroxylated to 2-amino-3-hydroxy-5-bromo-benzylpyridine. Glucuronidation leads in this case to a water soluble and rapidly excretable product, too (Schwartz et al., 1973; de Silva et al., 1974).

Interaction: Ochs et al. (1987) studied the influence of age, gender, oral contraceptives, cimetidine, and propranolol on the pharmacokinetics of bromazepam. Gender had no statistically significant influence and comparing the kinetics in young female users of oral contraceptive steroids with age- and weight-matched control women, no differences were observed. In the group of elderly subjects (aged 60 to 81 yr), statistically significant higher peak concentrations (132 vs. 82 hr) were determined than in young subjects (aged 21 to 29 yr). Distribution volumes and oral clearances were decreased and serum free fraction was increased. Coadministration of cimetidine, a non-specific inhibitor of CYP, reduced bromazepam clearance (34.8% vs. 28.8%) and prolonged half-life (29 vs. 23 hr). Using propranolol for coadministration, the influence only on the elimination half-life was statistically significant (28 vs. 23 hr). But it has not yet been clarified, which isoenzyme is involved. Fluconazole, an inhibitor of CYP2C9 and CYP3A4, caused no statistically significant changes in pharmacokinetics and pharmacodynamics of oral or rectal administered bromazepam (Ohtani et al., 2002).

Evaluation of studies: Table 89 and Figure 93 show the rapid absorption of bromazepam after oral administration with a lag time of 0.057 hr, a high absorption constant of 2.29 hr, and a low time of 1.5 hr at the peak concentration. The high bioavailability of 84% points to a low first-pass metabolism and may explain the conformity of the normalized pharmacokinetic parameters C_{max} and Cp0 at a dosage from 1.5 to 10 mg. That means, that a linear relation exists between concentration and dose in the range from 1.5 to 10 mg. Tablets, capsules, and drops were used as oral formulations and showed the same relative bioavailability (Podilsky et al., 2009). Pharmacokinetic parameters derived from the studies of Lerner et al., (2001) except for the elimination half-lives were not used for calculation of the mean values, because slow release formulations were administrated. The elimination half-lives from the study of Fujii et al. (1990) were not used for the calculation; because the space of observation time was too short (10 hr). The mean value of V% is high (68%). That means that the distribution process does not play an important part in the course of the plasma concentration- time curve, which can be described approximately by a one compartment model, too.

Table 89: 3 mg Bromazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Oda et al., 2003	(8M)	20-27	3	32.3(1!)	0.110(2!)	2.85(2!)	29.9(2!)	0.046(2!)	93.0(2!)
,,	+ itraconazol (8M)	20-27	3	34.7(1!)	0.314(2!)	1.43(2!)	31.1(2!)	0.024(2!)	72.1(2!)
Ascalone et al., 1984	healthy adult (6) capsule		3	36.8(1!)	0.289(2)	1.07(2!)	22.7(2)	0.012(2)	49.6(2)
"	vlunteers (6) drops		3	36.3(1!)	0.239(2!)	0.603(2!)	21.5(2!)	0.011(2!)	49.2(2!)
"	(6) drops		1.5	28.9(1!)	0.231(2!)	1.10(2!)	19.5(2!)	0.015(2!)	49.8(2!)
"	(1) capsule		3	38.45(1!)	0.151(2!)	0.408(2!)	17.2(2)	0.046 (2!)	42.4(2!)
"	(1) capsule		3	34.13(1!)	0.030(2!)	0.251(2!)	18.9(2)	0.009 (2!)	24.8(2!)
"	(1) capsule		3	36.1(1!)	0.257(2!)	0.700(2!)	18.9(2!)	0.009 (2!)	46.1(2!)
"	(1) capsule		3	33.3(1!)	0.630(2!)	0.845(2!)	25.8(2!)	0.290 (2!)	16.4(2!)
"	(1) capsule		3	44.53(1!)	0.161(2!)	6.30(2!)	18.3(2!)	0.007 (2!)	98.2(2!)
"	(1) capsule		3	63.6(1!)	0.231(2!)	1.47(2!)	17.0(2!)	0.055 (2!)	86.8(2!)
von Stetten et al., 1983	bioavailability from tablets (10M)	18-27	6	42.9(2!)	0.301(2!)	1.60(2!)	20.0(2!)	0.019 (2!)	96.1(2!)
"	(10M)	18-27	6	42.6(2!)	0.107(2!)	0.587(2!)	17.8(2!)	0.036 (2!)	73.8(2!)
Podilsky et al., 2009	bioavai. given by nasog. tube (4M/4F)	21-27	3	42.6(1!)	0.192(2!)	0.275(2!)	42.3(2!)	0.003(2!)	72.7(2!)
Gonçalves et al., 2005	reference (24M)	19-47	6	28.3(1!)	0.320(2!)	4.56(2!)	30.5(2!)	0.008(2!)	68.8(2!)
"	test (24M)	19-47	6	27.3(1!)	0.250(2!)	0.299(2!)	27.1(2!)	0.159(2!)	65.6(2!)
Fujii et al., 1990	fasting state (4M/4F)	22-30	10	52.4(2!)	0.265(2!)	0.601(2!)	(15.3)	0.007(2!)	99.2(2!)
"	non-fasting state (4M/4F)	22-30	10	36.1(2!)	1.15(2!)	1.35(2!)	(18.9)	0.215(2!)	21.7(2!)
Lerner et al., 2001	slow release reference (24)	18-43	3	(15.1)	(3.57)	(3.05)	18.02(2!)	(0.081)	(87.5)
"	slow release test (24)	18-43	3	(15.1)	(2.24)	(3.04)	15.57(2!)	(0.157)	(87.5)
	Mean ± SD			**36.9 ±8.1**	**0.303 ±0.229**	**1.65 ±1.60**	**23.7 ±7.0**	**0.057 ±0.072**	**68.2 ±19.8**
	Number of trials			13	13	13	18	13	13
	Number of observations			132	132	132	164	132	132

Continuation of Table 89: 3 mg Bromazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Oda et al., 2003	(8M)	43.1(1)	0.75(2)	1393(2!)	54-80		112	
„	+ itraconazol (8M)	45(1)	1.5(2)	1559(2!)	54-80		96	
Ascalone et al., 1984	healthy adult (6) capsule	50.7(1)	1.0(2)	1229(1!)				
“	vlunteers (6) drops	42.0(1)	1.25(2)	1034(1!)				
“	(6) drops	39.2(1)	0.83 (2)	838(1!)				
“	(1) capsule	50.5(1)	0.5(2)	964(1!)				
“	(1) capsule	58.6(1)	0.5(2)	947(1!)				
“	(1) capsule	46.3(1)	1.0(2)	950(1!)				
“	(1) capsule	39.8(1)	2.0(2)	1262(1!)				
“	(1) capsule	44.4(1)	1.0(2)	1179(1!)				
“	(1) capsule	64.9(1)	1.0(2)	1549(1!)				
von Stetten et al., 1983	bioavailability from tablets (10M)	45.5(2)	3.0(2)	1217(2!)				
“	(10M)	52.3(2)	1.1(2)	1078(2!)				
Podilsky et al., 2009	bioavai. given by nasog. tube (4M/4F)	46.0(1)	1.53(2)	2581(1)				
Gonçalves et al., 2005	reference (24M)	37.6(1)	1.25(2)	1007(1)				
“	test (24M)	33.9(1)	1.5(2)	881(1)				
Fujii et al., 1990	fasting state (4M/4F)	57.7(2)	2.3(2)	(1805)	52±1.6			
“	non-fasting state (4M/4F)	37.7(2)	2.8(2)	(1227)	52±1.6			
Lerner et al 2001	slow release reference (24)	(9.52)	(8.0)	(269)	65.27			
“	slow release test (24)	(10.3)	(8.0)	(266)	65.27			
	Mean **± SD**	**42.9** **±7.3**	**1-50** **±0.65**	**1163** **±399**				
	Number of trials	13	13	11				
	Number of observations	132	132	116				

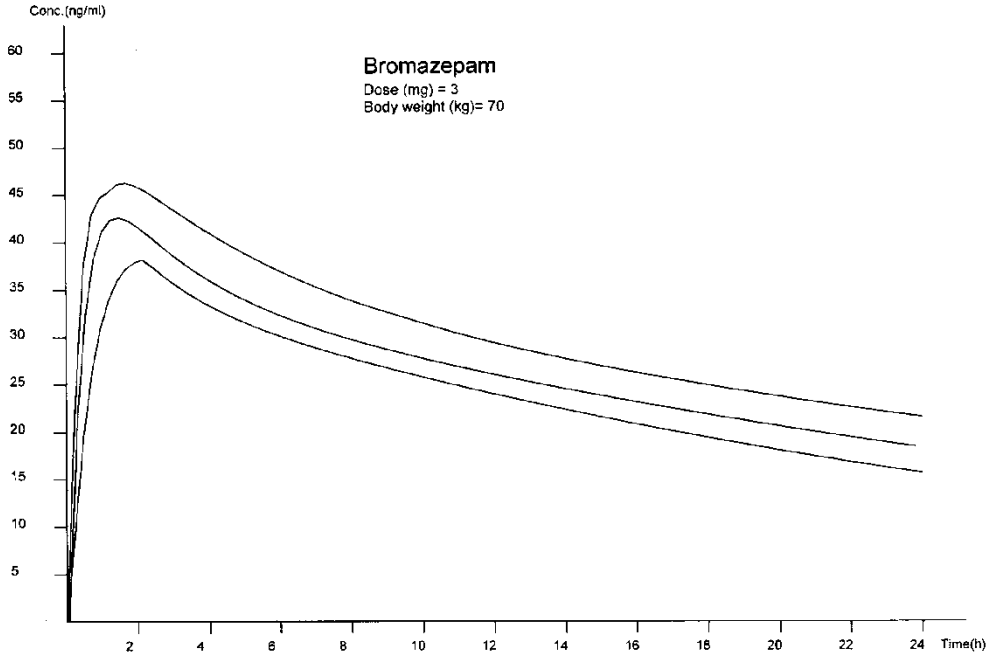


Figure 93: Plasma concentration-time curve of bromazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	36.9	±	8.1	ng/mL	
Ka:	2.29	±	0.99	h^{-1}	
α:	0.420	±	0.207	h^{-1}	
β:	0.0292	±	0.0066	h^{-1}	
t_0:	0.057	±	0.057	h	
V%:	68.2	±	19.8%		
B:	84%				

				derived from time-course of plasma concentrations
C_{max}:	42.9	±	7.3 ng/mL	42.6 (38.2-46.3) ng/mL
t_{max}:	1.50	±	0.65 h	1.56 (1.56-2.16) h
AUC_{o-oo}:	1183	±	399 ng_*h/mL	1275 (1019.6-1680) ng_*h/mL

7.3.3.1.2 Oxazepam

Application: Oxazepam is a benzodiazepine with predominantly sedative, antianxiety, and hypnotic effect. It has also importance as active metabolite of several benzodiazepines and represents the last degradation product with pharmacological effect. Those drugs are diazepam, desmethyldiazepam, chlordiazepoxide, prazepam, clorazepate, medazepam, and temazepam. Because no active metabolites are formed from oxazepam and the elimination half-life is relatively short ($t_{½}\beta$ ~8 hr), no accumulation of active substances occurs.

The absorption of oxazepam is relatively slow. Dreyfuss et al. (1986) compared the pharmacokinetics of oxazepam in healthy young and elderly subjects using different dosage forms, two 15 mg tablets or one 30 mg capsule. Time of peak concentration was prolonged after capsule intake (4.5 vs. 2.77 hr) in young volunteers and (5.0 vs. 3.25 hr) in elderly subjects. An increase of elimination half-lives was observed too (8.7 vs. 7.6 hr) and (17.5 vs. 12.5 hr). Sonne et al. (1991) compared the pharmacokinetics of oxazepam in a group of extremely old subjects (80-94 yr) with that in a control group of young volunteers. Elimination half-lives were increased (8.1 vs. 5.7 hr). Oxazepam may be not the best choice for patients with difficulty falling asleep but should be useful for patients with difficulty maintaining asleep (Dreyfuss et al., 1986).

Biotransformation: Oxazepam has a similar pharmacokinetic profile as the other in 3-position hydroxylated benzodiazepines temazepam, lorazepam, and lormetazepam. It is metabolized by conjugation and excreted into the urine as glucuronide and as sulphate. Up to 10% of the drug is excreted unchanged.

Interaction: Effect of gender seems to be a more important determinant of oxazepam clearance than is age. Elimination half-life was longer in females (mean 9.7 hr) than in males (mean 7.8 hr) (Greenblatt et al., 1980). Scott et al. (1984) investigated the pharmacokinetics of oxazepam in thyroid disease and found no statistically significant change in hypothyroid patients, but in untreated hyperthyroid patients. The elimination half-life was shorter and the apparent oral clearance higher than in treated patients. The pharmacokinetics of oxazepam in epileptic patients treated long-term with phenobarbitone or phenytoin was studied by Scott et al. (1983). Elimination half-lives were shorter (3.31 vs. 6.99 hr) and AUC lower (1030 vs. 1864 $ng_{*}h/mL$). The authors suggest that treatment with phenytoin alone or in combination with phenobarbitone leads to an increase of oxazepam glucuronyl transferase activity.

The co-administration of ethanol revealed no statistically significant influences on the course of the oxazepam plasma concentration-time curve and no alterations of the blood ethanol

curves were observed (Mallach et al., 1975). Benzodiazepines were frequently administered in combination with antidepressant drugs. Toon et al. (1990) found no pharmacokinetic or pharmacodynamic interactions after coadministration of oxazepam and the antidepressant tianeptine. Van Hecken et al. (1985) studied the influence of diflunisal on the pharmacokinetics of oxazepam. The salicylic derived anti-flammatory agent diflunisal and oxazepam are both extensively bound to plasmaprotein and are eliminated via the same route by glucuronidation and excretion of the glucuronides into the urine. The authors observed after a concomitant intake decreases of oxazepam peak concentration and an increase of AUC and elimination half-life concerning oxazepam glucuronide. They explained these alterations by displacement of oxazepam from its plasma protein binding and inhibition of the tubular secretion of oxazepam glucuronide by the glucuronide of diflunisal.

Evaluation of studies: Only control groups and groups with no statistically significant alterations of the pharmacokinetics were used for averaging the pharmacokinetic parameters. For instance Sonne et al. (1989) demonstrated a decrease of oxazepam metabolism after a very low diet, but the evaluated parameters (Tab. 28) Cp0 and $t_{½}\beta$ were nearly identical.

Table 90: 15 mg Oxazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Sonne et al., 1991	+(elderly) (6M/4F)	26-42	15	-	-	-	5.7(2)	-	-
van Hecken et al., 1985	+(diflunisal) (6M)	20-22	30	205.4 (2)	0.959(2)	1.02(2)	9.9(2)	0.286(2)	10.6(2)
Staak et al., 1976	+(ethanol) (14)	22-49	30	439(1!)	0.284(2!)	0.648(2!)	3.74(2!)	0.345(2!)	93.4(2!)
Toon et al., 1990	+(tianeptine (12M)	19-28	10	280(1!)	0.775(2!)	0.997(2!)	5.02(2!)	0.177(2!)	86.8(2!)
Scott et al., 1984	Hypothyroid patients before treatment +(hyperthyroid) (6F)	36-58	15	-	-	-	7.94(2)	-	-
"	Hypothyroid patients after treatment (6F)	36-58	15	-	-	-	8.41(2)	-	-
Scott et al., 1983	+(with epilepsy) (6M/3F)	21-60	15	-	-	-	6.99(2)	-	-
Greenblatt et al., 1980	effects of (1F)	63	30	430(1!)	0.369(2!)	0.315(2!)	14.75(2!)	0.466(2!)	17.3(2!)
"	age (1M)	64	30	379(1!)	0.986(2!)	0.888(2!)	8.08(2!)	0.172(2!)	10.6(2!)
"	and (1M)	30	30	382(1!)	0.757(2!)	2.15(2!)	7.98(2!)	0.230(2!)	72.7(2!)
"	sex (1M)	40	30	90(1!)	0.630(2!)	0.732(2!)	6.63(2!)	0.226(2!)	3.13(2!)
"	(18M)	22-76	30	-	0.695(2!)	-	7.80(2)	0.250(2)	-
"	(20F)	28-84	30	-	0.575(2!)	-	9.70(2)	0.137(2)	-
Sonne et al., 1989	control + very low (11F)	26-54	30	353(1!)	-	-	6.78(2!)	-	-
"	calorie diet (11F)	26-54	30	367(1!)	-	-	6.14(2!)	-	-
Dreyfuss et al., 1986	Young + (elderly) (9M/3F) tablet	23-44	30	162(2!)	0.986(2!)	2.13(2!)	8.03(2!)	0.075(2!)	24.8(2!)
"	(9M/3F) capsule	23-44	30	213(2!)	1.28(2!)	1.95(2!)	9.08(2!)	0.059(2!)	48.4(2!)
	Mean ± SD			**269.4 ±98.2**	**0.745 ±0.291**	**1.34 00.62±**	**7.35 ±1.92**	**0.190 ±0.099**	**54.6 ±32.4**
	Number of trials			8	8	6	14	8	6
	Number of observations			82	98	60	151	98	68

Continuation of Table 90: 15 mg Oxazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Sonne et al., 1991	+(elderly) (6M/4F)	268(2)	2.4 (2)	-	70			0.65(2)
van Hecken et al., 1985	+(diflunisal) (6M)	194(2)	2.8(2)	2852(2!)	68-75			
Staak et al., 1976	+(ethanol) (14)	332(1)	1.5(2)	2200(1!)	-			
Toon et al., 1990	+(tianeptine (12M)	161.7(1)	2.0(2)	1728(1!)	-			
Scott et al., 1984	Hypothyroid patients before treatment +(hyperthyroid) (6F)	258(2)	1.62(2)	1718(2)	-			
"	Hypothyroid patients after treatment (6F)	216(2)	2.60(2)	1582(2)	-			
Scott et al., 1983	+(with epilepsy) (6M/3F)	262(2)	2.2(2)	1864(2)	70			
Greenblatt et al., 1980	effects of (1F)	46(1)	6.0(2)	10791(1!)	-			
"	age (1M)	300(1)	4.0(2)	3422(1!)	-			
"	and (1M)	325(1)	2.0(2)	4252(1!)	-			
"	sex (1M)	229(1)	1.0(2)	1187(1!)	-			
"	(18M)	342(2)	2.2(2)	-	76.9	90		0.73(2)
"	(20F)	366(2)	3.1(2)	-	61.2			0.65(2)
Sonne et al., 1989	control + very low (11F)	-	-	-	-			0.69(2)
"	calorie diet (11F)	-	-	-	-			0.70(2)
Dreyfuss et al., 1986	Young + (elderly) (9M/3F) tablet	162(2)	2.8(2)	2444(2)	71			
"	(9M/3F) capsule	213(2)	4.5(2)	2616(2)	71			
	Mean ± SD	**270 ±75**	**2.6 ±0.9**	**2275 ±890**		**90**	**±**	**0.69 ±0.03**
	Number of trials	12	12	9				4
	Number of observations	151	151	81				60

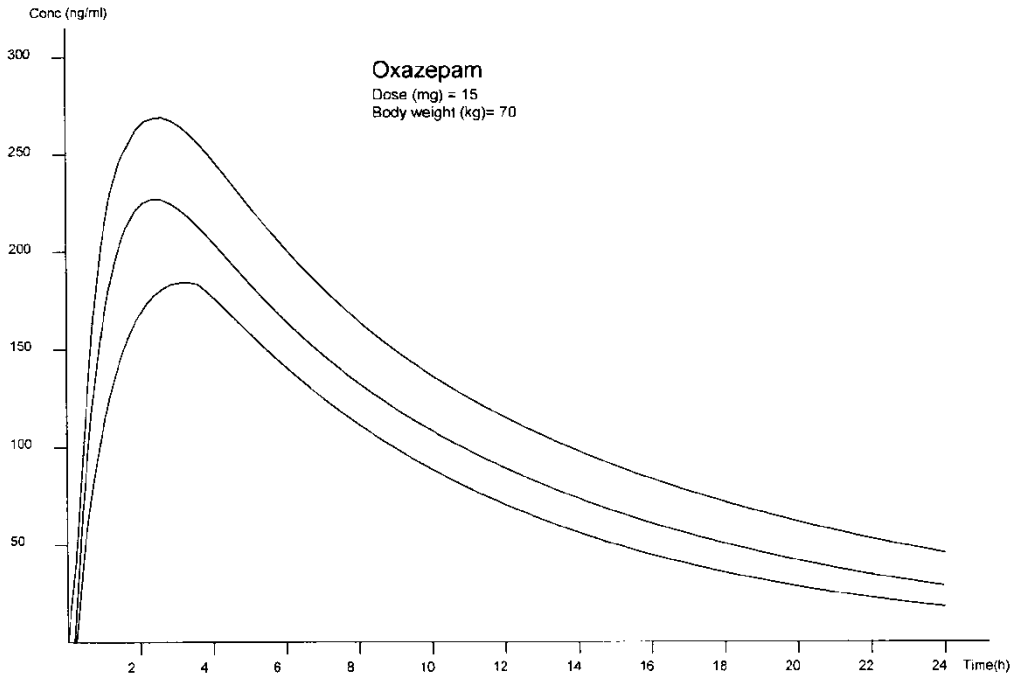


Figure 94: Plasma concentration-time curve of oxazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	269.4	±	98.2	ng/mL	
Ka:	0.930	±	0.261	h^{-1}	
α:	0.517	±	0.166	h^{-1}	
β:	0.0943	±	0.0195	h^{-1}	
t_0:	0.190	±	0.099	h	
V%:	54.6	±	32.4	%	
B:	90 %				

						derived from time-course of plasma concentrations
C_{max}:	270	±	75ng/mL			226.7 (184.2-268.6) ng/mL
t_{max}:	2.6	±	0.9h2.6 (2.6-3.1) h			
AUC_{o-oo}:	2275	±	890ng*h/mL			2763 (2099-3746) ng*h/mL
V_β/G:	0.69	±	0.03L/kg0.80	±		0.46L/kg

7.3.3.1.3 Lorazepam

Application: Lorazepam is used in clinical practice as sedative and antianxiety agent. Due to the relatively short elimination half-life of about 13 hours, it has a clinical value as hypnotic too and involves a single daily dose usually at bedtime. The treatment of moderate and severe anxiety involves divided doses of 2 to 7 mg daily (Bruguerolle et al., 1985). These authors compared in a randomized crossover study the pharmacokinetics of lorazepam at two different times, in the morning (7:00 a.m.) and in the evening (7:00 p.m.). The drug was absorbed more rapidly in the morning as in the evening (T_{max} = 2.37 vs. 3.68 hr). Greenblatt et al. (1979) investigated various administration routes of lorazepam using 2 and 4 mg doses, intravenous infusion, in tablet form in the fasting state, and by deltoid intramuscular injection. The absorption was nearly complete. The sublingual formulation has been proved by Caillé et al. (1983) as a more rapid administration form than the oral intake (t½Ka = 15 min vs. 55 min). Spénard et al. (1988) compared the pharmacokinetics and the anxiolytic activity of oral and sublingual chronically administered lorazepam. Maximal, minimal, and average steady-state plasma concentrations were nearly identical.

Biotransformation: As other 3-hydroxylated benzodiazepines, the main pathway of lorazepam metabolism is conjugation to the 3-glucuronide. After single dose of 2 mg lorazepam containing 2-^{14}C-lorazepam, Greenblatt et al. (1976) identified beside lorazepam glucuronide, which comprised 86% of urinary radioactivity, three further metabolites, hydroxy-lorazepam, a quinazolidone, and a quinazolidone carboxylic acid. Lorazepam glucuronide had a concentration coming up to twice as much lorazepam concentration in plasma at 4 hours after administration, whereas lorazepam had its maximum level 2 hours after drug intake. The elimination half-life of the glucuronide was higher than that of the parent drug (16.2 vs. 11.7 hr). Verbeeck et al. (1976) found only 3% of unchanged drug in the 24h urine of healthy subjects and traces in the urine of patients with renal failure. While the elimination half-life of the parent drug in the patients with end-stage renal insufficiency was not statistically significant altered, that of the glucuronide was considerably decreased. This was associated with accumulation of the conjugate in plasma.

Interaction: The influence of age and gender on the pharmacokinetics of lorazepam is low, which was stated by Aaltonen et al. (1982) beside others after 0.03 mg/kg intravenous administration in 14 surgical patients ranging from 25 to 86 years. This is in agreement with other reports of little effect of age on metabolism of benzodiazepines that are eliminated primarily by conjugation. The transfer of the glucuronic acid group from uridine 5´-

diphosphate-glucuronic acid to lorazepam is catalyzed by uridine 5´-diphosphate-glucuronyltransferases (UGT), which exist as a large group of human UGT isoforms. Polymorphism of UGT2B15 leads to different rates of glucuronidation of lorazepam, which is to be influenced by inhibition with valproate or by induction with rifampin (Chung et al., 2005).

Evaluation of studies: For averaging the pharmacokinetic parameters (Table 91), such studies were used, in which lorazepam was orally administered in form of different formulations (tablet or capsule) and in different time of the day. By that means absorption half-lives, times of peak concentrations and lag times show comparatively large deviations. The more rapid absorption from soft gelatin capsules than from hard capsules or tablets leads to a quicker onset of hypnotic effect, whereas the tablet formulation is more appropriate for treatment of anxiety.

Table 91: 2 mg Lorazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Greenblatt et al., 1979	bioavailability (1F)	30	2		0.948(3)		15.2(3)	0(3)	
"	oral (1M)	26	2		0.837(3)		9.3(3)	0.098(3)	
"	(intramusscular) (1M)	25	2		0.433(3)		9.0(3)	0.270(3)	
„	(intravenous) (1M)	31	2		-		25.9(3)	-	
„	„ (1F)	29	2		1.00(3)		18.6(3)	0.208(3)	
„	„ (1F)	27	2		0.142(3)		19.3(3)	0.692(3)	
„	„ (1F)	30	4		0.017(3)		16.7(3)	0.240(3)	
„	„ (1M)	26	4		0.735(3)		14.0(3)	0(3)	
„	„ (1M)	25	4		0.288(3)		11.1(3)	0.408(3)	
„	„ (1M)	31	4		0.288(3)		25.0(3)	0.442(3)	
„	„ (1F)	29	4		0.505(3)		15.5(3)	0.713(3)	
„	„ (1F)	27	4		0.513(3)		15.9(3)	0(3)	
„	„ (1F)	23	4		0.238(3)		10.8(3)	0.188(3)	
Friedman et al., 1991	humans and monkeys (24M)	18-40	2	22,8(2!)	0.478(2!)	0.658(2!)	11.6(2!)	0.168(2!)	49.2(2!)
Bruguerolle et al., 1985	morning dose (8M/6F)	46±7	3.5	12.1(2!)	1.42(2!)	1.07(2!)	10.6(2!)	0.147(2!)	90.8(2!)
„	evening dose (8M/8F)	46±7	3.5	12.1 (2!)	0.98(2!)	1.26(2!)	11.8(2!)	0.009(2!)	96.9(2!)
Blin et al., 2001	sedative and amnesic effects (8M/4F)	18-47	2	14.2 (2)	0.447(2!)	0.654(2!)	16.1(2!)	0.180(2!)	11.7(2!)
Ellinwood et al., 1985	(diazepam) (1M)	25	4.10	14.4(3)	-	-	19.9(3)	-	-
„	and (alprazolam) (1M)	25	4.80	15.7(3)	-	-	20.0(3)	-	-
„	„ (1M)	25	3.50	16.3(3)	-	-	19.4(3)	-	-
„	„ (1M)	26	3.50	20.9(3)	-	-	12.1(3)	-	-
„	„ (1M)	24	4.93	22.9(3)	-	-	17.6(3)	-	-
„	„ (1M)	26	4.15	20.9(3)	-	-	9.1(3)	-	-
„	„ (1M)	26	4.00	16.3(3)	-	-	14.8(3)	-	-
«	„ (1M)	22	4.80	16.2(3)	-	-	12.9(3)		

Greenblatt et al., 1976	(8M)	23-45	2	18.0(2!)	0.462(2!)	1.00(2!)	11.8 (2!)	0.570(2!)	69.8(2!)
Aaltonen et al., 1982	intravenously (8M/6F)	25-86	0.03 mg/kg				12.1(2)		
Verbeeck et al., 1976	control (renal failure) (6M)	21-25	2.5	22.4(1!)	0.662(2!)	1.24(2!)	11.3(2!)	0.092 (2!)	86.8(2!)
Blin et al., 1999	mnesic effects (12)		2	18.2(1)			16.6(2)		
	Mean			**17.3**	**0.718**	**0.931**	**13.3**	**0.187**	**65.9**
	± SD			**±4.4**	**±0.380**	**±0.256**	**±3.2**	**±0.171**	**±.29.3**
	Number of trials								
	Number of observations								

Continuation of Table 91: 2 mg Lorazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Cmax (ng/mL)	tmax (h)	AUCo-oo (ng*h/mL)	G (kg)	B (%)	Vβ/B (L)	Vβ/G (L/kg)
Greenblatt et al., 1979	bioavailability (1F)	27.7	1.0(3)	392(3)	53.6(3)	96.1		
"	oral (1M)	23.5	2.5(3)	305(3)	76.4(3)	109.9		
"	(intramuscular) (1M)	26.5	2.0(3)	387(3)	79.5(3)	93.2		
„	(intravenous) (1M)	25.8	6.0(3)	918(3)	69.5(3)	98.0		
„	„ (1F)	25.7	2.0(3)	457(3)	65.9(3)	96.2		
„	„ (1F)	24.1	1.5(3)	640(3)	53.6(3)	64.3		
„	„ (1F)	17.3	1.0(3)	403(3)	53.6(3)	85.2		
„	„ (1M)	25.9	1.5(3)	415(3)	76.4(3)	87.4		
„	„ (1M)	27.1	2.5(3)	470.4(3)	79.5(3)	94.4		
„	„ (1M)	19.3	1.5(3)	729(3)	69.5(3)	95.7		
„	„ (1F)	20.8	1.5(3)	391(3)	65.9(3)	88.8		
„	„ (1F)	26.1	2.0(3)	613(3)	53.6(3)	93.5		
„	„ (1F)	18.0	1.0(3)	270(3)	56.8(3)	104.1		
Friedman et al., 1991	humans and monkeys (24M)	22.3(2)	1.9(2)	365.4(2!)	71.2±1.9			
Bruguerolle et al., 1985	morning dose (8M/8F)	12.4(2)	2.37(2)	177.5(2!)	61.3			
„	evening dose (8M/8F)	11.6(2)	3.68(2)	184.9(2!)	61.3			
Blin et al., 2001	sedative and amnesic effects (8M/4F)	30.6(2)	0.92(2)	349.6 (2!)	67±12			
Ellinwood et al., 1985	(diazepam) (1M)	23.0(3)	1.58(3)	-	71.8			**2.05(3)**
„	and (alprazolam) (1M)	40.5(3)	0.583(3)	-	84.1			**1.87(3)**
„	„ (1M)	39.0(3)	0.583(3)	-	61.4			**1.81(3)**
„	„ (1M)	31.5(3)	0.333(3)	-	61.4			**1.41(3)**
„	„ (1M)	38.5(3)	0.583(3)	-	86.4			**1.29(3)**
„	„ (1M)	20.0(3)	0.583(3)	-	72.7			**1.41(3)**
„	„ (1M)	27.0(3)	0.583(3)	-	70.0			**1.80(3)**
«	„ (1M)	26.0(3)	0.583(3)	-	84.1			**1.82(3)**
Greenblatt et al., 1976	(8M)	17.5(2)	2.0(2)	305.6(2!)	72.6±6.2			**1.52(2)**

Aaltonen et al., 1982	intravenous (8M/6F)				73.1	(90 %)		**1.81(2)**
Verbeeck et al., 1976	control (renal failure) (6M)	22 (1)	2.3 (2)	353.2 (1)	79.2			
Blin et al., 1999	mnesic effects (12M)	33.4(1)		405(1)	60.4		111.6±19.4	
	Mean	**21.7**	**2.0**	**328**		**92.8**	**111**	**1.79**
	±SD	**±7.7**	**±.1.0**	**±135**		**±10.8**	**±19.4**	**±0.19**
	Number of trials	10	9	9		2	1	**3**
	Number of observations	115	103	107		13	12	**30**

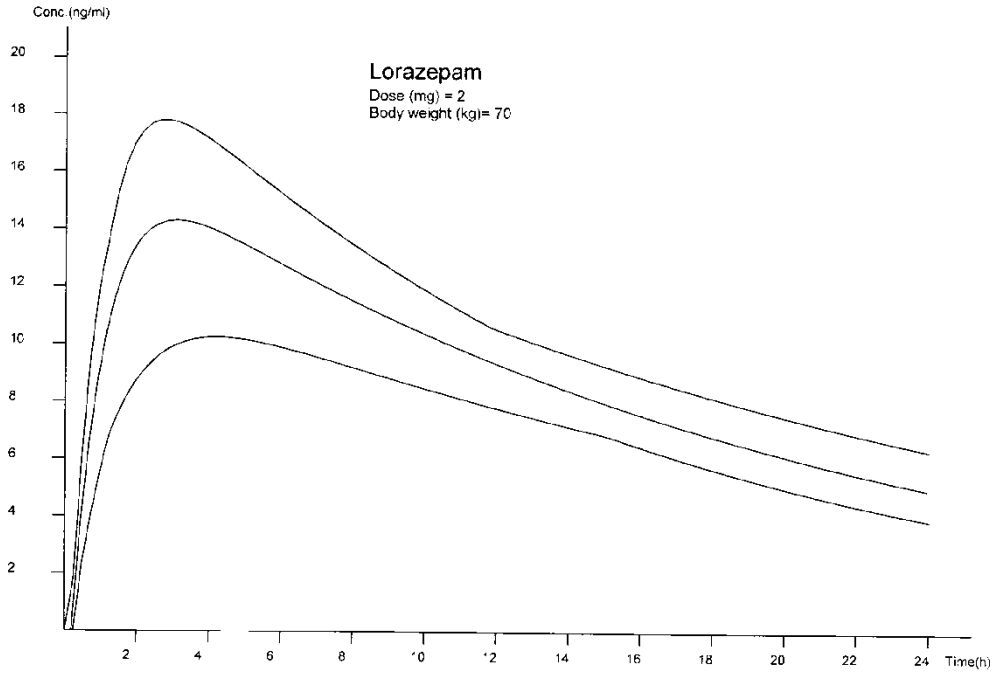


Figure 95: Plasma concentration-time curve of lorazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	17.3	±	4.4	ng/mL
Ka:	0.965	±	0.334	h^{-1}
α:	0.745	±	0.161	h^{-1}
β:	0.0521	±	0.0101	h^{-1}
t_0:	0.187	±	0.171	h
V%:	65.9	±	29.3	%
B:	92.8	±	10.8	%

				derived from time-course of plasma concentrations
C_{max}:	21.7	±	7.7 ng/mL	14.3 (10.2-17.8) ng/mL
t_{max}:	2.0	±	1.0 h	3.2 (2.9-4.1) h
AUC_{o-oo}:	328	±	135 ng*h/mL	317 (236-416) ng*h/mL
V_β/G:	1.79	±	0.19 L/kg	1.62 ± 0.55 L/kg

7.3.3.1.4 Alprazolam

Application: Alprazolam, a triazolo-benzodiazepine derivative closely related to midazolam, triazolam, loprazolam and brotizolam, is an immediate long acting sedative and is predominantly used for treatment of anxiety disorder and panic disorder in doses from 0.5 to 2 mg. The oral dose for anxiety is 0.5-4 mg/day, divided into 2-4 doses. For panic disorder, dosages range from 1 to 10 mg/day, divided into 3-4 doses (Erdman et al., 2007).

The absorption is nearly complete (92%) (Smith et al., 1984). Kaplan et al. (1998) compared pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. There were modest increases in plasma peak concentrations in the elderly group, but elimination half-lives and AUC were not statistically significant altered. Coadministration of food had no influence on the extent of absorption, because AUC values were nearly identical. But the absorption rate of drug was decreased, which became apparent by a lower absorption rate constant and a lower peak level (Erdman et al., 2007). No differences were observed in the pharmacokinetics of alprazolam, when 2 mg was administered 15 days apart in healthy volunteers (Barbanoj et al., 2007).

Biotransformation: Alprazolam is metabolized by oxidative hydroxylation to α-hydroxyalprazolam and 4-hydroxyalprazolam, which are rapidly excreted into the urine after glucuronidation. 29 metabolites have been identified in urine (Garzone & Kroboth 1989). The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam increased proportionally with doses in the range of 2-10 mg and the combined levels were less than 15% (Wright et al., 1997). A study of Wennerholm et al. (2005) revealed the courses of plasma concentrations of alprazolam, 4-hydroxyalprazolam, and α-hydroxyalprazolam after oral intake of 1 mg alprazolam with peak levels of 19.8, 12.3, and 0.40 ng/mL. The elimination half-lives of the metabolites were only slightly higher than that of alprazolam, so that no accumulation of the active metabolite can be assumed.

Interaction: Single dose pharmacokinetics of smoking men was not statistically significant different from that of nonsmoking men, but after multiple-dose treatment for six days, plasma concentrations were 15-30% lower in smokers and the elimination half-lives 49% greater in nonsmokers (Smith et al., 1983a). Otani et al. (1997) observed in a single dose study a statistically significant shortened elimination half-life of 13.1 hr vs. 20.0 hr in nonsmokers. An induction of cytochrome P450 could also be achieved with carbamazepine. After pretreatment of seven healthy subjects with 300 mg daily for 10 days, the plasma alprazolam

concentrations during the elimination phase were statistically significant decreased (7.7 vs. 17.1 hr) (Furukori et al., 1998).

An involvement of CYP3A4 is supported by the influence of inhibitors of this isoenzyme as erythromycin, which prolonged the elimination half-life from 16 to 40.3 hr (Yasui et al., 1996) or itraconazole with similar effects (from 15.7 to 40.3 hr (Yasui et al., 1998). Coadministration of sertraline (Hassan et al., 2000), venlafaxine (Amchin et al., 1998), or grapefruit juice (Yasui et al., 2000) had no statistically significant influence or only a minimal effect as sertindole (Wong et al., 1998) on single dose pharmacokinetics of alprazolam. The pharmacokinetics of alprazolam is extensively reviewed by Greenblatt and Wright (1993).

Evaluation of studies: Table 92 shows the evaluation results of studies after administration of immediately released and Table 93 those of extended-release formulations of alprazolam in doses of 0.5-10 mg. After normalization of the values to a dose of 1 mg and a body weight of 70 kg, peak concentrations, fictive initial concentrations, and areas under the concentration-time curves show a good conformity, indicating that linear relation exists between dose and plasma concentration. The observation period in the studies of Mumford et al. (1995) is too short for calculation of elimination half-life and AUC value, because by the slow release of the active agent from the retard formulation, the peak level is not attained until about 9 hours after drug administration. But even at the peak level, which is measured about half of the value after an immediate release formulation, the absorption is not yet terminated. The elimination rate is as expected not affected by the galenic form and the area under the plasma concentration-time curve is only decreased by about 14%. Figure 96 and Figure 97 are the related time courses of the plasma concentrations.

Table 92: 1 mg Alprazolam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Ellinwood et al., 1985	+ (diazepam) (1M)	25	2,05	12,0 (3)	-	-	13,6 (3)	-	**-**
„	+ (lorazepam) (1M)	25	2,41	10,4(3)	-	-	14,7(3)	-	**-**
„	(1M)	25	1,76	17,0(3)	-	-	13,5(3)	-	**-**
„	(1M)	26	1,76	9,6(3)	-	-	18,6(3)	-	**-**
„	(1M)	24	2,47	19,6(3)	-	-	11,6(3)	-	**-**
„	(1M)	26	2,08	18,8(3)	-	-	22,0(3)	-	**-**
„	(1M)	26	2,00	11,2(3)	-	-	(1,92)	-	**-**
„	(1M)	22	2,41	23,7(3)	-	-	9,7(3)	-	**-**
Mumford et al., 1995	+ (retard formulation) (14M)	21-44	1	16,0 (2!)	0,495(2!)	0,900(2!)	16,1(2!)	0,002(2!)	**37,5(2!)**
„	+ (retard formulation) (14M)	21-44	2	13,4(2!)	0,533(2!)	1,51(2!)	17,4(2!)	0,004(2!)	**49,9(2!)**
Friedman et al., 1991	+ (lorazepam) (22M)	27,3±1,2	1	21,7(2!)	0,495(2!)	0,856(2!)	10,4(2!)	0,150(2!)	**43,4(2!)**
Venkatakrishnan et al., 2005	+ (adinazolam) (9M) intravenous	20-40	1	-	-	-	14,6(2)	-	**-**
Smith et al., 1984	intravenous. (6M)	20-32	1	-	-	-	11,7(2)	-	**-**
„	oral (6M)	20-32	1	16,1(1!)	0,277(2!)	0,289(2!)	11,8(2!)	0,170(2!)	**6,05(2!)**
Smith et al., 1983a	smoking men (5M)	19-42	1	15,2(2!)	0,533(2!)	1,18(2!)	11,1(2!)	0,14(2!)	**48,4(2!)**
“	smoking men (5M)	19-42	1	13,5(2!)	0,301(2!)	2,17(2!)	14,0(2!)	0,17(2!)	**74,7(2!)**
Otani et al., 1997	+ (triazolam) (10M)	29,8±6,0	0,8	10,5(2!)	0,347(2!)	1,48(2!)	16,3(2!)	0,091(2!)	**74,7(2!)**
Kaplan et al., 2000	control (5M/3F)	37,2	1	11,4(2!)	0,385(2!)	1,39(2!)	17,5(2!)	0,094 2!)	**46,1(2!)**
„	panic disorder (5M/3F)	36,3	1	12,1(2!)	0,139(2!)	1,10(2!)	14,5(2!)	0,200(2!)	**45,5(2!)**
Otani et al., 1997a	poor metabolizers (6M)	25-41	0,8	11,7(2!)	0,673(2!)	0,889(2!)	15,5(2!)	0,103(2!)	**24,6(2!)**
«	extensive metabolizers 6M)	25-41	0,8	10,1(2!)	0,277(2!)	1,07(2!)	15,7(2!)	0,064(2!)	**74,7(2!)**
«	nonsmoker (5M)	25-41	0,8	9,66(2!)	0,578(2!)	0,667(2!)	18,0(2!)	0,15(2!)	**10,9(2!)**
«	smoker (7M)	25-41	0,8	12,5(2!)	0,315(2!)	0,630(2!)	13,5(2!)	0,065(2!)	**93,8(2!)**
Erdman et al., 2007	fasting (7M/9F)	20-50	1	11,8(2!)	0,693(2!)	1,24(2!)	14,5(2!)	0,103(2!)	**24,6(2!)**
„	high-fat breakfast (7M/9F)	20-50	1	13,6(2!)	1,48(2!)	2,31(2!)	15,0(2!)	0,262(2!)	**46,7(2!)**

Hassan et al., 2000	+ (sertraline) (2M/8F)	20-48	1	10,8(1!)	1,10(2!)	1,93(2!)	-	0,180(2!)	**43,1(2!)**
Wong et al., 1998	+ (sertindole) (11M/3F)	27±6	1	15,8(2!)	0,347(2!)	0,347(2!)	12,3(2!)	0,22(2!)	**1,6(2!)**
Kaplan et al., 1998	young (5M/3F)	29,8±2,5	1	10,9(2!)	0,257(2!)	1,14(2!)	14,1(2!)	0,11(2!)	**49,6(2!)**
	elderly (5M/3F)	68,4±1,9	1	11,4(2!)	0,198(2)	0,408(2!)	13,8(2!)	0,092(2!)	**24,2(2!)**
Amchin et al., 1998	+ (venlafaxine)(15M/1F)	18-44	2	13,2(2!)	0,630(2!)	1,61(2!)	17,8(2!)	0,031(2!)	**49,2(2!)**
Yasui et al., 1998	+ (itraconazole) (10M)	31,7±5,8	0,8	12,6(2!)	0,495(2!)	0,642(2!)	15,8(2!)	0,14(2!)	**24,2(2!)**
Yasui et al., 2000	+ (grapefruit juice) (8M)	31,1±6,3	0,8	12,4(2!)	0,385(2!)	1,39(2!)	15,8(2!)	0,025(2!)	**86,1(2!)**
Wennerholm et al., 2005	CYP3A (6M/6F)	27-53	1	-	-	-	12,3(2)	-	**-**
Barbanoj et al., 2007	Toleranz- (12M/12F)	18-39	2	13,4(2!)	0,433(2!)	1,73(2!)	16,3(2!)	0,028(2!)	**72,7(2!)**
„	entwicklung (12M/12F)	18-39	2	13,4(2!)	0,462(2!)	1,65(2!)	16,2(2!)	0,004(2!)	**69,2(2!)**
Suzuki et al., 1995	+ (DNN-2327) (12M)	41,3±3,6	0,8	13,3(1!)	1,06(2!)	1,73(2!)	10,55(2!)	0,595(2!)	**32,8(2!)**
Fleishaker et al., 1995	+(adinazolam) (12)	18-34	0,5	14,0(1!)	0,057(2!)	1,33(2!)	11,0(2!)	0,050(2!)	**99,8(2!)**
„	„	18-34	1,5	12,0(1!)	0,295(2!)	0,77(2!)	13,3(2!)	0,008(2!)	**48,4(2!)**
	Mean ± SD			**13,7 ±2,9**	**0,524 ±0,317**	**1,26 ±0,53**	**14,5 ±2,4**	**0,113 ±0,124**	**49,3 ±23,8**
	Number of trials			35	27	27	36	27	**27**
	Number of observations			314	306	306	331	296	**296**

Continuation of Table 92: 1 mg Alprazolam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Ellinwood et al., 1985	+ (diazepam) (1M)	13(3)	1,33(3)		71,8			**1,03(3)**
„	+ (lorazepam) (1M)	12,5(3)	2,58(3)		84,1			**1,09(3)**
„	(1M)	31(3)	0,333(3)		61,4			**0,72(3)**
„	(1M)	18,5(3)	0,333(3)		61,4			**0,94(3)**
„	(1M)	19,5(3)	1,58(3)		86,4			**0,74(3)**
„	(1M)	28(3)	0,333(3)		72,4			**0,40(3)**
„	(1M)	15,5(3)	1,58(3)		70,0			**1,25(3)**
„	(1M)	21,5(3)	3,5(3)		84,1			**0,72(3)**
Mumford et al., 1995	+ (retard formulation) (14M)	18,6(2)	1,8(2)	374,0(2!)	69,7			**-**
„	+ (retard formulation) (14M)	16,9(2)	1,6(2)	346,6(2!)	69,7			**-**
Friedman et al., 1991	+ (lorazepam) (22M)	22,9(2)	1,5(2)	337,0(2!)	77,,3			**-**
Venkatakrishnan et al., 2005	+ (adinazolam) (9M) intravenous	-	-	-	80		100±6,8	**-**
Smith et al., 1984	intravenous. (6M)	-	-	-	-	92 %		**0,72(2)**
„	oral (6M)	17,4(1)	1,2(2)	259,4(2!)	-			**0,84(2)**
Smith et al., 1983a	smoking men (5M)	17,6(2)	1,95(2)	231,5(2!)	79,9			**1,02**
“	smoking men (5M)	15,8(2)	1,55(2)	250,8(2!)	79,9			**0,97**
Otani et al., 1997	+ (triazolam) (10M)	12,3(2)	1,5(2)	245,7(2!)	60,8			**-**
Kaplan et al., 2000	control (5M/3F)	24,6 (2)	1,4(2)	300,5(2!)	80,8			**1,23(2)**
„	panic disorder (5M/3F)	25,2 (2)	1,1(2)	269,0(2!)	79,3			**1,2(2)**
Otani et al., 1997a	schwache Metabol. (6M)	13,8(2)	1,6(2)	261,4(2!)	61,3±5,5			**1,2(2)**
«	starke Metabol.(6M)	12,5(2)	1,3(2)	199,4(2!)	61,3±5,5			**1,52(2)**
«	Nichtraucher(5M)	12,0(2)	1,3(2)	212,0(2!)	61,3±5,5			**1,79(2)**
«	Raucher (7M)	13,9(2)	1,6(2)	216,7(2!)	61,3±5,5			**1,09(2)**
Erdman et al., 2007	nüchtern (7M/9F)	16,5(2)	2,5(2)	261,4(2!)	71,7			
„	mit Mahlzeit (7M/9F)	12,7(2)	4,0 (2)	282,9(2!)	71,7			

Hassan et al., 2000	Placebo + (sertralin) (2M/8F)	12,7(1)	2,7(2)	166,9(1!)	-			
Wong et al., 1998	Placebo + (sertindol) (11M/3F)	19,8(2)	1,2(2)	280(2!)	75±12		70,1(2)	
Kaplan et al., 1998	jüngere (5M/3F)	21,8(2)	1,3(2)	230,0(2!)	71,6±3,5		84(2)	
	ältere (5M/3F)	23,9(2)	0,84(2)	237,7(2!)	67,6±3,2		81(2)	
Amchin et al., 1998	+ (venlafaxine)(15M/1F)	15,7(2)	2,5(2)	344,8(2!)	77,8		80,7(2)	
Yasui et al., 1998	+ (itraconazole) (10M)	14,4(2)	2,0(2)	283,5(2!)	62,3±4,6		-	
Yasui et al., 2000	+ (grapefruit juice) (8M)	13,6(2)	3,0(2)	269,9(2!)	61,5±4,7		-	
Wennerholm et al., 2005	CYP3A (6M/6F)	19,4(2)	1,0(2)	323,4(2)	-		-	
Barbanoj et al., 2007	Toleranz- (12M/12F)	15,9(2)	1,8(2)	314,6(2!)	64,5		81,3(2)	
„	entwicklung (12M/12F)	16,3(2)	2,2(2)	312,2(2!)	64,5		73,6(2)	
Suzuki et al., 1995	+ (DNN-2327) (12M)	14,4(1)	3,5(2)	237,1(2!)	-			
Fleishaker et al., 1995	+(adinazolam) (12)	18,8(1)	1,21(2)	218,2(1!)	-			
„	„	17,0(1)	1,33(2)	174,8(1!)	-			
	Mean ± SD	**17,4 ±3,8**	**1,86 ±0,77**	**284,6 ±49,5**		**92 %**	**80,0 7,6±**	**1,11 ±0,30**
	Number of trials	36	36	28			7	**18**
	Number of observations	326	326	318			103	**62**

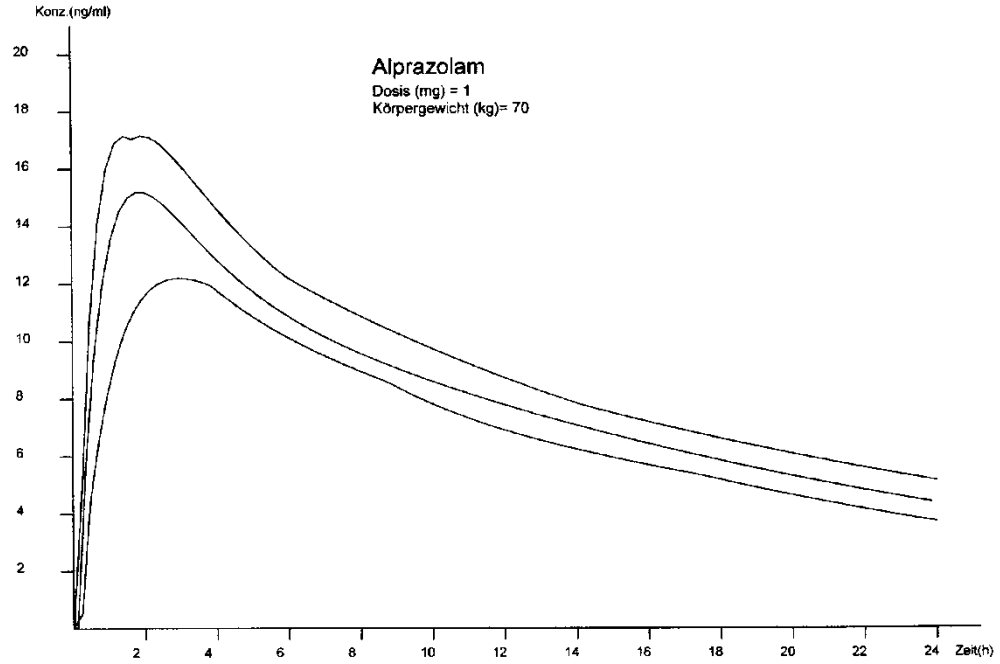


Figure 96: Plasma concentration-time curve of alprazolam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	13,7	±	2,9	ng/mL		
Ka:	1,32	±	0,50	h^{-1}		
α:	0,551	±	0,164	h^{-1}		
β:	0,0478	±	0,0068	h^{-1}		
t_0:	0,113	±	0,124	h		
V%:	49,3	±	23,8	%		
B:	92 %					

				derived from time-course of plasma concentrations		
C_{max}:	17,4	±	3,8 ng/mL	15,21 (12,2-17,2) ng/mL		
t_{max}:	1,86	±	0,77 h	1,31 (1,91-2,88) h		
AUC_{o-oo}:	284,6	±	49,5 ng*h/mL	290,9 (241,0,6-353,3) ng*h/mL		
V_β/B:	80,0	±	7,6 L	75,7	±	20,3 L
V_β/G:	1,11	±	0,30 L/kg	0,995	±	0,267 L/kg

Table 93: 1 mg Alprazolam retard (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Mumford et al., 1995	+ (immediate release) (14M)	21-44	2	11,1 (2!)	1,85(2!)	1,69(2!)	-	0,008(2!)	**96,9 (2)**
„	(14M)	21-44	3	9,85(2!)	1,91(2!)	1,65(2!)	-	0,012 (2!)	**96,9 (2)**
Wright et al., 1997	dose effect (21M)	19-49	2	14,6(2!)	3,01(2!)	1,26(2!)	12,8 (2)	0,230(2!)	**99,2 (2)**
„	relation (21M)	19-49	4	14,2(2!)	3,01(2!)	1,26(2!)	13,3 (2)	0,110(2!)	**99,2 (2)**
«	(21M)	18-49	8	14,8(2!)	2,17(2!)	1,41(2!)	13,1 (2)	0,092 (2!)	**48,4 (2)**
„	(21M)	19-49	10	14,4(2!)	2,89(2!)	1,58(2!)	13,6 (2)	0,077(2!)	**86,1 (2)**
Glue et al., 2006	adolescent volunteers (5M/7F)	13-17	1	14,2(2!)	2,77(2!)	3,65(2!)	16,5 (2!)	0,020(2!)	**93,8 (2)**
„	(5M/7F)	13-17	3	14,0(2!)	2,48(2!)	2,17(2!)	17,1 (2!)	0,023(2!)	**87,5 (2)**
„	adult volunteers (4M/8F)	20-45	1	13,4(2!)	2,48(2!)	3,01(2!)	15,6(2!)	0,090(2!)	**87,5 (2)**
	(4M/8F)	20-45	3	11,6(2!)	2,39(2!)	2,17 (2!)	17,6(2!)	0,03(2!)	**87,5 (2)**
	Mean ± SD			**13,4 ±1,6**	**2,54 ±0,42**	**1,84 ±0,70**	**14,5 ±1,8**	**0,078 ±0,068**	**87,4 ±16,0**
	Number of trials			10	10	10	8	10	**10**
	Number of observations			160	160	160	132	160	**160**

Continuation of Table 93: 1 mg Alprazolam retard (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Mumford et al., 1995	+ (immediate release) (14M)	8,65(2)	7,81(2)	-	69,7			
„	(14M)	7,83(2)	8,41(2)	-	69,7			
Wright et al., 1997	dose effect (21M)	8,31(2)	11,0(2)	233,0 (2!)	77			
„	relation (21M)	8,66(2)	9,76(2)	234,8 (2!)	77			
«	(21M)	8,62(2)	9,48(2)	237,3 (2!)	77			
„	(21M)	7,76(2)	9,38(2)	231,1 (2!)	77			
Glue et al., 2006	adolescent volunteers (5M/7F)	8,45(2)	9,80(2)	282,3 (2!)	65,0			
„	(5M/7F)	7,61(2)	10,0(2)	251,4 (2)	65,0			
«	adult volunteers (4M/8F)	7,76(2)	8,3(2)	254,8(2!)	69,6			
«	(4M/8F)	7,82 (2)	9,0(2)	253,9(2!)	69,6			
	Mean ± SD	**8,19 ±0,41**	**9,4 ±0,9**	**243,7 ±15,0**				
	Number of trials	10	10	8				
	Number of observations	160	160	132				

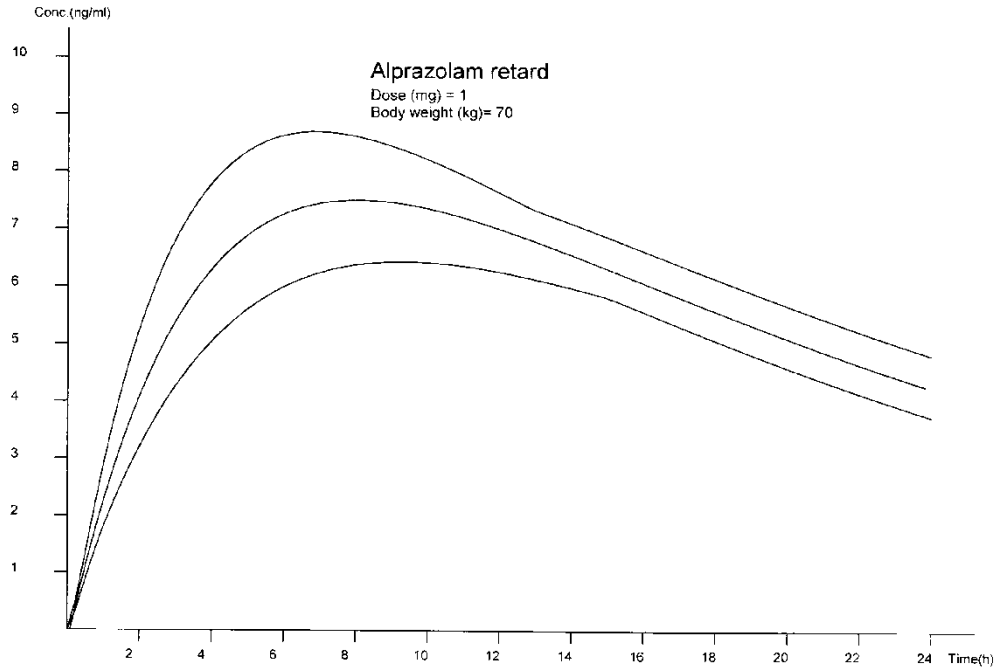


Figure 97: Plasma concentration-time curve of alprazolam retard after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	13,4	±	1,6	ng/mL	
Ka:	0,273	±	0,039	h^{-1}	
α:	0,377	±	0,104	h^{-1}	
β:	0,0478	±	0,0052	h^{-1}	
t_0:	0,07813	±	0,068	h	
V%:	87,4	±	16,0	%	
B:	92 %				
					derived from time-course of plasma concentrations
C_{max}:	8,19	±	0,41 ng/mL		7,51 (6,44-8,70) ng/mL
t_{max}:	9,4	±	0,9 h		1,31 (1,91-2,88) h
AUC_{o-oo}:	243,7	±	15,0 ng∗h/mL		229,2 (192,8-273,1) ng∗h/mL
V_β/G:	1,188	±	0,161 L/kg		

7.3.3.2 Long-acting tranquillizers

7.3.3.2.1 Diazepam

Application: Chlordiazepoxide and diazepam are the two oldest benzodiazepines. While chlordiazepoxide is unstable in aqueous solution and is chemically altered during absorption after oral intake, the oral bioavailability of diazepam is high, about 80% (Dhillon et al., 1982). Further administration forms are intramuscular, intravenous, and rectal (Hillestad et al., 1974, Wichlinski et al.1985, Dhillon et al., 1982). Indications for treatment with diazepam are manifold, for instance anxiety, epilepsy, symptoms of alcohol or opiate withdrawal, tetanus, or pre/postoperative sedation.

Biotransformation: Diazepam is the parent drug of several pharmacologically active metabolites, which are used as active agents of pharmaceutical preparations, too. The first degradation step leads by oxidative demethylation to desmethyldiazepam, which is also formed by rapid hydrolysis of clorazepate and fast degradation of medazepam and prazepam in the gastro-intestinal tract or on the first passage through the liver. After single-dose administration of 10 mg diazepam, the mean peak concentration is 320 ng/mL at 1.28 ± 0.6 hr (Figure 98), whereas desmethyldiazepam level ascends forward until to the maximum of about 30 ng/mL at 10-20 hr after drug intake because of the slow elimination of desmethydiazepam. During chronic administration, the ratio of desmethyldiazepam and diazepam increases and the steady-state concentrations of diazepam and its metabolite are in the same order of magnitude. Greenblatt et al. (1981c) determined a mean desmethyldiazepam to diazepam concentration ratio of 1.26 in 110 patients during long-term therapy. Predominantly during the elimination phase of diazepam and chronic administration of diazepam, the pharmacological effect cannot be disregarded. Further metabolites, hydroxylation products of diazepam and desmethyldiazepam, oxazepam and temazepam, reach no such high concentrations in plasma that they contribute to the pharmacological effect of the parent drug and desmethyldiazepam. The hydroxylated metabolites are conjugated to their respective glucuronides with oxazepam as the main urinary excretion product (Klotz et al., 1976).

Interaction: The influence of age and gender was investigated in some studies. MacLeod et al. (1979) observed that women had lower clearance of total diazepam than men. Klotz et al. (1975) reported that age was associated with larger values of distribution volume and $t_{½}\beta$. Greenblatt et al. (1980a) confirmed these results by a study with intravenous diazepam. $t_{½}\beta$

was longer in the elderly than in the young of both sexes. Differences in elimination rate due to gender were lower than due to age. Prolongation of elimination half-life was more pronounced in males. Following intravenous administration, Herman and Wilkinson (1996) estimated elimination half-lives and volumes of distribution in elderly subjects approximately twofold greater than in younger subjects. But chronic dosing of 2 mg diazepam every 12 hr for 6 weeks showed no age-related differences in the levels of accumulated diazepam and desmethyl diazepam. Klotz et al. (1975) compared the pharmacokinetics of diazepam in patients with liver disease with those in age-matched control groups. A more than twofold prolongation of diazepam half-life was observed in the case of alcoholic cirrhosis and patients with acute viral hepatitis had a diazepam $t_{½}\beta$ of 74.5 ± 27.5 hr vs. 32.7 ± 8.9 hr in the control group.

The main steps of diazepam biotransformation are mediated by isoenzymes of cytochrome P450, the demethylation by CYP2C19 and the hydroxylation by CYP3A8/4. A lot of substances, which are substrates of these isoenzymes, are inhibitors of diazepam metabolism, for instance cimetidine (Ruffalo et al., 1981, Greenblatt et al., 1984b), the antimycotic itraconazole (Ahonen et al., 1996), omeprazole (Andersson et al., 1990), erythromycin (Luurila et al. 1996), and fluoxetine (Lemberger et al., 1988). The lack of statistically significant first-pass metabolism of diazepam explains the smaller interaction of diazepam compared with midazolam or triazolam.

Evaluation of studies: Table 94 contains the pharmacokinetic data from 14 publications with oral administration of diazepam in doses of 2 to 20 mg. After normalizing to 10 mg and 70 kg body weight, peak concentrations, fictive initial concentrations, and AUC values show a good accordance, so that a linear dependence between these parameters and time exists. The elimination half-lives from some studies were not used for averaging, because observation periods were too short in comparison with the elimination half-lives. That applies to the $t_{½}\beta$ values of desmethyl-diazepam in Table 95, too. An observation period of 12 hours is by far too short for a calculation of elimination half-lives with the order of 40 to 80 hr.

Table 94: 10 mg Diazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Hillestad et al., 1974	(9)	19-35	20	118.7(1!)	0.116(2!)	1.46(2!)	27.8(21)	0.094(2!)	**41.4(2!)**
Ellinwood et al., 1985	+ (alprazolam) (1M)	25	20.5	-		-	19.4(3)	-	**-**
“	+ (lorazepam) (1M)	25	24.1	-	-	-	22.7(3)	-	**-**
„	(1M)	25	17.6	-	-	-	36.8(3)	-	**-**
„	(1M)	26	17.6	-	-	-	24.8(3)	-	**-**
„	(1M)	24	24.7	-	-	-	22.9(3)	-	**-**
„	(1M)	26	20.8	-	-	-	85.0(3)	-	**-**
„	(1M)	26	20.0	-	-	-	27.2(3)	-	**-**
„	(1M)	22	24.1	-	-	-	27.4(2)	-	**-**
Friedman et al., 1992	effect of (8M/3F)	19-35	2	164(1!)	0.137(2!)	0.636(2!)	(15.2)	0.21(2!)	**32.6(2!)**
„	dose (8M/3F)	19-35	5	182.2(1!)	0.206(2!)	0.361(2!)	(11.1)	0.22(2!)	**23.1(2!)**
„	and time (8M/3F)	19-35	10	173(1!)	0.506(2!)	0.608(2!)	(12.1)	0.26(2!)	**8.2(2!)**
Swift et al., 1985	(elderly) (6M/6F))	19-26	10	156.4(2!)	0.492(2!)	0.963(2!)	(14.3)	0.30(2!)	**24.9(2!)**
Dhillon et al., 1982	bioavailability (6)	18-40	10	-	-	-	-	-	**-**
„	(intravenous) (1)	19	10	160.9(3!)	0.318(3!)	0.465(3!)	(5.3)	0.62(3!)	**18.5(3!)**
„	oral (1)	25	10	-	-	-	-	-	**-**
„	rectal (1)	35	10	116.8(3!)	0.063(3!)	0.745(3!)	(7.1)	0.078(3!)	**19.4(3!)**
«	epileptic (1)	39	10	194.2(3!)	0.183(3!)	0.386(3!)	(6.0)	0.136(3!)	**36.3(3!)**
«	patients (1)	18	10	110.8(3!)	0.462 (3!)	0.654(3!)	(17.7)	0.50(3!)	**9.1(3!)**
„	(1)	33	10	331.5(3!)	0.147(3!)	0.495(3!)	(8.8)	0.20(3!)	**4.7(3)**
Wichlinski et al., 1985	(i.v, im, and) oral (11M/1F)	37.5	20	146.8(2!)	0.686(2!)	1.97(2!)	(15.4)	0(2!)	**37(2!)**
Giles et al. 1977	plasma (+saliva) (5M)	24-33	10	172.9(2!)	0.456(2!)	0.533(2!)	(18.2)	0.047(2!)	**4.7(2!)**
Van Steveninck et al., 1996	+ (ethanol) (12)	19-26	10	248.1(1!)	0.304(2!!	0.666(2!)	(6.35)	0.21(2!)	**9.4(2!)**
Gardner et al., 1997	intravenous (10M)	21-35	10	-	-	-	55.0(2)	-	**-**
«	placebo (10M)	21-35	10	-	-	-	49.2(2)	-	**--**
«	+ (sertraline) day 1 (10M)	18-35	10	-	-	-	38.5(2)	-	**-**

Gugler et al., 1996	iv. + (pantoprazole) (5M/7F)	20-29	0.1 mg/kg	-	-	-	40.4(2)	-	**-**
Herman & Wilkinson, 1996	young +(elderly) (7)	25.3±3.9	2	-	-	-	44.5(2)	-	**-**
Darragh et al., 1982	+ (RO15-1788) (6M)	19-34	40	177.4(2!)	0.143(2!)	0.979(2!)	26.2(2!)	0(2!)	**32.8(2!)**
Kaplan et al., 1973	(4M)	35±8.5	10	(65.7)	0.167(2!)	1.07(2!)	36.8(2!)	0.29(2!)	**26.3(2)**
Klotz et al., 1976	single + (subchronic) (5M)	29-35	10	-	-	-	33.9(2)	-	**-**
	Mean			**170.0**	**0.336**	**0.905**	**39.4**	**0.102**	**23.8**
	± SD			**±39.6**	**±0.195**	**±490**	**±11.6**	**±123**	**±12.0**
	Number of trials			10	11	11	10	11	**11**
	Number of observations			95	99	99	81	99	**99**

Continuation of Table 94: 10 mg Diazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Hillestad et al., 1974	(9)	244(1)	0.5(2)	4270(1!)				
Ellinwood et al., 1985	+ (alprazolam) (1M)	370(3)	1.583(3)	-	71.8			**0.69(3)**
“	+ (lorazepam) (1M)	572(3)	1.333(3)	-	84.1			**0.76(3)**
„	(1M)	519(3)	1.083(3)	-	61.4			**0.50(3)**
„	(1M)	420(3)	1.833(3)	-	61.4			**0.66(3)**
„	(1M)	534(3)	0.583(3)	-	86.4			**0.71(3)**
„	(1M)	543(3)	1.083(3)	-	72.7			**1.13(3)**
„	(1M)	672(3)	0.583(3)	-	70.0			**0.73(3)**
„	(1M)	446(3)	1.333(3)	-	84.1			**0.83(3)**
Friedman et al., 1992	effect of (8M/3F)	375(1)	0.89(2)	3806(1!)				
„	dose (8M/3F)	374(1)	1.0(2)	3002(1!)				
„	and time (8M/3F)	317(1)	1.32(2)	3149(1!)				
Swift et al., 1985	(elderly) (6M/6F))	213.8(2)	2.5 (2)	3424 (2!)	65.7±8.0			
Dhillon et al., 1982	bioavailability (6)			(2682)	63.7±4.9			
„	(intravenous) (1)	264(3)	1.25(3)	(1708)	66	64		
„	oral (1)	274.3(3)	0.26(3)	(2939)	64	69		
„	rectal (1)	411.3(3)	0.41(3)	(1469)	64	53		
«	epileptic (1)	311.1(3)	0.5(3)	(2337)	67	97		
«	patients (1)	270(3)	1.5(3)	(2588)	54	83		
„	(1)	363.7(3)	0.83(3)	5133(2!)	67	90		
Wichlinski et al., 1985	(i.v, im, and) oral (11M/1F)	205.4(2)	2.1(2)	3577(2!)	75			
Giles et al., 1977	plasma (+saliva) (5M)	323.7(1)	1.0(2)	4796(2!)	70.0			
Van Steveninck et al., 1996	+ (ethanol) (12)	318(1)	1.3(2)	(2273)				
Gardner et al., 1997	intravenous (10M)				76.8			**1.17(2)**
«	placebo (10M)				76.8			**0.92(2)**
«	+ (sertraline) day 1 (10M)				75.0			**0.94(2)**

Gugler et al., 1996	iv. + (pantoprazole) (5M/7F)				65			**1.22(2)**
Herman & Wilkinson, 1996	iv. young +(elderly) (7)				57.6-90.0			**0.88(2)**
Darragh et al., 1982	+ (RO15-1788) (6M)	347.5(2)	1.0(2)	6803 (2!)	69.5			
Kaplan et al., 1973	(4M)	(65.0)	0.94(3)	3399(3 !)	75.6±12.9			
Klotz et al., 1976	single + (subchronic) (5M)							
	Mean	**320**	**1.28**	**3941**		**76**	**0.99**	**1.79**
	±SD	**±107**	**±0.60**	**±1056**		**±16**	**±0.19**	**±0.19**
	Number of trials	11	12	10		1	6	**3**
	Number of observations	103	107	82		6	57	**30**

Table 95: Desmethyldiazepam from 10 mg Diazepam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	MetAnteil %	$t_{½}$Ka (h)	$t_{½}\beta$ (h)	AUC_{o-oo} ($ng_{*}h/mL$)	Cmax	Tmax
Hillestad et al., 1974	(9)	19-35	20	21.0(2!)	3.85(2!)	139(2!)	8474(2!)	38.4(2!)	**20.3(2!)**
Friedman et al., 1992	effect of (8M/3F)	19-35	2	15.5(2!)	0.693(2!)	(231)	(3000)	29.5(2!)	**(12)**
„	dose (8M/3F)	19-35	5	15.6(2!)	1.98(2!)	(26.7)	(1016)	23.9(2!)	**(12)**
„	and time (8M/3F)	19-35	10	16.5(2!)	2.31(2!)	(23.1)	(994)	23.8(2!)	**(12)**
Swift et al., 1985	+(elderly) (6M/6F))	19-26	10	16.0(2!)	0.866(2!)	46.2(2!)	1818(2!)	27.1(2!)	**5.34(2!)**
Giles et al., 1977	plasma (+saliva) (5M)	24-33	10	18.0(2!)	6.93(2!)	77.0(2!)	3351(2!)	27.2(2!)	**26.5(2!)**
	Mean ± SD			**16.9 ±1.9**	**2.15 ±1.7**	**84.2 ±41.8**	**4417 ±3035**	**28.1 ±4.9**	**14.6 ±8.9**
	Number of trials			6	6	3	3	6	**3**
	Number of observations			59	59	26	26	59	**26**

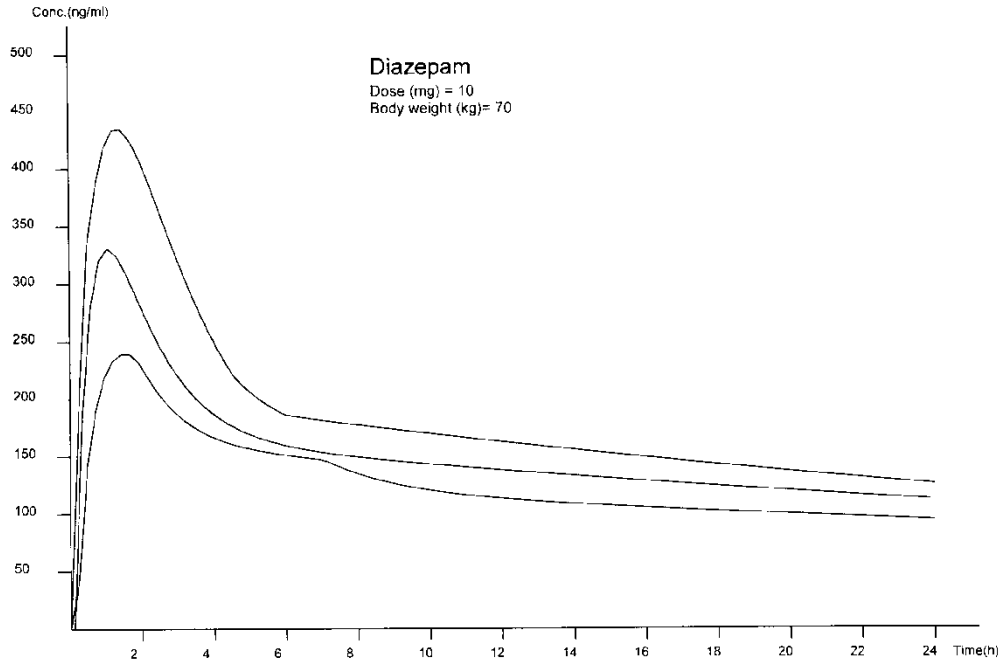


Figure 98: Plasma concentration-time curve of diazepam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	170.0	±	39.6	ng/mL
Ka:	2.06	±	0.75	h^{-1}
α:	0.76	±	0.26	h^{-1}
β:	0.0176	±	0.0040	h^{-1}
t_0:	0.102	±	0.102	h
V%:	23.8	±	12.0	%
B:	76	±	16	%

				derived from time-course of plasma concentrations
C_{max}:	320	±	107 ng/mL	330 (239-435) ng/mL
t_{max}:	1.3	±	0.6 h	1.0 (1.0-1.44) h
AUC_{o-oo}:	3941	±	1056 ng*h/mL	9971 (7680-13091) ng*h/mL
V_β/G:	0.99	±	0.19 L/kg	0.64 ± 0.20 L/kg

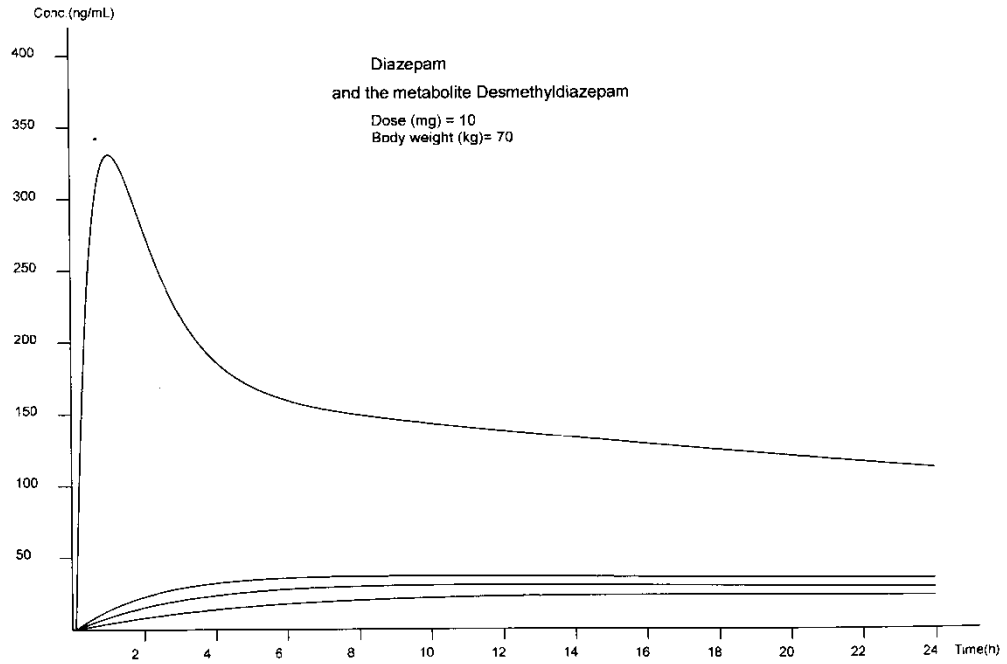


Figure 99: Plasma concentration-time curves of diazepam and desmethyldiazepam after oral administration of diazepam.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

% Formation:	16.9	±	1.9	%
Ka:	0.322	±	0.142	h^{-1}
β:	0.00823	±	0.00273	h^{-1}

				derived from time-course of plasma concentrations
C_{max}:	28.1	±	4.9 ng/mL	30.6 (23.5-30.6) ng/mL
t_{max}:	14.6	±	8.9 h	11.9 (9.7-16.7) h
AUC_{o-oo}:	4417	±	3035ng*h/mL	3510 (2373-5158) ng*h/mL

7.3.3.2.2 Chlordiazepoxide

Application: Chlordiazepoxide has been the first benzodiazepine introduced into clinical practice (Randall et al., 1960). Because of its complex metabolism to pharmacologically active products with long elimination half-lives, its main use is as tranquilizer with anticonvulsant activity and appetite stimulation effect (Randall et al., 1960). For understanding the clinical action of the drug, the pharmacokinetics of chlordiazepoxide during long-term therapy following multiple dose administration is of more importance than that after single dose administration. The active metabolites with long half-lives accumulate and their pharmacological effects may exceed that of the parent drug. and metabolites at single dose studies. Investigations of Lin and Friedel (1979) revealed statistically significant correlations between anxiety reduction and plasma levels of desmethyl-chlordiazepoxide and demoxepam and not the concentration of chlordiazepoxide. They suggest that the antianxiety properties of the metabolites surpass those of the parent drug.

Biotransformation: Chlordiazepoxide is unstable in solutions or when exposed to ultraviolet light. The isomerisation product is a cyclic epoxide. Therefore a solution must be freshly prepared just prior to use (Greenblatt et al., 1978a). Almost no unchanged chlordiazepoxide is excreted into the urine. The mayor elimination pathway has been shown to be the desmethylation product desmethyl- chlordiazepoxide. Metabolites are in succession of their formation: desmethyl- chlordiazepoxide, demoxepam, desmethyldiazepam, oxazepam. All the four metabolites have psychopharmacological activity similar to that of the parent drug (Randell & Kapell 1973). This must be considered in attempts to interpret the clinical effects of chlordiazepoxide in humans. The large elimination mean half-life of 48 hours determinated after discontinuation of large chronic doses of chlordiazepoxide (Hollister et al. 1961) may be due to a non-specific analytic method, which has recorded the metabolite desmethyldiazepam, the product with the longest elimination half-life.

Interaction: Advanced age and liver disease led to statistically significant prolongation of the elimination phase of chlordiazepoxide and its metabolites (2 or 3 times) due to a decrease of biotransformation. In acutely intoxicated alcolholics, Whiting et al. (1979) estimated a mean elimination half-life of 20.65 hr (5.68 + 49.5 hr) and suggested a slower conversion of chlordiazepoxide to desmethyl- chlordiazepoxide during the acute phase of the patients, whereas the elimination of this metabolite appeared to be faster. Absorption of chlordiazepoxide was shown to be shortened when given in combination with a magnesium and aluminium hydroxide mixture (Maalox), but elimination half-life and area under the 24 h

blood concentration-time curve for chlordiazepoxide and its metabolites were not affected. Sellers et al. (1980) studied the pharmacokinetics of intravenous chlordiazepoxide administration in 6 volunteers before and after treatment with disulfiram (0.5 g/day for 14 days). The elimination half-life was prolonged by the disulfiram therapy from 8.5 to 19 hr, the total metabolic clearance was reduced from 0.74 to 0.24 mL/min/kg.

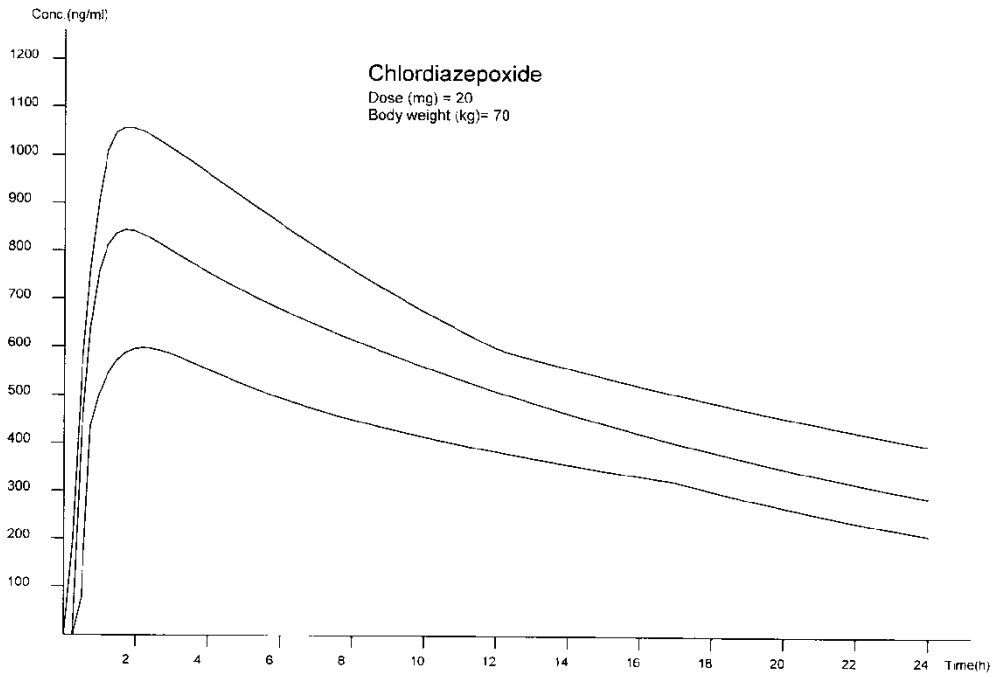
Evaluation of studies: Having a look on Table 96 and Figure 100, a rapid absorption of chlordiazepoxide is obvious with peak concentrations at a time up to 2 hours. The course of the plasma concentrations can be described by a one compartment model, because the part of distribution phase is very low (V% = 90%). Peak concentrations, fictive initial concentrations, and values of AUC deviate extensively from the average. This may be due to different influence of first-pass metabolism. Still more obvious are the deviations of demoxepam curves, which have a peak maximum at about 13 hr and an elimination half-life of 20-30 hr.

Table 96: 20 mg Chlordiazepoxide (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Schwartz et al., 1971	half-life (1M)	25-43	20	1589(2!)	0.401(2!)	1.20(2!)	6.72(2!)	0.039(2!)	**96.9(2!)**
„	of chlotdiazepoxide (1F)	25-43	20	1171(2!)	0.691(2!)	0.603(2!)	7.37(2!)	0.666(2!)	**87.5(2!)**
„	and ist metabolite (1F)	25-43	20	730(2!)	0.587(2!)	5.83 (2!)	29.9(2!)	0.082(2!)	**87.2 (2!)**
„	demoxepam (1F)	25-43	20	1505(2!)	0.881(2!)	1.31(2!)	12.1(2!)	0.837(2!)	**87.5 (2!)**
„	(1F)	25-43	20	842(2!)	0.710(2!)	1.52(2!)	14.8(2!)	0.037(2!)	**93.0(2!)**
“	(1M)	25-43	20	1174(2!)	0.828(2!)	0.845(2!)	21.6(2!)	0.717(2!)	**2.73(2!)**
Greenblatt et al., 1978	single and (1F)	25	50	682(2!)	0.433(2!)	1.20(2!)	7.21	0.008(2!)	**99.2(2!)**
„	multiple (1M)	23	50	467(2!)	0.271(2!)	1.23(2!)	12.6(2!)	0.074(2!)	**46.1(2!)**
„	doses (1M)	30	50	676(2!)	1.25(2!)	1.18(2!)	11.48 (2!)	0.053(2!)	**8.51(2!)**
Greenblatt et al., 1976a	influence of maalox (10M)	23-30	25	526(2!)	0.125(2!)	1.00(2!)	9.76(2!)	0.149(2!)	**96.5(2!)**
“	on absorption (10M)	23-30	25	515(2!)	0.274(2!)	1.66(2!)	9.87(2!)	0.180(2!)	**93.0(2!)**
Smith & Moyer, 1976	preparation A (12M)	25-47	20	1010(1)	0.158(2!)	1.20(2!)	22,1(2!)	0.0535(2!)	**93.8(2!)**
“	preparation B (12M)	25-47	20	1114(1)	0.201(2!)	1.22(2!)	18.3(2!)	0.016(2!)	**99.6(2!)**
Whiting et al., 1979	(effect of acute) (1M)	28-36	25	805(1!)	0.369(2!)	0.648(2!)	6.9(2!)	0.439(2!)	**42.4(2!)**
“	(alcohol intoxication) (1M)	28-36	25	1269(1!)	0.221(2!)	1.33(2!)	8.9(2!)	0.217(2!)	**98.4(2!)**
“	(1M)	28-36	25	1055(1!)	0.781(2!)	1.33(2!)	6.4(2!)	0.016(2!)	**93.8(2!)**
	Mean ± SD			**885 ±315**	**0.281 ±0.226**	**1.32 ±0.67**	**14.8 ±5.9**	**0.234 ±0.226**	**90.3 ±19.2**
	Number of trials			7	7	7	7	7	**7**
	Number of observations			56	56	56	56	56	**56**

Continuation of Table 96: 20 mg Chlordiazepoxide (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (.kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Schwartz et al., 1971	half-life (1M)	1246(2)	02 (2)	14520(2!)	85.5	81		
„	of chlotdiazepoxide (1F)	812(2)	2 (2)	11257(2!)	67.7			
„	and ist metabolite (1F)	751(2)	2 (2)	31575(2!)	59.1			
„	demoxepam (1F)	971(2)	2 (2)	25513(2!)	61.8			
„	(1F)	1095(2)	2 (2)	17218(2!)	61.8			
“	(1M)	764(2)	2 (2)	36157(2!)	68.6			
Greenblatt et al., 1978	single and (1F)	682(1)	1 (2)	9045(1!)				
„	multiple (1M)	725(1)	1 (2)	22610(1!)				
„	doses (1M)	480(1)	6(2)	23041(1!)				
Greenblatt et al., 1976a	influence of Maalox (10M)	473(1)	0.9(2)	7298(1!)				
“	on absorption (10M)	510(1)	1.7(2)	7191(1!)				
Smith & Moyer, 1976	preparation A (12M)	1091 (1)	2.0(2)	31910(1!)	66-90			
“	preparation B (12M)	1042 (1)	4,0(2)	28970(1!)	66-90			
Whiting et al., 1979	(effect of acute) (1M)	698(1)	2,0(2)	7289(1!)				
“	(alcohol intoxication) (1M)	1239(1)	1,0(2)	15864(1!)				
	(1M)	668(1)	3,0(2)	8645(1!)				
	Mean ± SD	**826 ±274**	**2.1 ±1.3**	**19910 ±11047**				
	Number of trials	7	7	7				
	Number of observations	56	56	56				



Plasma concentration-time curve of chlordiazepoxide after oral administration

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	885	±	315	ng/mL
Ka:	2.47	±	1.10	h^{-1}
α:	0.525	±	0.177	h^{-1}
β:	0.0468	±	0.0133	h^{-1}
t_0:	0.234	±	0.226	h
V%:	90.3	±	19.2	%
B:	81 %			

				derived from time-course of plasma concentrations
C_{max}:	826	±	274	844 (598-1056) ng/mL
t_{max}:	2.1	±	1.3	1.73 (1.68-2.16) h
AUC_{o-oo}:	19910	±	11047	18677 (12426-27517) ng_*h/mL

Table 97: Demoxepam from 20 mg Chlordiazepoxide (absorption, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	MetAnteil %	$t_{½}$Ka (h)	$t_{½}$β (h)	AUC_{0-oo} ($ng_{*}h/mL$)	Cmax	Tmax
Schwartz et al., 1971	half-life (1M)	25-43	20	66.8(2!)	5.33(2!)	6.93(2!)	7378(2!)	307.7(2!)	**9.2(2!)**
„	of chlotdiazepoxide (1F)	25-43	20	50.6(1!)	4.95(2!)	13.9(2!)	15402(2!)	434.7(2!)	**12.2(2!)**
„	and ist metabolite (1F)	25-43	20	29.0(1!)	10.7(2!)	46.2(2!)	15276(2!)	147.7(2!)	**29.4(2!)**
„	demoxepam (1F)	25-43	20	47.6(1!)	5.78(2!)	14.9(2!)	17983(2!)	459.0(2!)	**13.8(2!)**
„	(1F)	25-43	20	76.2(1!)	8.66(2!)	13.1(2!)	17165(2!)	405.6(2!)	**15.4(2!)**
“	(1M)	25-43	20	44.4(1!)	10.7(2!)	27.7(2!)	23076(2!)	317.5(2!)	**24-5(2!)**
Greenblatt et al., 1978	single and (1F)	25	50	35.2(2!)	3.46(2!)	18.7(2!)	11544(1!)	291.0(1!)	**10.5(2!)**
„	multiple (1M)	23	50	42.0(2!)	5.78(2!)	27.7(2!)	11707(1!)	177.2(1!)	**16.6(2!)**
„	doses (1M)	30	50	30.0(2!)	2.90(2!)	27.7(2!)	10374 (1!)	199.3(1!)	**10.5(2!)**
Greenblatt et al., 1976a	influence of Maalox (10M)	23-30	25	40.2(2!)	3.47 (2!)	24.2(2!)	10540(1!)	219.0(1!)	**11.4(2!!)**
“	on absorption (10M)	23-30	25	42.8(2!)	4.62(2!)	25.9(2!)	11786(1!)	217.6(1!)	**14.1(2!)**
Smith & Moyer, 1976	preparation A (12M)	25-47	20	40.7(2!)	3.55(2!)	23.9(2!)	20346(1!)	423(1!)	**11.6(2!)**
“	preparation B (12M)	25-47	20	39.9(2!)	3.19(2!)	23.9(2!)	22070(1!)	470(1!)	**10.8(2!)**
Whiting et al., 1979	(effect of acute) (1M)	28-36	25	39.4(2!)	3.15(2!)	27.7(2!)	18499(1!)	358(1)	**12(2)**
“	(alcohol intoxication) (1M)	28-36	25	30.0(2!)	4.62(2!)	53.3(2!)	35207(1!)	400(1)	**10(2)**
	(1M)	28-36	25	34.9(2!)	4.62(2!)	30.1(2!)	20725(1!)	382(1)	**12(2)**
	Mean			**41.5**	**4.15**	**24.7**	**16659**	**339.3**	**12.5**
	± SD			**±6.8**	**±1.6**	**±6.1**	**±5501**	**±112.2**	**±3.2**
	Number of trials			7	7	7	7	7	**7**
	Number of observations			56	56	56	56	56	**56**

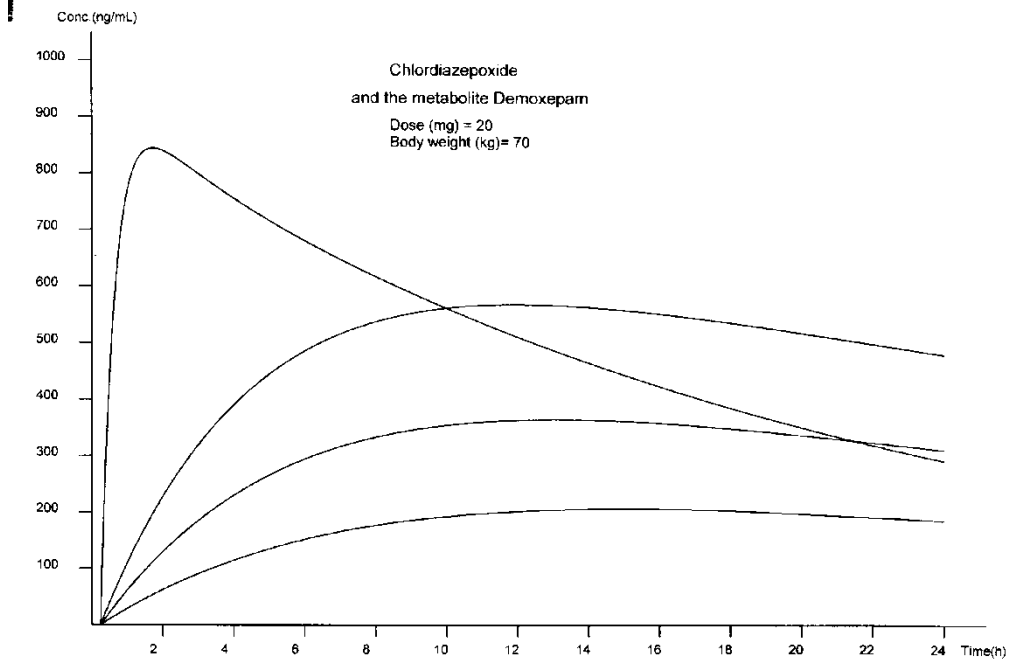


Figure 100: Plasma concentration-time curves of chlordiazepoxide and demoxepam after oral administration of chlordiazepoxide.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Demoxepam:

% Formation :	41.5	±	6.8	%
Ka:	0.67	±	0.047	h^{-1}
β:	0.0 281	±	0.0056	h^{-1}

				derived from time-course of plasma concentrations
C_{max}:	339	±	112 ng/mL	364 (206-364) ng/mL
t_{max}:	12.5	±	3.2 h	13.0 (12.0-14.9) h
AUC_{o-oo}:	16659	±	5501 $ng_{*}h/mL$	18556 (10031-32716) $ng_{*}h/mL$

7.3.3.2.3 Clobazam

Application: Clobazam has in contrast to other benzodiazepines a 1,5-diazepine structure. That means that carbon and nitrogen in 4- and 5-position are interchanged and hydrolysis does not result in a benzophenone but in an acetamido derivative. Pharmacological properties are antianxiety and anticonvulsant effects in doses of 10-30 mg. Clobazam is less sedative than typical 1,4-benzodiazepines in chronic dosage (Wildin et al., 1990). The major metabolite of clobazam, desmethylclobazam, contributes essentially to the efficacy of the parent drug, particularly after multiple doses. During 28 days of medication, desmethylclobazam accumulated to near steady-state levels about 8 times higher than those of the unchanged compound. After i.v. infusion of pentylenetetrazole as the convulsive stimulus, in mice a treatment with desmethylclobazam was associated with less anticonvulsant tolerance than with clobazam (Haigh et al., 1987). Especially in case of coadministration of other antiepileptic drugs such as phenobarbitone, carbamazepine, or primidone, which are cytochrome P450 inducing substances, the antiepileptic properties may be more attributed to its metabolite than to the parent drug (Jawad et al., 1984).

Biotransformation: In addition to demethylation, hydroxylation of clobazam and its major metabolite are degradation steps of biotransformation in man (Volz et al., 1979). A characteristic of 1,5-benzodiazepines is obviously that in contrast to 1,4-benzodiazepines, the 3-position is not hydroxylated, but the 4'-position of the phenyl ring. 4'-Hydroxyclobazam and 4'-hydroxydesmethylclobazam were detected in serum and urine. Clobazam was not excreted into the urine in unchanged form. The hydroxylated metabolites were partially conjugated (Volz et al., 1979).

Interaction: The influence of age and gender has been evaluated by Greenblatt et al. (1981b) in series of 29 healthy volunteers aged 18 to 72 yr. Half-lives and volumes of distribution increases statistically significant with age (48 vs. 17 hr in men and 49 vs. 31 hr in women). $t_{½}\beta$ and Vd were statistically significant larger in young female than in young male subjects. Tedeschi et al. (1981) observed a still more extensive metabolism in children than in adults. Cenraud et al. (1983) investigated the influence of food on the pharmacokinetics of clobazam. The mean areas under the plasma concentration-time curves were not affected by the time of drug administration (3 hr before, during, and 3 hr after a standard meal). A concomitant administration of ethanol results in a marked interaction with increased peak serum levels and area under the serum concentration-time curves. But no influence of clobazam on the ethanol curve was observed (Taeuber et al., 1979). Coadministration of cimetidine, an inhibitor of

cytochrom P450 system, caused enhancement of clobazam plasma levels as well as to a higher extent that of desmethylclobazam concentrations (Pullar et al., 1987a).

Evaluation of studies: The determination of V% (Table 98) resulted in a high standard deviation. This value is too high to be compatible with the calculation of Cmax and AUC. Thus a value of 10% was taken. Figure 101 and Figure 102 show the time courses of clobazam and desmethylclobazam after oral intake of 20 mg clobazam. Up to few hours after administration, the parent drug predominates, but 24 hr after intake, the concentrations of clobazam and its metabolite are in the same order of magnitude. Some days later (Figure 104 and Figure 105) desmethylclobazam predominates. The relationship of diazepam and clobazam and its metabolites is obvious.

Following clobazam administration, a longer $t_{½}\beta$ value of desmethylclobazam (58.9 ± 10.7 hr) was calculated than following desmethylclobazam intake (46.6 ± 1.1 hr). A similar difference was stated by Pullar et al. (1987), who explained this finding by a tissue reservoir of clobazam, which is available for metabolism to desmethylclobazam and leads to falsely long estimation of desmethylclobazam $t_{½}\beta$.

Table 98: 20 mg Clobazam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Jawad et al., 1984	normal (1F)	21	30	184(2!)	0.987(3!)	1.18(3!)	28.6(3!)	0.840(3!)	**8.8(3!)**
"	volunteers and (1M)	18	30	321(2!)	0.762(3!)	1.22(3!)	23.5(3!)	0.670(3!)	**32.6(3!)**
"	(epileptic) (1M)	20	30	135(2!)	1.083(3!)	1.48(3!)	36.9(3!)	0.640(3!)	**4.5(3!)**
„	(patients) (1M)	20	30	206(2!)	0.354(3!)	1.47(3!)	31.4(3!)	0.410(3!)	**69.8(3!)**
„	(1M)	24	30	228(2!)	1.035(3!)	1.22(3!)	28.4(3!)	0.370(3!)	**12.3(3!)**
„	(1M)	20	30	456(2!)	0.296(3!)	1.39(3!)	13.5(3!)	0.280(3!)	**24.6(3!)**
Rupp et al., 1979	single and (8)		20	-	-	-	-	-	**-**
„	multiple (8)		30	-	-	-	18(2)	-	**-**
„	(8)		40	-	-	-	-	-	**-**
Sticht, Käferstein, 1978	detection (1M)	20	10	416(3!)	0.161 (3!)	1.20(3!)	12.8 (3!)	0.140(3!)	**96.9(3!)**
„	in (1M)	20	10	356(3!)	0.336(3!)	0.889(3!)	18.6 (3!)	0.120(3!)	**43.6(3!)**
„	biological material (1M)	33	20	256(3!)	0.213(3!)	0.806(3!)	21.3(3!)	0.008(3!)	**43.6(3!)**
„	(1M))	39	20	237(3!)	0.444(3!)	0.537(3!)	33.3(3!)	0.870(3!)	**6.1(3!)**
„	(1F)	40	20	289(3!)	0.114(3!)	0.304(3!)	11.2(3!)	0.052(3!)	**24.2(3!)**
Tedeschi et al., 1981	Control (1F)	26	10	168(3!)	0.154(3!)	0.335(3!)	17.1(3!)	0.720(3!)	**12.4(3!)**
„	+ (epileptical patients) (1F)	23	10	190(3!)	0.269(3!)	0.654(3!)	24.1(3!)	0.170(3!)	**18.5(3!)**
„	(1M)	24	10	247(3!)	0.303(3!)	1.08(3!)	19.6(3!)	0.420(3!)	**35.2(3!)**
„	(1M)	27	10	187(3!)	0.830(3!)	1.14(3!)	18.5(3!)	0.780(3!)	**10.6(3!)**
„	(1M)	25	10	435(3!)	0.375(3!)	0.478(3!)	10.7(3!)	0.870(3!)	**18.6(3!)**
„	(1F)	26	10	160(3!)	0.979(3!)	1.26(3!)	39.2(3!)	0.480(3!)	**5.86(3!)**
Greenblatt et al., 1981b	young and (8M)	27.5	20	328(3!)	-	-	16.6(3!)	-	**-**
„	(elderly), sex (8F)	21.3	20	209(3!)	-	-	30.7(3!)	-	**-**
Taeuber et al., 1979	+ (ethanol) (8M)	39.4	20	248(2!)	0.619(2!)	2.72(2!)	23.8(2!)	0.320(2!)	**75.0(2!)**
Cenraud et al., 1983	before (4M/2F)	23-30	20	312.5(1!)	0.573(2!)	0.990(2!)	11.5(2!)	0.386(2!)	**9.08(2!)**
„	with (4M/2F)	23-30	20	351(1!)	0.872(2!)	1.33(2!)	12.5(2!)	0.407(2!)	**68.1(2!)**
„	after food (4M/2F)	23-30	20	240.6(1!)	1.51(2!)	1.91(2!)	17.8(2!)	0.363(2!)	**17.3(2!)**

Pullar et al., 1987	(epileptic) (8M)	23-40	30	201.9(2!)	0.529(2!)	1.26 (2!)	25.4(2!)	0.003(2!)	**24.6(2!)**
Pullar et al., 1987a	+ (cimetidine) (9M/1F)	20-40	30	275(1!)	0.555(2!)	0.892(2!)	20.4(2!)	0.128(2!)	**4.4(2!)**
Wildin et al., 1990	respiratory and (6M/4F)	22-37	10	231.6(1!)	0.189(2!)	1.90(2!)	23.7(2!)	0.041(2!)	**48.4(2!)**
«	sedative effects (6M/4F)	22-37	20	284.5(1!)	0.257(2!)	1.91(2!)	20.0(2!)	0.134(2!)	**46.7(2!)**
	Mean			**262**	**0.558**	**1.44**	**21.2**	**0.273**	**34.2**
	± SD			**±65**	**±0.356**	**±0.60**	**±6.3**	**±0.233**	**±24.8**
	Number of trials			13	11	11	14	11	**11**
	Number of observations			97	91	91	103	91	**91**

Continuation of Table 98: 20 mg Clobazam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Jawad et al., 1984	normal (1F)	257(2)	3.0(3)	7703(2!)				
"	volunteers and (1M)	363(2)	3.0(3)	10723(2!)				
"	(epileptic) (1M)	391(2)	2.0(3)	8350(2!)				
„	(patients) (1M)	234(2)	2.0(3)	9170(2!)				
„	(1M)	261(2)	3.0(3)	9260(2!)				
„	(1M)	1059(2)	1.0(3)	10602(2!)				
Rupp et al., 1979	single and (8)	244(1)	-	-				
„	multiple (8)	287(1)	-	-				
„	(8)	264(1)	-	-				
Sticht, Käferstein, 1978	detection (1M)	389(3)	2.0(3)	7580(3!)	80			
„	in (1M)	421(3)	2.0(3)	9737(3!)	64			
„	biological material (1M)	415(3)	1.0(3)	8020(3!)	69			
„	(1M))	408(3)	2.0 (3)	11790 (3!)	84			
"	(1F)	369(3)	1.0(3)	4795(3!)	68			
Tedeschi et al., 1981	Control (1F)	264(3)	1.0(3)	4270(3!)	62.5			
„	+ (epileptical patients) (1F)	274.3(3)	0.5(3)	6856(3!)	50			
„	(1M)	411.3(3)	1.0(3)	7348(3!)	62.5			
«	(1M)	311.1(3)	2.0(3)	5450(3!)	76.9			
«	(1M)	270(3)	2.0(3)	6830(3!)	58.8			
„	(1F)	363.7(3)	2.0(3)	7228(3!)	52.6			
Greenblatt et al., 1981b	young and (8M)	425(2)	2.1(2)	7559(2)	73.0			
„	(elderly), se (8F)	406(2)	1.0(2)	8503(2)	59.0			
Taeuber et al-, 1979	+ (ethanol) (8M)	244(2!)	3.8(2!)	8537(2!)	77.3±8.3			
Cenraud et al., 1983	before (4M/2F)	491(1!)	2.0(2!)	5297(1!)	51-80			
„	with (4M/2F)	498(1!)	1.6(2!)	6199(1!)	51-80			
„	after food (4M/2F)	364(1!)	2.3(2!)	6312(1!)	51-80			

Pullar et al., 1987	(epileptic) (1)	389(1!)	1.5(2!)	7751(1!)		
Pullar et al-, 1987a	+ (cimetidine(9M/1F)	415(1!)	1.7(2!)	9519(1!)		
Wildin et al., 1990	respiratory and (6M/4F)	231.6(1!)	1.3(2!)	8456(1!)	55-85	
	sedative effects (6M/4F)	284.5(1!)	1.6(2!)	8872(1!)	55-85	
	Mean ±SD	**352 ±113**	**1.84 ±0.74**	**7934 ±1460**		**±**
	Number of trials	16	13	13		
	Number of observations	121	97	97		

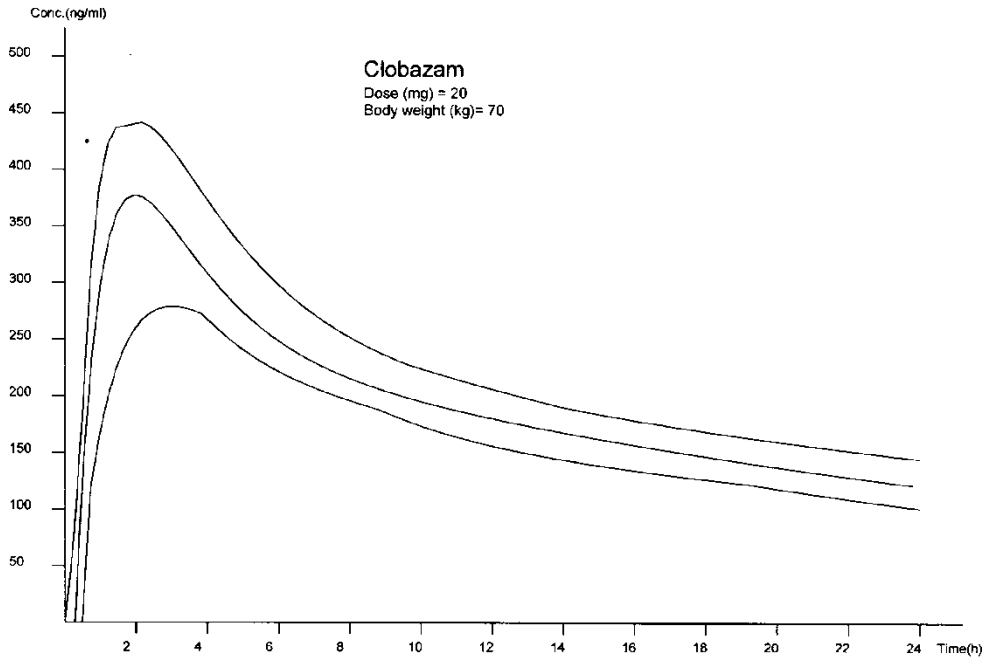


Figure 101: Plasma concentration-time curve of clobazam after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	262	±	65	ng/mL
Ka:	1.24	±	0.48	h^{-1}
α:	0.481	±	0.141	h^{-1}
β:	0.0327	±	0.0075	h^{-1}
t_0:	0.272	±	0.233	h
V%:	34.2	±	10	%
B:	87 %			

				derived from time-course of plasma concentrations
C_{max}:	352	±	113 ng/mL	377 (279-441) ng/mL
t_{max}:	1.84	±	0.74 h	2.07 (2.07-3.12) h
AUC_{o-oo}:	7914	±	1460 ng*h/mL	8436 (6461-11313) ng*h/mL

Table 99: Desmethylclobazam from 20 mg Clobazam (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Jawad et al. 1984	normal (1F)	21	30	107.4(1!)	4.88(2!)	14.2(2!)	64.8(2!)	0.070(2!)	37.2(2!)
"	volunteers and (1M)	18	30	186.1(1!)	3.47(2!)	3.05(2!)	47.8(2!)	0.170(2!)	87.5(2!)
"	(epileptic) (1M)	20	30	152.2(1!)	5.17(2!)	3.05(2!)	58.7(2!)	0.116(2!)	93.8(2!)
„	(patients) (1M)	20	30	148.4(1!)	4.03(2!)	3.05(2!)	81.5(2!)	0.116(2!)	46.9(2!)
„	(1M)	24	30	236.4(1!)	9.76(2!)	3.17(2!)	57.8(2!)	0.108(2!)	99.2(2!)
„	(1M)	20	30	429.4(1!)	6.66(2!)	3.05(2!)	45.3(2!)	0.097(2!)	99.2(2!)
Greenblatt et al. 1981b	+(elderly) (1M)	27	20	178.9(1!)	10.3(2!)	0.842(2!)	32.1(2!)	0.032(2!)	99.9(2!)
Pullar et al. 1987	(epileptic) (8M)	23-40	30	166.7(1!)	13.3(2!)	1.203(2!)	61.9(2!)	0.048(2!)	99.9(2!)
	Mean ± SD			**184.8 ±72.5**	**10.0 ±3.95**	**2.67 ±3.26**	**58.9 ±10.7**	**0.073 ±0.039**	**90.9 ±19.8**
	Number of trials	3	3	3	3	3	3	3	3
	Number of observations	15	15	15	15	15	15	15	15

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Jawad et al. 1984	normal (1F)	136.6(1!)	24(2!)	11687(1!)				
"	volunteers and (1M)	153.8(1!)	12(2!)	11087(1!)				
"	(epileptic) (1M)	103.8(1!)	6(2!)	11722(1!)				
„	(patients) (1M)	160.9(1!)	24(2!)	16351(1!)				
„	(1M)	150.7(1!)	24(2!)	16345(1!)				
„	(1M)	294.0(1!)	36(2!)	23900(1!)				
Greenblatt et al. 1981b	+(elderly) (1M)	71.5(1!)	24(2!)	5608(1!)	-	-		
Pullar et al. 1987	(epileptic) (8M)	84.0(1!)	41(2!)	11664(1!)				
	Mean ± SD	**116.2 ±58.0**	**31.9 ±11.7**	**12667 ±3923**				
	Number of trials	3	3	3				
	Number of observations	15	15	15				

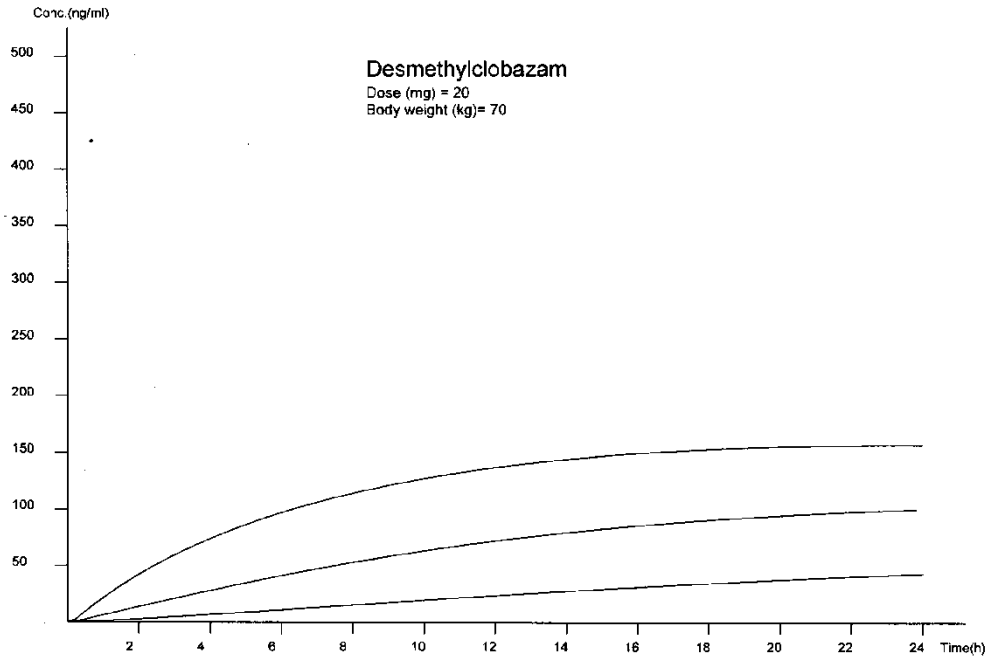


Figure 102: Plasma concentration-time curve of desmethylclobazam after oral administration of clobazam.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	184.8	±	72.5	ng/mL
Ka:	0.0693	±	0.0196	h^{-1}
α:	0.260	±	0.143	h^{-1}
β:	0.0120	±	0.0020	h^{-1}
t_0:	0.073	±	0.039	h
V%:	90.9	±	19.8	%

				derived from time-course of plasma concentrations
C_{max}:	116.2	±	58 ng/mL	103.7 (55.1-156.3) ng/mL
t_{max}:	31.9	±	11.7 h	2.07 (2.07-3.12) h
AUC_{o-oo}:	12667	±	3923 ng*h/mL	12535 (7525-17994) ng*h/mL

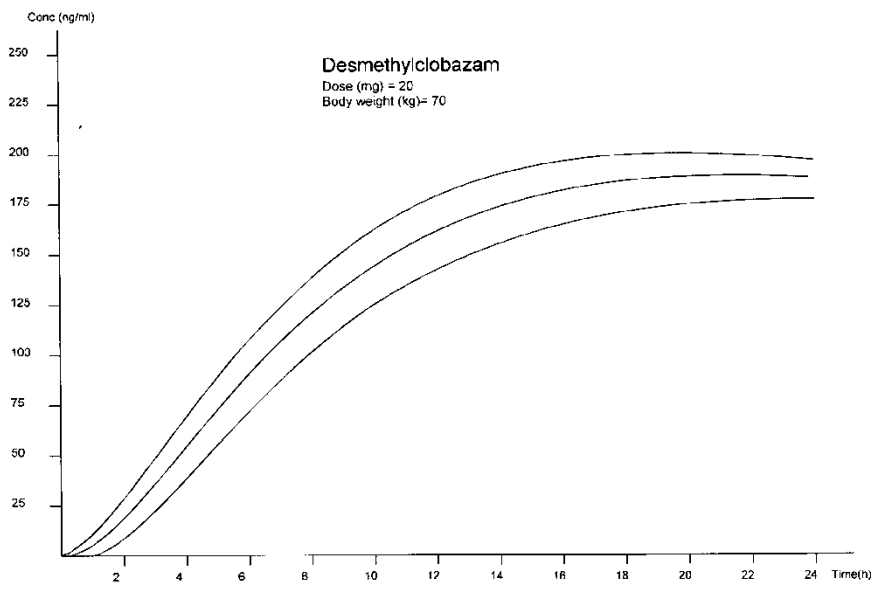


Figure 103: Plasma concentration-time curve of desmethylclobazam after oral administration of clobazam.

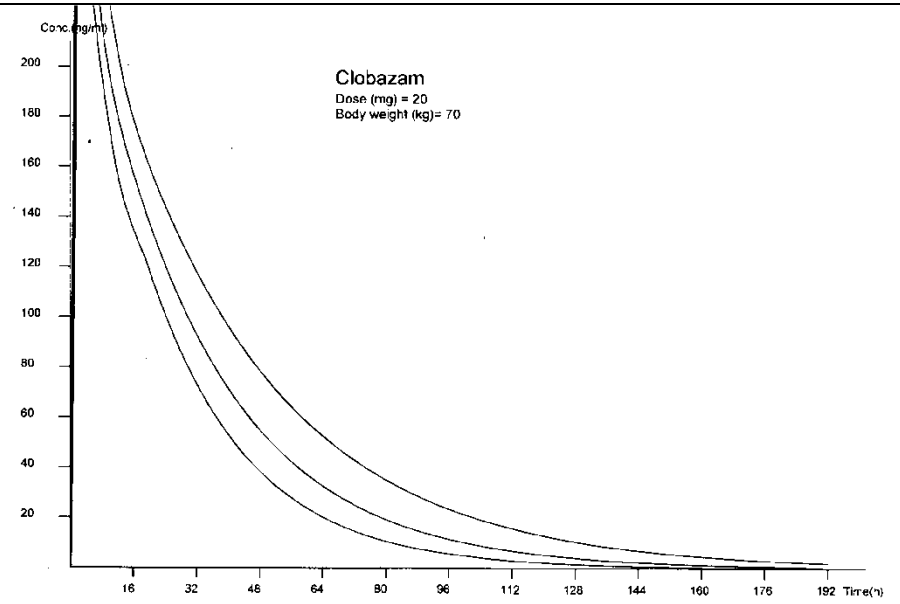


Figure 104: Plasma concentration-time curve of clobazam after oral administration over a period of 8 days.

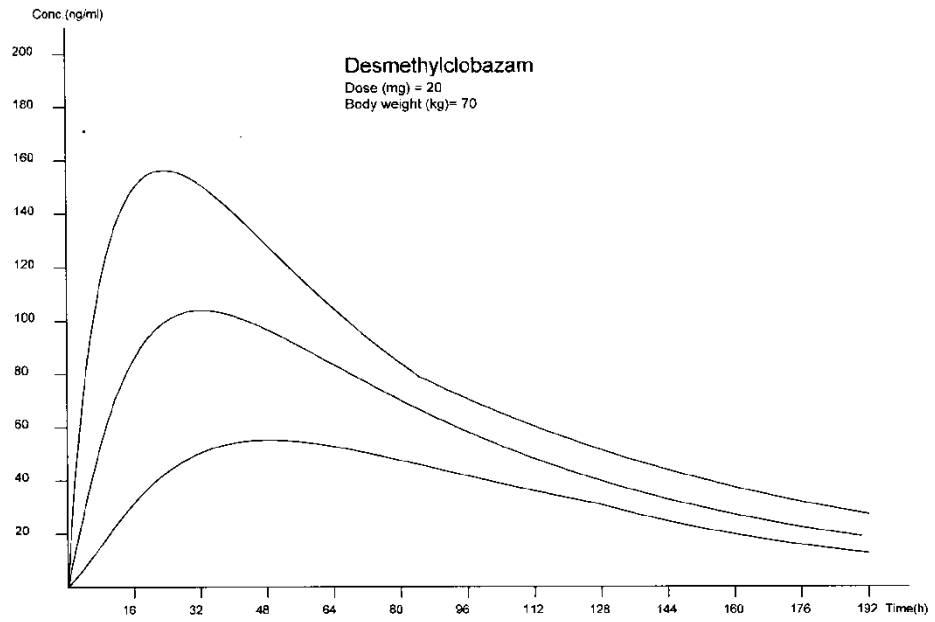


Figure 105: Plasma concentration-time curve of desmethylclobazam after oral administration of clobazam over a period of 8 days.

7.3.3.3 Other tranquillizers

7.3.3.3.1 Buspirone

Application: Buspirone is the first component of a novel class of anxiolytic drugs, the azaspirones, and is prescribed for the treatment of generalized anxiety disorder. In contrast to benzodiazepines anxiolytics, it lacks anticonvulsant, muscle relaxant, and sedative effects (Riblet et al., 1984; Jann, 1988) It is prescribed for adults with an average daily dose of 30 mg divided in two or three single doses. Higher interindividual variations in buspirone absorption have been reported, which may be due to the extensive first-pass metabolism, but the mean dose normalized AUC and C_{max} values after administration of 10, 20, and 40 mg were not statistically significant different. Also t_{max} values and elimination half-lives were conformable, so that it was concluded that buspirone exhibits linear pharmacokinetics following doses in the therapeutic range (Gammans et al., 1985). It has been suggested that the treatment of autistic children with buspirone is useful, because during a period of high brain serotonin synthesis in healthy children, in autistic children this synthesis may be disrupted and may be compensated by the serotonin agonist activity of buspirone (Edwards et al., 2006).

Biotransformation: The extensive first-pass metabolism of buspirone results in a low bioavailability of approximately 4% (Gammans et al., 1986) and several-fold higher concentrations of two pharmacologically active metabolites in plasma. 1-(2-pyrimidinyl)-piperazine (1-PP) is formed by N-dealkylation of the 8-azaspiro[4,5]decane-7,9-dione-8-butyl group (Caccia et al., 1986). This metabolite was supposed to be 1% to 20% as potent as the parent drug (Gammans et al., 1986). A further metabolite, 6-hydroxybuspirone, was found to have partial agonist activity at the 5-HT_{1A} receptors and may contribute to the clinical efficacy of buspirone (Dockens et al., 2007), particularly if it is taken into account that plasma concentrations of the metabolite are up to ten times higher than that of the parent drug. This is to be applied to the active metabolite 1-PP, too. Dockens et al. (2007) studied the pharmacokinetics of 6-hydroxybuspirone (6-OHB) by administration of the racemate, S-enantiomer, and R-enantiomer. They observed an interconversion between the enantiomers and compared the 6-OHB/1-PP ratios with those after buspirone incorporation. Many other metabolites are formed by N-oxidation and hydroxylation and excreted into the urine in free and glucuronidated form.

Interaction: The biochemical effect of buspirone is as agonist of serotonin 5-HT_{1A} receptors. Its efficacy may be influenced by factors, which alter the pharmacokinetics of buspirone. Salazar et al. (2001) compared the pharmacokinetics of buspirone after oral administration of 5,7.5, 15, and 30 mg in children (aged 6-12 yr), adolescents with anxiety disorder (13-17 yr), and normal healthy adults. Elimination half-lives of buspirone were in the range from 2.0 to 3.4 hr, those of 1-PP in the range of 3.7 to 4.7 hr. Peak plasma concentrations were highest in children and lowest in adults at all three dosages (7.5, 15, and 30 mg). C_{max} and AUC values were statistically significant higher in children than in the other groups. Pharrmacokinetics in still younger children with autism (aged 2-4 yr) showed after administration of 2.5-5.0 mg doses no distinct differences to that of older children after intake of 7.5 to 15 mg (Edwards et al., 2006).

The main use of buspirone in depression is augmentation therapy. The influence of concomitant administered antidepressants is therefore of importance. After a pretreatment with the novel anxiolytic drug deramciclane for 8 days the coadministration of buspirone had no inhibition effect on CYP3A4 activity, whereas the further, not CYP3A4 dependent biotransformation of the active metabolite 1-PP was inhibited, which became apparent in a 84% increase of AUC and a 20% prolongation of the elimination half-life (Laine et al., 2003). Compared with placebo, the mean area under the plasma buspirone concentration-time curve was increased after concomitant administration of erythromycin sixfold and following intake of itraconazole 13-fold (Kivistö et al., 1997). Fluvoxamine increased only moderately plasma buspirone concentrations and decreased the production of 1-PP (Lamberg et al., 1998a). Grapefruit juice increased the mean peak plasma concentration of buspirone 4.3-fold and the mean AUC value 9.2-fold (Lilja et al., 1998). Rifampicin, an antibiotic drug, had a marked induction effect on buspirone biotransformation, when volunteers were pretreated wit 600 mg rifampicin daily for 5 days. On day 9, 30 mg buspirone was administered orally. Rifampicin decreased the peak plasma concentrations from 6.6 ± 3.7 to 0.84 ± 0.23 ng/mL and the elimination half-life from 2.8 ± 0.7 to 1.3 ± 0.5 hr (Lamberg et al., 1998).

Buspirone is highly protein bound (more than 95%), but did not replace dilantin, propranolol, digoxin, or warfarin from plasma proteins (Gammans et al., 1986).

Evaluation of studies: Single dose studies have been performed with oral doses of 5 to 30 mg buspirone. Despite of the relatively high range, the normalized fictive initial concentrations Cp0 (15 mg basis) are in good conformity with a mean value of 1.78 ± 0.89 ng/mL. The peak level, which is in the same order of magnitude, is reached in extraordinary short time (less

than 1 hour). The both active metabolites 1-PP and 6-hydroxybuspirone have similar short t_{max} values (1.6 hr resp. 0.9 hr), caused by high absorption constants and low lag times.

Table 100: 15 mg Buspirone (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Sakr et al. 2001	+ (extended-release) (16M)	43.1	15	2.27 (2!)	0.244(2!)	0.255(2!)	2.01 (2!)	0.24 (2!)	9.08 (2!)
Laine et al. 2003	+(deraminciclane) (8M/8F))	19-31	20	1.855 (1!)	0.300(2!)	1.26(2!)	1.64 (2!)	0. 149 (2!)	99.6 (2!)
Dockens et al. 2006	+ active metabolite (13)	19-45	5	1.182 (1!)	0.203(2!)	0.290(21)	2.02 (2!)	0.21 (2!)	43.8 (2!)
„	therapeutic (13)	19-45	7.5	1.10 (1!)	0.172(2!)	0.294(2!)	1.73 (2!)	0.182 (2!)	36.19 (2!)
„	range (13)	19-45	15	1.40 (1!)	0.224(2!)	0.234(2!)	1.48 (2!)	0.224 (2!)	4.54 (2!)
„	(13)	19-45	20	1.526 (1!)	0.135(2!)	0.603(2!)	1.48 (2!)	0.216 (2!)	99.2 (2!)
„	(13)	19-45	30	1.095 (1!)	0.138(2!)	0.268(2!)	2.10 (2!)	0.215 (2!)	32.3 (2!)
Sakr et al. 2001a	+ (extended-release (17M/16F)	35±10	15	0.975 (2!)	0.261(2!)	0.670(2!)	2.57 (2!)	0.133 (2!)	34.88 (2!)
Dockens et al. 2007	+6-OH-buspirone (20M)	18-45	10	2.574 (2!)	0.110(2!)	0.630(2!)	2.065 (2!)	0.158 (2!)	93.03 (2!)
Salazar et al. 2001	+(adolescents (14)	18-45	15	1.215 (2!)	0.338(2!)	0.559(2!)	3.054 (2!)	0.016 (2!)	34.88 2!)
„	and children) (14)	18-45	30	1.83 (2!)	0.546(2!)	0.654(2!)	2.89 (2!)	0.026 (2!)	17.6 (2!)
Lamberg et al. 1998	+(rifampicin) (5M/5F)	18-26	30	4.34(2!)	0.530(2!)	0.986(2!)	2.81(2!)	0.308(2!)	24.0(2!)
	Mean ± SD			**1.78 ±0.89**	**0.258 ±0.126**	**0.573 ±0.293**	**2.20 ±0.51**	**0.165 ±0.075**	**45.4 ±32.4**
	Number of trials			12	12	12	12	12	12
	Number of observations			188	188	188	188	188	188

Continuation of Table 100: 15 mg Buspirone (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Sakr et al. 2001	+ (extended-release) (16M)	2.03 (2)	0.85 (2)	6.10 (2!)	74			
Laine et al. 2003	+(deraminciclane) (8M/8F))	1.28 (1)	1.1 (2)	3.58 (1!)				
Dockens et al. 2006	+ active metabolite (13)	0.75 (1)	0.75 (2)	3.279 (1!)				
„	therapeutic (13)	0.88 (1)	0.75 (2)	2.798 (1!)				
„	range (13)	1.1 (1)	0.5 (2)	2.99 (1!)				
„	(13)	0.975 (1)	0,75 (2)	2,955 (1!)				
„	(13)	1,0 (1)	0,75 (2)	3,285 (1!)				
Sakr et al. 2001a	+ (extended-release (17M/16F)	1,76(2)	0,924 (2)	4,31 (2!)	72±11			
Dockens et al. 2007	+6-OH-buspirone (20M)	2,31 (2)	0,75 (2)	7,386 (2!)	77.6			
Salazar et al. 2001	+(adolescents (14)	1,03 (2)	1,0 (2)	5,48 2!)	77.6±12.9			
„	and children) (14)	1,79 (2)	1,5 (2)	7,36 (2!)	77.6±12.9			
Lamberg et al. 1998	+(rifampicin) (5M/5F)	3.3	1.5	11.7(2!)				
	Mean	**1.70**	**0.92**	**5.50**				
	± SD	**±0.66**	**±0.26**	**±2.31**				
	Number of trials							
	Number of observations							

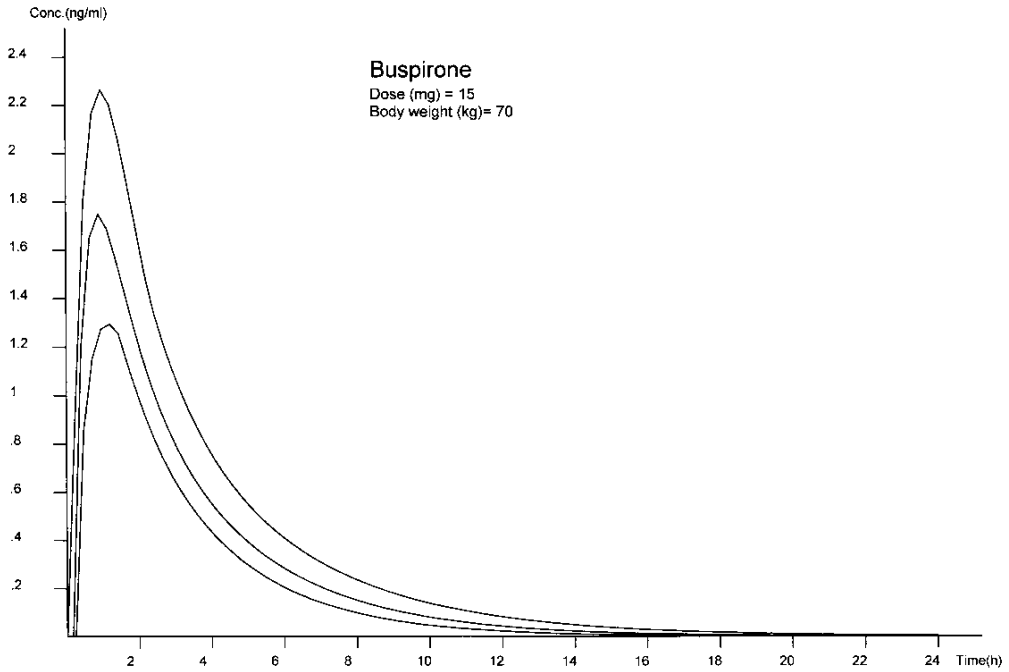


Figure 106: Plasma concentration-time curve of buspirone after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	1.78	±	0.89	ng/mL
Ka:	2.69	±	0.88	h^{-1}
α:	1.21	±	0.41	h^{-1}
β:	0.315	±	0.055	h^{-1}
t_0:	0.165	±	0.075	h
V%:	45.4	±	32.4	%
B:	4 %			

				derived from time-course of plasma concentrations
C_{max}:	1.70	±	0.66 ng/mL	1.73 (1.29-2.26) ng/mL
t_{max}:	0.92	±	0.26 h	0.77 (0.77-1.20) h
AUC_{o-oo}:	5.50	±	2.31 ng*h/mL	5.91 (4.37-8.39) ng*h/mL

Table 101: 1-(2-pyrimidinyl)piperazine (1-PP) from 15 mg Buspirone (absorption, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	MetAnteil %	$t_{½}Ka$ (h^{-1})	$t_{½}\beta$ (h^{-1})	AUC_{o-oo} ($ng_{*}h/mL$)	Cmax	Tmax
Sakr et al. 2001	+ (extended-release) (16M)	43.1	15	76(2!)	0.330(2!)	5.55(2!)	54.0(2!)	5,61(2)	1,7(2)
Laine et al. 2003	+(deraminciclane) (8M/8F))	19-31	20	82(1!)	0.408(2!)	3.85(2!)	41.9(1!)	7.05(1)	1.8(2)
Dockens et al. 2006	+ active metabolite (13)	19-45	5	89.8(1!)	0.231(2!)	5.78(2!)	83.1 (1!)	11.2(1)	1.5(2)
„	therapeutic (13)	19-45	7.5	91(1!)	0.277(2!)	5.13(2!)	77.82 (1!)	8.6(1)	1.0(2)
„	range (13)	19-45	15	88.2(1!)	0.198(2!)	6.03(2!)	87.9 (1!)	9.1(1)	1.5(2)
„	(13)	19-45	20	85.9(1!)	0.210(2!)	5.83(2!)	75.1 (1!)	75(1)	1.5(2)
„	(13)	19-45	30	89.4(1!)	0.257(2!)	6.30(2!)	80.42 (1!)	8.0(1)	1.52(2)
Sakr et al. 2001a	+ (extended-release (17M/16F)	35±10	15	89.0(2!)	0.365(2!)	5.46(2!)	57.9 (2!)	6.65(2)	1.52(2)
Dockens et al. 2007	+6-OH-buspirone (20M)	18-45	10	74.2(2!)	0.231(2!)	5.33(2!)	54.4 (2!)	6.08(2)	0.75(2)
Salazar et al. 2001	+(adolescents (14)	18-45	15	89.0(2!)	0.365(2!)	5.78(2!)	69.2 (2!)	6.62(2)	1.0(2)
„	and children) (14)	18-45	30	85.5(2!)	0.542(2!)	5.78(2!)	71.8 (2!)	6.37(2)	1.5(2)
	Mean			**85.2**	**0.317**	**5.49**	**66.1**	**7.31**	**1.39**
	± SD			**±5.7**	**±0.095**	**±0.59**	**±13.6**	**±1.46**	**±0.32**
	Number of trials			11	11	11	11	11	11
	Number of observations			178	178	178	178	178	178

Table 102: 6-Hydroxybuspirone from 15 mg Buspirone (absorption, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	MetAnteil %	$t_{½}Ka$ (h^{-1})	$t_{½}\beta$ (h^{-1})	AUC_{0-oo} ($ng_{*}h/mL$)	Cmax	Tmax
Dockens et al. 2006	+ active metabolite (13)	19-45	5	95.5(1!)	0.198(2!)	2,79	124,5(1!)	26(1)	1,0
„	therapeutic (13)	19-45	7.5	96.0(1!)	0.173(2!)	2,77	98,54(1!)	22(1)	0,75
„	range (13)	19-45	15	95.1(1!)	0.182(2!)	2,78	101,6(1!)	23(1)	1,0
„	(13)	19-45	20	94.2(1!)	0.154(2!)	2,72	91,16(1!)	21(1)	0,75
„	(13)	19-45	30	95.0(1!)	0.124(2!)	3,3	95,04(1!)	19,5(1)	1,0
Dockens et al. 2007	+6-OH-buspirone (20M)	18-45	10	82.8(2!)	0.224(2!)	3,08	76,16(2!)	13,68(2)	0,88
	Mean			**92.3**	**0.180**	**2.92**	**96.0**	**20.3**	**0.90**
	± SD			**±5.3**	**±0.033**	**±0.21**	**±15.1**	**±4.1**	**±0.11**
	Number of trials			6	6	6	6	6	6
	Number of observations			85	85	85	85	85	85

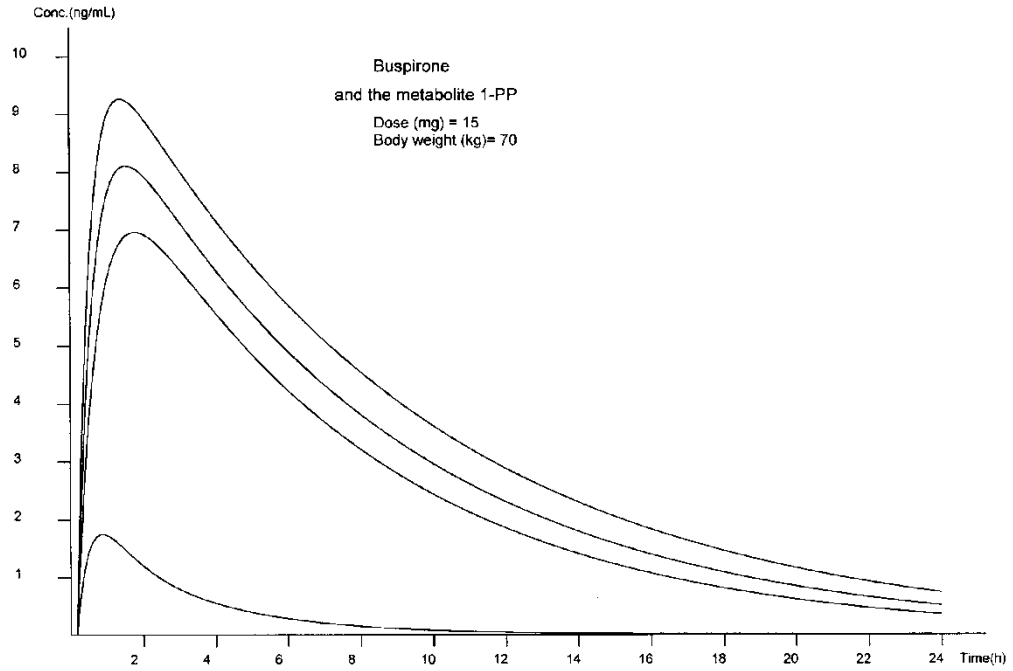


Figure 107: Plasma concentration-time curve of 1-(2-pyrimidinyl)piperazine after oral administration of buspirone.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

%Formation:	85.2	±	5.7	%
Ka:	2.19	±	0.51	h^{-1}
β:	0.126	±	0.012	h^{-1}

				derived from time-course of plasma concentrations
C_{max}:	7.32	±	1.46 ng/mL	8.11 (6.96-9.26) ng/mL
t_{max}:	1.39	±	0.32 h	1.61 (1.37-1.85) h
AUC_{o-oo}:	66.1	±	13.6 ng*h/mL	76.5 (63.0-93.3) ng*h/mL

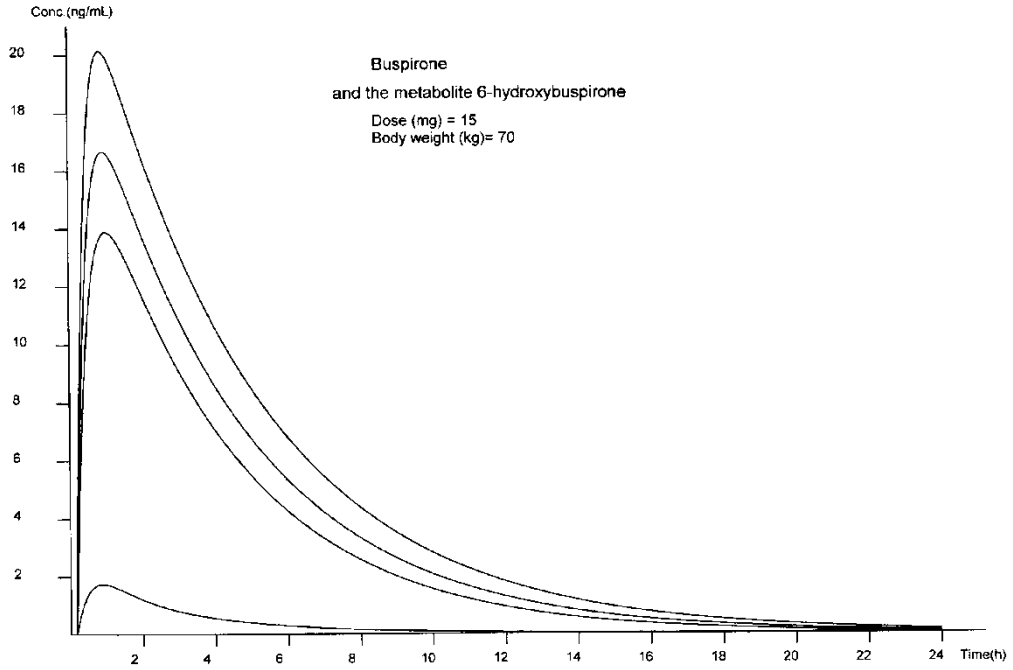


Figure 108: Plasma concentration-time curve of 6-hydroxybuspirone after oral administration of buspirone.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

%Formation:	92.3	±	5.3	%
Ka:	3.85	±	0.60	h^{-1}
β:	0.237	±	0.016	h^{-1}

				derived from time-course of plasma concentrations
C_{max}:	20.3	±	4.1 ng/mL	16.7 (13.8-20.1) ng/mL
t_{max}:	0.90	±	0.11 h	0.89 (0.89-1.13) h
AUC_{o-oo}:	96.0	±	15.1 ng_*h/mL	84.1 (67.8-109.1) ng_*h/mL

7.3.3.3.2 Meprobamate

Application: Meprobamate prescription is indicated for treatment of anxiety disorders or for the short-term relief of the symptoms of anxiety. It is less sedating at effective doses than barbiturates. The absorption from the gastrointestinal tract occurs rapidly with a half-life of about half an hour and a mean lag-time of 4 min. After an average time of 2 hours, the peak level is reached. The drug is widely distributed in the body and the plasma protein binding is not very pronounced (14-24%) (Olsen et al., 1994).

Biotransformation: The drug undergoes extensive metabolism in the liver with 8-20% excretion of the unchanged drug into the urine. The remainder is eliminated as hydroxyl derivative and as glucuronide (Meyer & Straughn, 1977).

Meprobamate is an active metabolite of the muscle relaxant carisoprodol, the N-isopropyl derivative of meprobamate (Littrell et al., 1993), which was rapidly eliminated with a half-life of 99 ± 46 min. Within 2.5 hour after carisoprodol intake, meprobamate serum concentrations exceeded those of the parent drug (Olsen et al., 1994). The oxidative dealkylating degradation step is catalyzed by an isoenzyme of cytochrome P450 (CYP2C19). This was proved by Dalén et al. (1996). The disposition of carisoprodol was clearly correlated to the mephenytoin dehydroxylation phenotype. The mean serum clearance of carisoprodol was four times lower in poor metabolizers of mephenytoin than in extensive metabolizers. Studies of Gonzalez et al. (2009) suggested that sedation via GABA(A) receptors are not only attributed to the metabolite meprobamate but also to the parent drug.

Interaction: In patients receiving chronic treatment with meprobamate for more than 1 month (1.2-1.6 g/day), amount of urinary hydroxyl metabolite increased. This finding suggested some degree of hepatic enzyme induction with chronic therapy (Meyer & Straughn, 1977).

Evaluation of studies: Table 103 contains bioavailability studies of drug manufactures, submitted to the authors of two publications (Meyer & Straughn, 1977; Meyer et al., 1978). Most of the studies present plasma levels of meprobamate from a period of 32 hours after drug administration. A minimum period of 12 hours was required for a calculation of pharmacokinetic parameters of meprobamate. Because only ranges of body weights were given in the studies, a mean body weight was estimated from the ranges and the number of volunteers of each study. Mean values of Cp0, C_{max}, and AUC were dose and body weight normalized (400 mg; 70 kg). Even results from the studies with drugs containing several components and considerably smaller doses (Gilbert et al., 1984) are compatible with those after a 400 mg dose, so that a linear dependence of plasma levels on the dose in the range

from 10 to 400 mg is supposed. Distribution phase of meprobamate is not pronounced, so that a one compartment model describes the time course of plasma concentrations sufficiently, too (V% = 91.1 ± 13.4%).

Table 103: 400 mg Meprobamate (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (mg/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Meyer et al. 1978	(6) I/1 Wyeth relative	22-27	400	7.75(1!)	0.295(2!)	3.67 (2!)	10.9(2!)	0.064(2!)	93.0(2!)
«	(6) I/2 ICN bioavailability	22-27	400	8.42(1!)	0.373(2!)	3.17(2!)	9.85(2!)	0.007(2!)	99.8(2!)
«	(6) I/3 Towne, Paulsen	22-27	400	7.84(1!)	0.303(2!)	3.65(2!)	10.5(2!)	0.037(2!)	85.8(2!)
«	(6) I/4 Stanley	22-27	400	9.11(1!)	0.124(2!)	4.20(2!)	10.2(2!)	0.054(2!)	98.4(2!)
«	(6) I/5 Smith, Kline	22-27	400	8.86(1!)	0.083(2!)	3.12(2!)	9.68(2!)	0.045(2!)	98.4(2!)
«	(6) I/6 Heather	22-27	400	7.92(1!)	0.314(2!)	5.46(2!)	10.2(2!)	0.028(2!)	98.2(2!)
«	(6) II/1 Wyeth	22-27	400	8.50(1!)	0.499(2!)	3.18(2!)	10.7(2!)	0.017 (2!)	99.6(2!)
«	(6) II/7 Lannett	22-27	400	8.04(1!)	0.568(2!)	3.17(2!)	12.6(2!)	0.009(2!)	99.8(2!)
«	(6) II/8 Zenith	22-27	400	7.98(1!)	0.568(2!)	4.42(2!)	11.7(2!)	0.014(2!)	93.4(2!)
«	(6) II/9 Westward	22-27	400	7.30(1!)	0.568(2!)	3.17(2!)	13.6(2!)	0.006(2!)	99.9(2!)
«	(6) II/10 Wallace	22-27	400	7.39(1!)	0.396(2!)	2.81(2!)	11.3(2!)	0.008(2!)	87.3(2!)
«	(6) II/11 Danbury	22-27	400	8.41(1!)	1.13(2!)	3.77(2!)	11.2(2!)	0.081(2!)	86.1(2!)
Gilbert et al. 1984	Visano®-mini dragee (9M)	18-40	12.5	7.70(1!)	0.284(2!)	0.925(2!)	7.90(2!)	0.190(2!)	84.8(2!)
«	DoloVisano® dragee (9M)	18-40	10	8.14(1!)	0.768(2!)	0.849 (2!)	9.33(2!)	0.250(2!)	43.4(2!)
«	VisanoCor® dragee (9M)	18-40	12.5	8.08(1!)	0.210(2!)	0.972(2!)	8.63(2!)	0.173(2!)	69.1(2!)
Meyer & Straughn 1977	(20) Towne, Paulsen tablet /relative		400	9.37(1!)	0.642(2!)	1.20(2!)	8.63(2!)	0.004(2!)	98.4(2!)
«	(20) Wallace tablet /bioavailability		400	10.16(1!)	0.642(2!)	3.17(2!)	7.27(2!)	0.09(2!)	98.4(2!)
«	(12) Vangard tablet		400	8.79(1!)	0.410(2!)	2.05(2!)	14.7(2!)	0.087(2!)	86.1(2!)
«	(12) Wallace tablet		400	13.3(1!)	0.472(2!)	1.51(2!)	9.61(2!)	0.016(2!)	98.4(2!)
«	(14) Wyeth tablet		400	9.24(1!)	0.495(2!)	1.51(2!)	8.74(2!)	0.008(2!)	98.4(2!)
«	(2) Wyeth suspension		400	6.83(1!)	0.487(2!)	2.04(2!)	11.3(2!)	0.048(2!)	86.1(2!)
	Mean ± SD			**8.93 ±1.43**	**0.485 ±0.210**	**2.47 ±1.22**	**9.96 ±1.99**	**0.062 ±0.069**	**91.1 ±13.4**
	Number of trials			21	21	21	21	21	21
	Number of observations			179	179	179	179	179	179

Continuation of Table 103: 400 mg Meprobamate (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (mg/L)	t_{max} (h)	AUC_{o-oo} (mg*h/L)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Meyer et al. 1978	(6) I/1 Wyeth relative	7.80(1)	2.2(2)	121(1!)	70.5-95.5			
«	(6) I/2 ICN bioavailability	7.60(1)	2.3(2)	115(1!)	70.5-95.5			
«	(6) I/3 Towne, Paulsen	7.90(1)	1.7(2)	121(1!)	70.5-95.5			
«	(6) I/4 Stanley	8.90(1)	1.7(2)	132(1!)	70.5-95.5			
«	(6) I/5 Smith, Kline	8.80(1)	1.5(2)	122(1!)	70.5-95.5			
«	(6) I/6 Heather	7.40(1)	1.5(2)	113(1!)	70.5-95.5			
«	(6) II/1 Wyeth	7.70(1)	3.5 (2)	125(1!)	70.5-95.5			
«	(6) II/7 Lannett	7.30(1)	3.0(2)	139(1!)	70.5-95.5			
«	(6) II/8 Zenith	7.40(1)	3.0(2)	131(1!)	70.5-95.5			
«	(6) II/9 Westward	6.80(1)	2.7 (2)	137(1!)	70.5-95.5			
«	(6) II/10 Wallace	7.80(1)	1.8(2)	119(1!)	70.5-95.5			
«	(6) II/11 Danbury	6.90(1)	3.8(2)	127(1!)	70.5-95.5			
Gilbert et al. 1984	Visano®-mini dragee (9M)	6.52(1)	1.36(2)	85.6(1!)	54-94			
«	DoloVisano® dragee (9M)	6.36(1)	1.59(2)	106(1!)	54-94			
«	VisanoCor® dragee (9M)	7.16(1)	1.79(2)	98.4(1!)	54-94			
Meyer & Straughn 1977	(20) Towne, Paulsen tablet /relative	6.94(1!)	3.0(2)	100(1!)				
«	(20) Wallace tablet /bioavailability	7.35(1!)	1.5(2)	99.9(1!)				
«	(12) Vangard tablet	8.36(1!)	2.0(2)	183(1!)				
«	(12) Wallace tablet	10.76(1!)	2.0(2)	172(1!)				
«	(14) Wyeth tablet	6.60(1!)	2.0(2)	108(1!)				
«	(2) Wyeth suspension	6.10(1!)	2.0(2)	110(1!)				
	Mean ± SD	**7.56 ±1.08**	**2.15 ±0.67**	**120.7 ±26.1**	**80.5**			
	Number of trials	21	21	21				
	Number of observations	179	179	179				

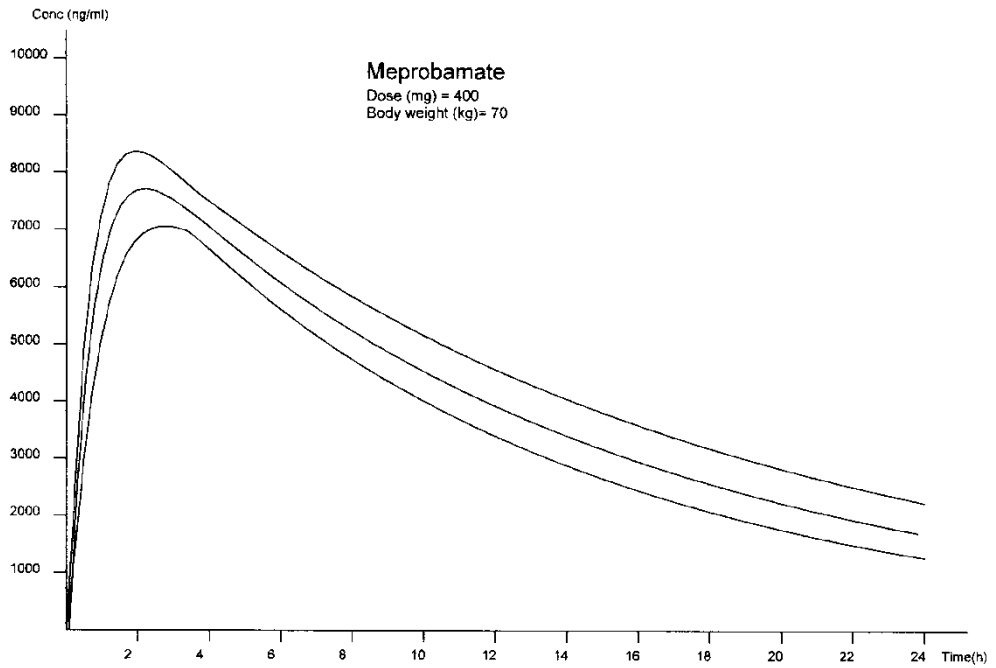


Figure 109: Plasma concentration-time curve of meprobamate after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	8.93	±	1.43	mg/L
Ka:	1.43	±	0.43	h^{-1}
α:	0.281	±	0.093	h^{-1}
β:	0.0696	±	0.0116	h^{-1}
t_0:	0.062	±	0.069	h
V%:	91.1	±	13.4	%
B:	100 %			

				derived from time-course of plasma concentrations
C_{max}:	7.56	±	1.08 mg/L	7.71 (7.06-8.37) mg/L
t_{max}:	2.15	±	0.67 h	2.17 (1.92-2.88) h
AUC_{o-oo}:	120.7	±	26.1 mg_*h/L	124 (103-153) mg_*h/L

7.4 Antihistamines

7.4.1 Diphenhydramine

Application: Diphenhydramine is an antihistaminic agent by blocking the effect of histamine at H_1 receptor sites. A concentration from 25 to 50 ng/mL appears to be in a range, within which there is a statistically significant antihistaminic effect without relevant sedation. The sedative effect of 50 mg intravenously administered diphenhydramine differed in healthy volunteers from that of placebo only during the first 3 hours (Carruthers et al., 1978). The oral dose for antiallergic and antiemetic treatment of adults is 25 to 50 mg every 6-8 hours. The dose for nighttime sedation is 50 mg at bedtime. In addition to intravenous and oral dosing, intramuscular, sublingual, and topical formulations, including creams, gels, and sprays, are used for antiallergic treatment.

Dimenhydrinate, the diphenhydramine salt of 8-chlorotheophylline, is used among others for preventing motion sickness. Mean peak plasma concentration of diphenhydramine was slightly higher after sublingual administration than after oral dosing (Scavone et al., 1990). 8-Chlorotheophylline as additive to diphenhydramine is supposed to intensify the sedative effect, but Gielsdorf et al. (1986) did not substantiate this presumed effect, which might be caused by an increase of the absorption rate.

Biotransformation: Metabolic degradation of diphenhydramine occurs by stepwise demethylation via desmethyldiphenhydramine to didesmethyl-diphenhydramine, which is transformed to diphenylmethylmethoxyacetic acid by oxidation of the primary amine to the carboxylic acid. The acid is excreted into the urine in free and conjugated form. Only up to 2% (Gielsdorf et al., 1986), less than 4% (Albert et al., 1975), of an administered dose was detected in urine as unchanged drug. 30 to 60% of an oral dose is degraded during the first-pass metabolism, thus the bioavailability is only 40 to 70%. The yield of desmethyldiphenhydramine was higher after oral than after intravenous administration (Blyden et al., 1986). The authors pointed out to a falsification of the pharmacokinetic data of diphenhydramine caused by nearly identical elution times of diphenhydramine and desmethyldiphenhydramine on standard GC systems.

In vitro investigations with human liver microsomes demonstrated that the polymorphic cytochrome P450 (CYP) isoenzyme CYP2D6 is inhibited competitively by diphenhydramine, suggesting that clinically relevant interactions with CYP2D6 substrates might occur (Hamelin et al., 1998; He et al., 2002). This finding was confirmed by Akutsu et al. (2007), who

showed, using specific human cytochrome P450 isoenzymes, that diphenhydramine is not only a potent inhibitor but also a high-affinity substrate of CYP2D6. In addition CYP1A2, CYP2C9, and CYP2C19 were identified as low-affinity components.

Interaction: In vivo experiments with high (extensive metabolizers) and low (poor metabolizers) CYP2D6 activity in the presence of steady-state diphenhydramine concentrations, revealed an interaction of diphenhydramine in extensive metabolizers by competitive inhibition of metoprolol α-hydroxylation. After administration of an oral 100 mg dose, the clearance of metoprolol was reduced to about half the value, but not in poor metabolizers (Hamelin et al., 2000). A similar modulating of metoprolol pharmacokinetics by diphenhydramine coadministration was shown in healthy premenopausal women (Sharma et al., 2005). Using debrisoquine as a model substrate of CYP2D6, an influence could not be derived from the 8 hr urinary debrisoquine metabolic ratio (Kortunay et al., 2002). After concomitant administration of venlafaxine in extensive metabolizers, the clearance of venlafaxine was decreased from 104 ± 60 to 43 ± 23 L/hr by the inhibitory effect of diphenhydramine (Lessard et al., 2001). Pharmacokinetics of naproxen was not affected by coadministration of diphenhydramine (Toothaker et al., 2000).

The influence of age on the pharmacokinetics of diphenhydramine was studied by Simons et al. (1990a). The elimination half-lives differed statistically significant between elderly adults 69.4 ± 4.3 yr), young adults (31.5 ± 10.4 yr), and children (8.9 ±1.7 yr): 13.5 ± 4.2 hr, vs. 9.2 ±2.5 hr vs. 5.4 ± 1.8 hr. Accordingly the clearance rates were reduced with increasing age. The influence of race was observed by Spector et al. (1980), who determined after both intravenous and oral diphenhydramine at all times Orientals had plasma levels approximately half those of Caucasians. They interpreted these findings by higher distribution volumes and plasma clearance but not elimination half-lives of Orientals than Caucasians.

Evaluation of studies: The determined standard deviation of V% is higher than the average (Table 104). Usage of such a standard deviation for a calculation of the maximal curve is ineffective because a negative value would be formed from calculating the difference between mean and standard deviation. Thus the standard deviation was not used for the calculation of time courses of diphenhydramine plasma concentrations. Peak levels and AUC values from calculation of the averages and from time courses (Figure 110) are then in good conformance relating to average and deviation.

Table 104: 50 mg Diphenhydramine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Toothaker et al., 2000	control (14M/14F)	19-40	50	55.9(2!)	0.992(2!)	1.08(2!)	9.76(2!)	0.381(2!)	3.13(2!)
"	+ naproxen (14M/14F)	19-40	50	55.8(2!)	1.06(2!)	1.10(2!)	9.78(2!)	0.373(2!)	1.56(2!)
Valoti et al., 2003	dimenhydrinat chewing gum (4M/3F)	23.3±1.2	12.7	40.7(2!)	0.937(2!)	1.24(2!)	12.3(2!)	0.500(2!)	18.2(2!)
Berlinger et al., 1982	elderly women (12F)	65-81	50	152(2!)	0.780(2!)	0.630(2!)	3.14(2!)	0.708(2!)	87.5(2!)
Scavone et al., 1990	+(sublingual) (8)	18-45	27.6	89.6(1!)	0.760(2!)	0.836(2!)	5.84(2!)	0.546(2!)	12.1(2!)
Gielsdorf et al., 1986	tablet (8M/4F)	27.7±7.8	50	39.2(2!)	0.930(2!)	1.39(2!)	10.6(2!)	0.187(2!)	18.2(2!)
«	solution (8M/4F)	27.7±7.8	50	34.9(2!)	0.979(2!)	1.47(2!)	12.2(2!)	0.180(2!)	18.2(2!)
«	dimenhydrinate (8M/4F)	27.7±7.8	31	38.9(2!)	0.805(2!)	1.04(2!)	12.8(2!)	0.178(2!)	12.1(2!)
Gengo et al., 1989	pharmacodynamics (15M)	19-41	50	100(1!)	0.485(2!)	1.62(2!)	5.0(2!)	0.512(2!)	86.1(2!)
Tavares et., 2007	reference: tablet (6)		54.4	65.7(1!)	0.882(2!)	1.31(2!)	7.63(2!)	0.469(2!)	24.8(2!)
«	test: capsule (6)		54.4	61.4(1!)	0.371(2!)	1.02(2!)	7.88(2!)	0.472(2!)	36.3(2!)
Gilbert et al., 1984	Visano®-mini dragee (9M)	18-40	12.5	140.9(1!)	0.992(2!)	1.16(2!)	2.85(2!)	0.307(2!)	23.4(2!)
«	DoloVisano® dragee (9M)	18-40	10	54.4(1!)	0.930(2!)	1.20(2!)	7.87(2!)	0.549(2!)	21.2(2!)
«	VisanoCor® dragee (9M)	18-40	12.5	56.0(1!)	0.422(2!)	1.76(2!)	8.53(2!)	0.490(2!)	65.4(2!)
	Mean ± SD			**64.9 ±34.2**	**0.853 ±0.207**	**1.19 ±0.27**	**8.59 ±2.96**	**0.401 ±0.147**	**26.8 ±29.6**
	Number of trials			14	14	14	14	14	14
	Number of observations			173	173	173	173	173	173

Continuation of Table 104: 50 mg Diphenhydramine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Toothaker et al., 2000	control (14M/14F)	83.3(2	2.2(2)	920(2!)	66.6±8.2			
"	+ naproxen (14M/14F)	82.7(2	2.2(2)	937(2!)	66.6±8.2			
Valoti et al., 2003	dimenhydrinat chewing gum (4M/3F)	51.4(2)	2.58(2)	747(2!)	63.1±4.1			
Berlinger et al., 1982	elderly women (12F)	77.8(2)	3.0(2)	512(2!)	70	42		
Scavone et al., 1990	+(sublingual) (8)	87.9 (1)	2.3(2)	537(1!)	-	69		
Gielsdorf et al., 1986	tablet (8M/4F)	59.6(2)	2.46(2!)	665(2!)	68.8±10.1			
«	solution (8M/4F)	51.6(2)	2.52(2!)	673(2!)	68.8±10.1			
«	dimenhydrinate (8M/4F)	62.6(2)	2.08(2!)	767(2!)	68.8±10.1			
Gengo et al., 1989	pharmacodynamics (15M)	75.01)	2.5(2)	676(1!)				
Tavares et., 2007	reference: tablet (6)	73.6(1)	2.46(2)	763(1!)				
«	test: capsule (6)	73.7(1)	2.17(2)	699(1!)				
Gilbert et al., 1984	Visano®-mini dragee (9M)	83.6(1!)	1.8(2!)	484(1!)	54-94			
«	DoloVisano® dragee (9M)	54.4(1!)	2.2(2!)	622(1!)	54-94			
«	VisanoCor® dragee (9M)	70.1(1!)	1.8(2!)	880(1!)	54-94			
	Mean ± SD	**72.7± 12.2**	**2.30 ±0.28**	**769 ±152**		**52.8 ±13.4**		
	Number of trials	14	14	14		2		
	Number of observations	173	173	173		20		

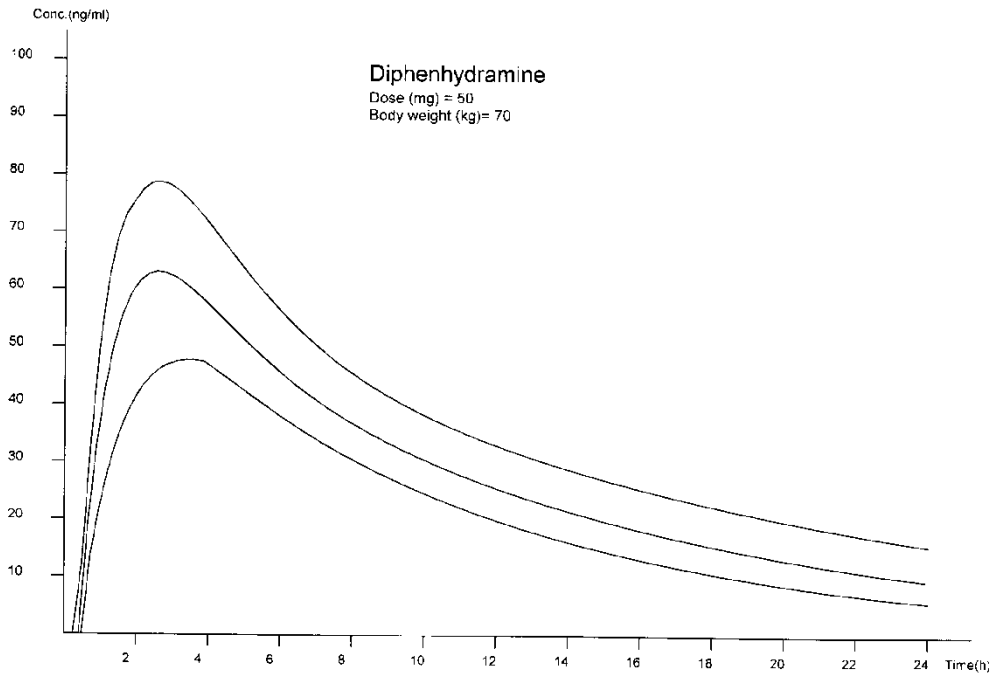


Figure 110: Plasma concentration-time curve of diphenhydramine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	64.9	±	10.5	ng/mL	
Ka:	0.813	±	0.159	h^{-1}	
α:	0.583	±	0.108	h^{-1}	
β:	0.0807	±	0.0207	h^{-1}	
t_0:	0.401	±	0.147	h	
V%:	26.8			%	
B:	52.8	±	13.4	%	
					derived from time-course of plasma concentrations
C_{max}:	72.7	±	12.2 ng/mL		63.0 (47.7-78.7) ng/mL
t_{max}:	2.30	±	0.28 h		2.50 (2.50-3.36) h
AUC_{o-oo}:	769	±	152ng∗h/mL		810 (583-1162) ng∗h/mL

7.4.2 Terfenadine

Application: Terfenadine is a histamine H_1 receptor antagonist with lack of sedative effect and is used for the treatment of histamine-related allergic reactions. It is nearly completely degraded during its rapid absorption by first-pass metabolism to the active form fexofenadine, which possesses most if not all of the pharmacological activity. Okerholm et al. (1981) demonstrated that after administration of 60 mg ^{14}C terfenadine, only 0.5% was absorbed as unchanged drug, the rest was biotransformed to fexofenadine. The recovery of ^{14}C in the urine of the subjects was about 40% while about 60% was recovered in the feces, but only in traces as parent drug. A dose response study with 60 and 180 mg terfenadine showed that peak concentrations and AUC values were approximately linearly dependent on dosage.

Biotransformation: In vivo (Garteiz et al., 1982) and in vitro experiments (Yun et al., 1993) showed that two major metabolic products are formed by oxidative degradation of terfenadine. The main route leads by oxidation of a tert-butyl group via a primary alcohol to terfenadine carboxylic acid, the active principle of terfenadine. Another route is the oxidative N-dealkylation to 4-(hydroxydiphenylmethyl)-piperidine (azacyclonol). Both routes were catalyzed by purified human liver microsomal P450/3A4 (CYP3A4) isoenzyme. The oxidation of both enantiomers was inhibited by gestogene, a selective inactivator of P450/3A and by antibodies, raised against CYP3A4 (Yun et al., 1993). A proposed metabolite of fexofenadine is the dehydrogenation product, keto-fexofenadine. The absolute bioavailability of fexofenadine is unknown because of lack of studies after intravenous administration. A negligible hepatic metabolism and excretion mainly in the feces is supposed (Chen, 2007).

Interaction: Interactions of terfenadine and substrates of CYP3A4 are of extraordinary importance, because an increase of terfenadine plasma concentrations may lead to cardiovascular adverse events with QT interval prolongation and life-threatening ventricular arrhythmias. After concomitant administration of antifungal agents like ketoconazole (Honig et al., 1993a), itraconazole (Honig et al., 1993b), levels of unmetabolized terfenadine were detectable in plasma, which was associated with QT prolongation. The mean area under the concentration-time curve of the active metabolite was statistically significant increased after coadministration of fluconazole (Honig et al., 1993c) or erythromycin (Honig et al., 1992). Terfenadine plasma concentrations were also augmented by interaction with grapefruit juice resulting in prolongation of repolarization in the electrocardiogram (Benton et al., 1996; Honig et al., 1996; Rau et al., 1997). Further substrates of CYP3A4 had lower influence on the pharmacokinetics of terfenadine as for instance atorvastatin (Stern et al., 1998) or

cimetidine and ranitidine (Honig et al., 1993d), or venlafaxine (Amchin et al., 1998a). Caused by the side effects, terfenadine-containing drugs were removed from the market in some countries as the USA, Canada, and the United Kingdom and replaced by fexofenadine.

Evaluation of studies: Comparing peak concentrations, fictive initial concentrations, and AUC values of terfenadine and fexofenadine (Table 105 and Table 106) the low bioavailability of the parent drug in the absence of inhibiting components becomes obvious, with values of 0.37, 0.47, and 0.78%, which correspond to the results of Okerholm et al. (1981). The evaluated pharmacokinetic parameters relating to fexofenadine as metabolite of terfenadine can differ considerably from those determined after oral administration of fexofenadine itself. Though fexofenadine is formed very rapidly from terfenadine during its absorption, the elimination half-life of terfenadine is two times longer than that of fexofenadine. An explanation is the high protein-binding of terfenadine in plasma.

Table 105: 60 mg Terfenadine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Okerholm et al. 1981	bioavailability (14M)		60	0.524(1!)	0.224(2!)	0.851(2!)	14.0(2!)	0.025(2!)	21.5(2!)
„	(14M)		180	0.552(1!)	0.468(2!)	0.908(2!)	17.3(2!)	0.014(2!)	12.1(2!)
Stern et al. 1998	+(atorvastatin)(5M/7F)	22-52	120	0.884(2!)	0.169(2!)	3.03(2!)	16.4(2!)	0.012(2!)	49.8(2!)
Lalonde et al. 1996	population (121-132)	27.9±6.5	120	0.503(2)	-	-	15.1(2)	-	-
“	pharmacokinetic (12)	27.9±6.5	120	0.769(2!)	0.210(2!)	4.18(2!)	24.5(2!)	0.021(2!)	49.9(2!)
	Mean ± SD			**0.580 ±0.132**	**0.274 ±0.120**	**2.14 ±1.42**	**16.4 ±2.9**	**0.018 ±0.005**	**34-5 ±14.3**
	Number of trials			5	4	4	5	4	4
	Number of observations			195	72	72	195	72	72

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Okerholm et al. 1981	bioavailability (14M)	1.54(2)	0.79(2)	11.0(1!)	-	0.5		
„	(14M)	1.51(2)	1.07(2)	15.9(1!)	-			
Stern et al. 1998	+(atorvastatin)(5M/7F)	0.788(2)	1.8(2)	13.1(2!)	77.1			
Lalonde et al. 1996	population (121-132)	0.77(2)	1.3(2)	10 .9 (2!)	72.6±7.1		119200	
“	pharmacokinetic (12)	-	-	15.5(2!)	72.6±7.1			
	Mean ± SD	**0.797 ±0.079**	**1.26 ±0.26**	**12.1 ±1.9**				
	Number of trials	4	4	5				
	Number of observations	192	192	195				

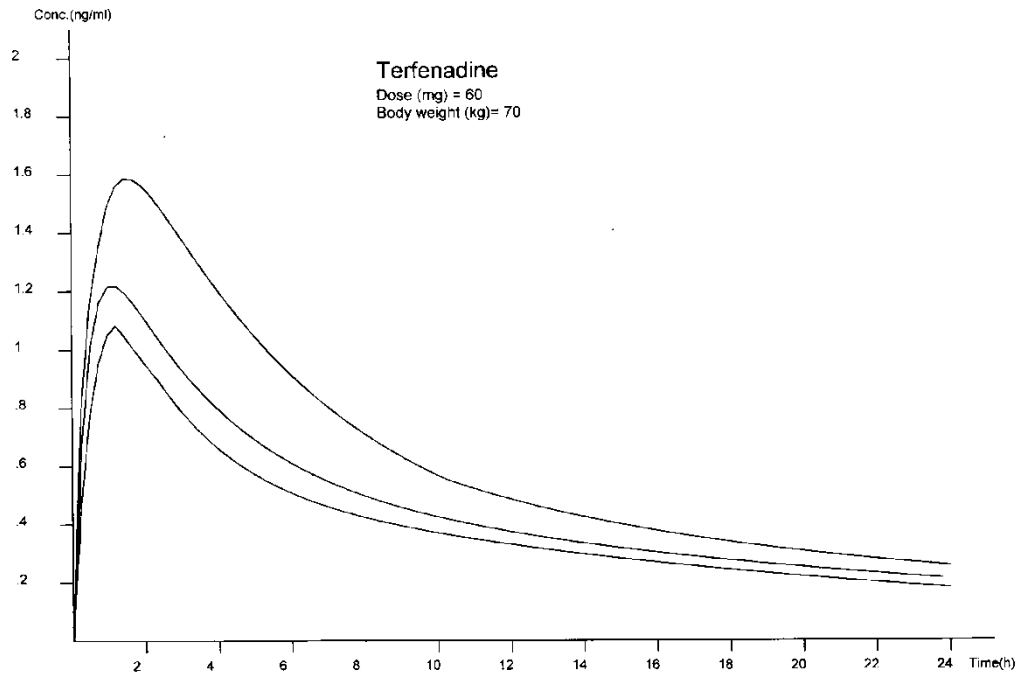


Figure 111: Plasma concentration-time curve of terfenadine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	0.58	±	0.132	ng/mL	
Ka:	2.53	±	0.77	h^{-1}	
α:	0.324	±	0.129	h^{-1}	
β:	0.0423	±	0.0064	h^{-1}	
t_0:	0.018	±	0.005	h	
V%:	34.5	±	14.3	%	
B:	0.5 %				
					derived from time-course of plasma concentrations
C_{max}:	0.80	±	0.08	ng/mL	1.22 (1.20-1.44) ng/mL
t_{max}:	1.26	±	0.26 h		1.2 (1.2-1.44) h
AUC_{o-oo}:	12.1	±	1.9 ng∗h/mL		16.4 (13.5-22.4) ng∗h/mL

Table 106: Fexofenadine from 60 mg Terfenadine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (yr)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Eller et al. 1992	fasting (24)	33.6±10.3	120	108(2!)	1.03(2!)	1.33(2!)	6.09(2!)	0.368(2!)	8.79(2!)
„	postprandial (24)	33.6±10.3	120	160(2!)	1.34(2!)	.62(2!)	4.78(2!)	0.546(2!)	11.7(2!)
Rau et al. 1997	+(grapefruit juice) (12M)	23-40	60	(365)	1.17(2!)	1.20(2!)	4.27(2!)	0.312(2!)	6.25(2!)
Stern et al. 1998	+(atorvastatin)(5M/7F)	22-52	120	72.6(2!)	1.23	1.51	9.16(2)	293	2.20(2!)
Simons et al. 1990a	elderly volunteers (8F)	67.8±0.8	1mg/kg	83.9(1!)	0.699(2!)	2.11(2!)	8.23(2!)	0.017(2!)	24.8(2!)
Lalonde et al. 1996	population (121-132)	27.9±6.5	120	-	-	-	9.5(2!)	-	-
“	pharmacokinetic (12)	27.9±6.5	120	148.9(2!)	1.06(2!)	1.51(2!)	5.82(2!)	0.333(2!)	12.4(2!)
	Mean ± SD			**123.9 ±33.0**	**1.13 ±0.18**	**1.50 ±0.24**	**7.45 ±2.09**	**0.362 ±0.43**	**10.2 ±5.6**
	Number of trials			5	6	6	7	6	6
	Number of observations			80	92	92	217	92	92

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Eller et al. 1992	fasting (24)	169.2 (2)	2.5(2)	1262(2!)	58.2±8.2
„	postprandial (24)	190.4(2)	3.4(2)	1283(2!)	58.2±8.2
Rau et al. 1997	+(grapefruit juice)(12M)	229.0(1)	2.5(2)	1198(1!)	
Stern et al. 1998	+(atorvastatin)(5M/7F)	270.4(2)	2.5(2)	2126(2!)	77.1
Simons et al. 1990a	elderly volunteers (8F)	(162.9)	2.0(2)	(1427)	
Lalonde et al. 1996	population (121-132)	230.2(1)	2.5(1)	1681(1)	72.6±7.1
“	pharmacokinetic (12)	-	-	1686(2)	72.6±7.1
	Mean ± SD	**215.4 ±30.0**	**2.6 ±0.4**	**1559 ±263**	
	Number of trials	5	6	6	
	Number of observations	203	212	209	

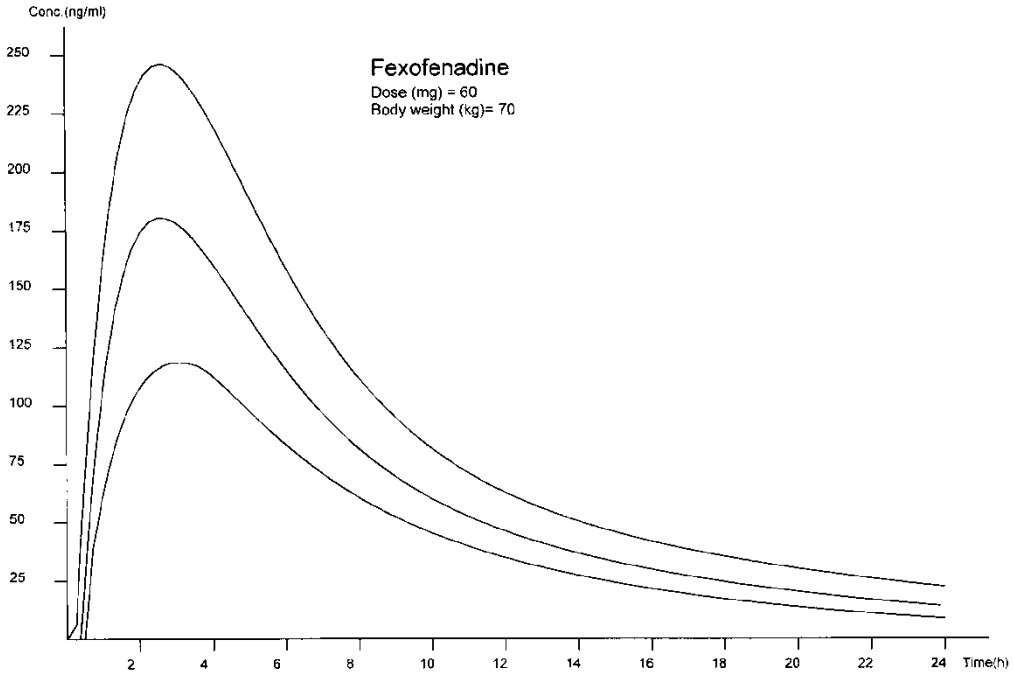


Figure 112: Plasma concentration-time curve of fexofenadine after oral administration of terfenadine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	123.9	±	33.0	ng/mL
Ka:	0.613	±	0.084	h^{-1}
α:	0.462	±	0.064	h^{-1}
β:	0.0930	±	0.020	h^{-1}
t_0:	0.362	±	0.143	h
V%:	10.2	±	5.6	%
B:	99.5 %			

				derived from time-course of plasma concentrations
C_{max}:	215.4	±	30.0 ng/mL	180 (119-246) ng/mL
t_{max}:	2.6	±	0.4 h	2.8 (2.6-3.1) h
AUC_{o-oo}:	1559	±	263 ng*h/mL	1710 (1159-2487) ng*h/mL

7.4.3 Loratadine

Application: Loratadine is an orally active histamine H_1 receptor antagonist, widely used as antiallergic agent without statistically significant sedating or anticholinergic properties. Causes for this are threefold greater activity for peripheral as compared for central histamine H_1 receptors and that, deduced from animal experiments, only small amounts of loratadine enter the brain (Barenholtz & McLeod, 1989). A once-daily dosing is sufficient, because the main metabolite desloratadine, which is supposed to be four times more active than the parent drug, has a long duration of effectiveness. The onset of action is rapid. About 1 hour after oral administration, the peak level of loratadine and after about 2 hours the peak concentration of the active metabolite is reached. A linear relationship between mean peak level and dose in the range of 10 to 40 mg loratadine was shown by Hilbert et al. (1987). In the same way, peak levels and AUC values of desloratadine increase with rising dosage. Loratadine and desloratadine are available as tablets, oral suspension, and syrup. Using a chewing gum as administration form, the bioavailability was threefold higher compared with tablets, which was most likely due to a bypass of first-pass metabolism in the oral mucosa (Noehr-Jensen et al., 2006).

The pharmacokinetics of loratadine in pediatric subjects, who received 10 mg loratadine syrup (body weight >30 kg) or 5 mg (body weight <30 kg), was similar to that in adult healthy volunteers (Lin et al., 1995). This also holds true for children aged 2 to 5 years after dosing of 5 mg loratadine syrup (Salmun et al., 2000). In normal geriatric volunteers the clearance of loratadine tended to be lower than in young adults, but the mean elimination half-life of loratadine corresponded with the calculated average in Table 107 (Hilbert et al., 1988).

Biotransformation: In vitro experiments demonstrated that the oxidative degradation of loratadine to desloratadine (descarboethoxyloratadine) is mediated by cytochrome P450 isoenzymes, mainly by CYP3A4 and to a less extent by CYP2D6 (Yumibe et al., 1996). The CYP2D6 polymorphism affected loratadine pharmacokinetics in studies of Yin et al. (2005), who administrated 20 mg loratadine to 3 groups of Chinese subjects with different CYP2D6 activity. The contribution of CYP3A4 relative to CYP2D6 for the loratadine metabolism is supposed to vary in different ethnic groups. Further isoenzymes as CYP2C19 and others seem to be involved in loratadine metabolism (Ghosal et al., 2009) including hydroxylation of loratadine and desloratadine. The hydroxylated compounds are partly excreted as glucuronides. About 13% of a dose was eliminated as 3-hydroxydesloratadine glucuronide. Less than 2% of a dose was detected in urine as desloratadine and only trace amounts as

unchanged drug (Ramanathan et al., 2007). The glucuronidaton of 3-hydroxydesloratadine is demonstrated to be mediated via UGT 1A1, 1A3, and 2B15 in human liver (Ghosal et al., 2004). In poor metabolizers of loratadine, the increased exposure to desloratadine was not associated with any changes in the safety and tolerability of loratadine Prenner et al. (2006).

Interaction: In patients with severe renal insufficiency, disposition of In-patients with severe renal insufficiency was not statistically significant altered, hemodialysis augmented endogenous clearance by less than 1% (Matzke et al., 1990). Concomitant administration of loratadine and CYP3A4 inhibitors led to increased plasma concentrations, indicating that CYP3A4 is essentially involved in loratadine metabolism (Chaikin et al., 2005). Kosoglou et al. (2000) found in their interaction study after 10 day treatment with loratadine alone, concomitant administration of cimetidine or ketoconazole statistically significant increases of plasma concentrations by inhibition of CYP3A4 (103% by cimetidine and 307% by ketoconazole). Plasma levels of desloratadine were only enhanced by ketoconazole. No changes in the QTc interval were observed. Coadministration of loratadine and erythromycin for 10 consecutive days caused 40% resp. 46% increases of loratadine and desloratadine AUC values (Brannan et al., 1995), while combined giving of desloratadine and erythromycin showed no relevant interaction (Banfield et al., 2002).

Evaluation of studies: The calculated pharmacokinetic parameters (table 107) exhibit high standard deviations, presumally V% with a value higher than that of the mean. For the same reason as in the case of diphenhydramine the standard deviation of V% was not used.The evaluated pharmacokinetic parameters referring to desloratadine as metabolite of loratadine can differ considerably from those determined after oral administration of desloratadine itself.

Table 107: 20 mg Loratadine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Hilbert et al. 1987	dose proportionality (12M)	21-38	10	4.86(2!)	0.369(2!)	0.499(2!)	2.69(2!)	0.398(2!)	10.9(2!)
„	effect (12M)	21-38	20	9.38(2!)	0.307(2!)	3.98(2!)	1.76(2!)	0.174(2!)	96.5(2!)
“	(12M)	21-38	40	8.67(2!)	0.272(2!)	0.300(2!)	1.87(2!)	0.462(2!)	5.47(2!)
Zhang et al. 2003	active metabolite (20M)	21-24	20	6.02(2!)	0.338(2!)	0.841(2!)	2.91(2!)	0.178(2!)	16.4(2!)
Chen et al. 2004	HPLC-ESI-MS (18M)	18-24	40	3.92(2)	0.244(2!)	0.831(2!)	8.66(2)	0.232(2!)	8.79(2!)
Yin et al. 2005	effect of (4M)	21-26	20	-	-	-	4.11(1)	-	-
“	CYP2D6*10 allele (6M)	21-26	20	-	-	-	4.12(1)	-	-
“	(7M)	21-26	20	-	-	-	10.32(1)	-	-
	Mean ± SD			**6.30 ±2.05**	**0.304 ±0.045**	**1.204 ±1.24**	**4.20 ±2.89**	**0.272 ±0.113**	**24.9 ±31.8**
	Number of trials			5	5	5	8	5	5
	Number of observations			74	74	74	101	74	74

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Hilbert et al. 1987	dose proportionality (12M)	10.42(2)	1.5 (2)	23.55(1!)	77.6			
„	effect (12M)	9.38(2)	1.0(2)	21.41(1!)	77.6			
“	(12M)	8.67(2)	1.2(2)	26.1(2!)	77.6			
Zhang et al. 2003	active metabolite (20M)	15.6(2)	1.2(2)	40.8(2!)	64.3±0.8			
Chen et al. 2004	HPLC-ESI-MS (18M)	20.9(2)	1.0(2)	80.7(2!)	72.6±7.1			
Yin et al. 2005	effect of (4M)	5.72(1)	-	20.3(1)	-		14.6(1)	
“	CYP2D6*10 allele (6M)	7.88(1)	-	25.9(1)	-		11.06(1)	
“	(7M)	12.7(1)	-	45.5(1)	-		7.17(1)	
	Mean ± SD	**14.4 ±4.3**	**1.2 ±0.2**	**41.2 ±22.3**				
	Number of trials	8	5	8				
	Number of observations	91	74	101				

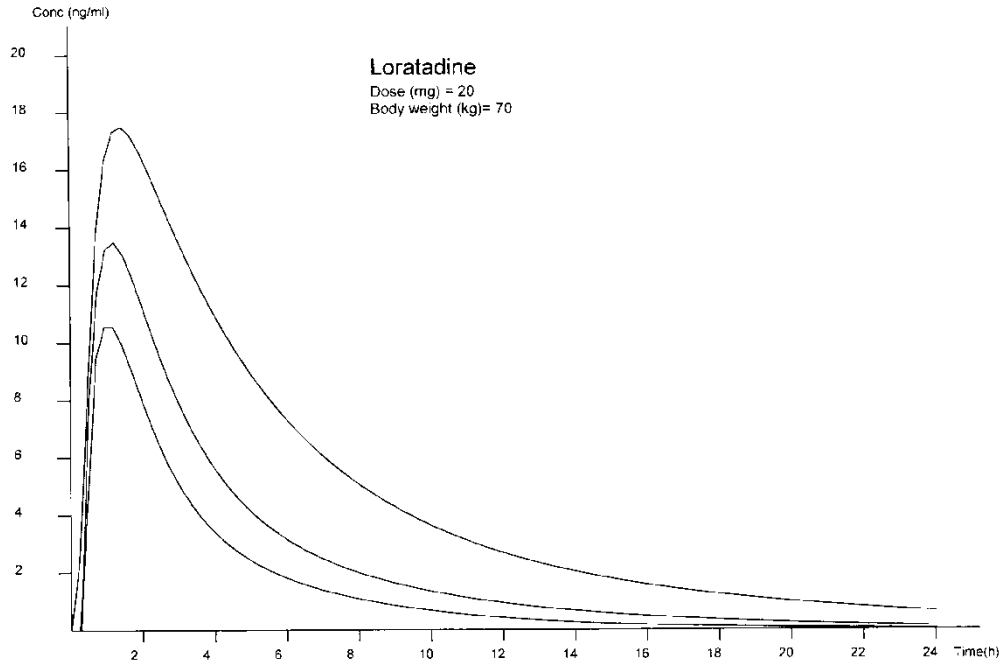


Figure 113: Plasma concentration-time curve of loratadine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	6.3	±	2.05	ng/mL	
Ka:	2.28	±	0.064	h^{-1}	
α:	0.272	±	0.113	h^{-1}	
β:	0.165	±	0.067	h^{-1}	
t_0:	0.272	±	0.113	h	
V%:	24.9			%	
B:	81 %				
					derived from time-course of plasma concentrations
C_{max}:	14.4	±	4.3 ng/mL		13.5 (10.6-17.5) ng/mL
t_{max}:	1.2	±	0.2h		1.2 (1.0-1.4) h
AUC_{o-oo}:	41.2	±	22.3 ng∗h/mL		59.7 (37.5-120.6) ng∗h/mL

Table 108: Desloratadine from 20 mg Loratadine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}Ka$ (h^{-1})	$t_{½}\alpha$ (h^{-1})	$t_{½}\beta$ (h^{-1})	t_0 (h)	V% (%)
Hilbert et al. 1987	dose propotionality (12M)	21-38	10	8.87(2!)	1.01(2!)	2.31(2!)	21.7(2!)	0.133(2!)	23.25(2!)
„	effect (12M)	21-38	20	11.0(2!)	0.478(2!)	2.03(2!)	17.7(2!)	0.174(2!)	36.3(2!)
“	(12M)	21-38	40	8.87(2!)	0.154(2!)	3.29(2!)	20.8(2!)	0.197(2!)	49.9(2!)
Zhang et al. 2003	active metabolite (20M)	18-24	20	7.74(2!)	0.533	0.947(2!)	13.9(2)	0.237(2!)	18.8(2!)
Yin et al. 2005	effect of (4M)	21-26	20	-	-	-	-	-	-
“	CYP2D6*10 allele (6M)	21-26	20	-	-	-	-	-	-
“	(7M)	21-26	20	-	-	-	-	-	-
	Mean ± SD			**5.89 ±1.43**	**0.542 ±0.284**	**1.97 ±0.88**	**17.9 ±3.3**	**0.193 ±0.039**	**30.2 ±12.2**
	Number of trials			4	4	4	4	4	4
	Number of observations			56	56	56	56	56	56

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)
Hilbert et al. 1987	dose propotionality (12M)	8.87(2)	3.7(2)	160.5(2!)	77.6
„	effect (12M)	11.0(2)	1.5(2)	157.2(2!)	77.6
“	(12M)	8. 87((2))	2.0(2)	155.6(1!)	77.6
Zhang et al. 2003	active metabolite (20M)	14.7(2)	1.5(2)	162.6(2!)	64.3±0.8
Yin et al. 2005	effect of (4M)	4.45(2)	-	-	-
“	CYP2D6*10 allele (6M)	5-34(2)	-	-	-
“	(7M)	6.15(2)	-	-	-
	Mean ± SD	**9.96 ±3.43**	**2.1 ±0.9**	**159.6 ±2.9**	
	Number of trials	7	4	4	
	Number of observations	73	56	56	

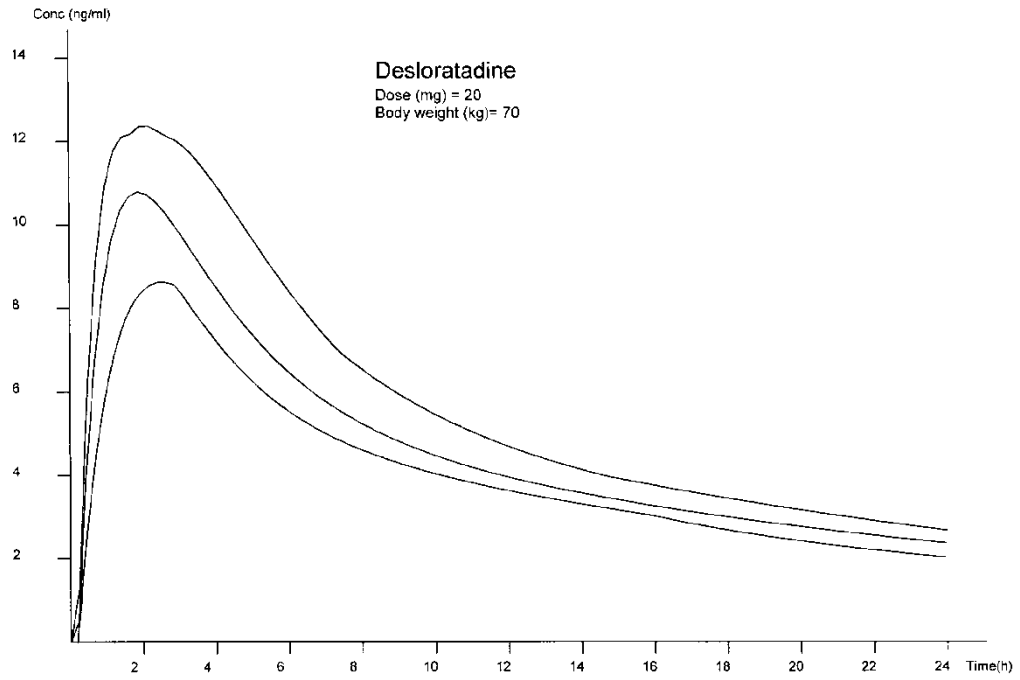


Figure 114: Plasma concentration-time curve of desloratadine after oral administration of loratadine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	5.89	±	1.43	ng/mL
Ka:	1.28	±	0.44	h^{-1}
α:	0.352	±	0.109	h^{-1}
β:	0.0387	±	0.006	h^{-1}
t_0:	0.193	±	0.039	h
V%:	30.2	±	12.2	%

				derived from timd-course of plasma concentrations
C_{max}:	9.96	±	3.43 ng/mL	10.8 (8.6-12.4) ng/mL
t_{max}:	2.1	±	0.9h	2.0 (2.0-2.6) h
AUC_{o-oo}:	159.5	±	2.9 ng*h/mL	175.4 (142.7-223.4) ng*h/mL

7.4.4 Triprolidine

Application: Triprolidine is an H_1-histamine receptor antagonist and widely used for prevention and treatment of upper respiratory symptoms associated with allergic rhinitis. The usual initial oral dose of the drug, recommended for adults is 2.5 mg. This dose has been administered in most of the pharmacokinetic studies. Even this dose was associated in some studies with adverse effects such as dizziness, sedation or dry mouth. In five of seven subjects in the study of Simons et al. (1986), drowsiness was observed. The non-sedating effect of modern H_1-antagonists like cetrizine, loratadine, and desloratadine in contrast to sedating like hydroxycine, diphenhydramine, and triprolidine may be explainable by the results of animal experiments (Chen et al., 2003), which revealed that the sedating H_1-antagonists are not substrates of P-glycoprotein (P-gp), which reduces drug concentrations in cells of the body e.g. brain tissue by transporting from the cell's interior.

Transdermal controlled release, which is dependent on temperature, drug concentration, and added plasticizers, can prevent sedating effects (Shin & Yoon, 2002). A comparison of oral and transdermal application showed further advantages of transdermal treatment, e.g. consistent plasma concentrations over a long period, the maximum of which was reached only after an average of 12 hours (5 mg dose), whereas T_{max} after oral intake was about 2 hr. The relative bioavailability showed no statistically significant differences (Miles et al., 1990). An absolute bioavailability is only known, if a formulation for intravenous administration is available. Triprolidine is excreted in the breast milk of nursing mothers. The amount after a single dose was estimated to 0.06-0.2% over 24 hr after administration (Findlay et al., 1984a).

Biotransformation: Only about 1% of orally administered triprolidine was recovered as unchanged drug in urine of the subjects over 24 h interval after drug intake, demonstrating a primarily elimination by biotransformation (Simons et al., 1986). Comparing pharmacokinetics of triprolidine in dogs, rabbits, rats, and humans, Findlay et al. (1984b) found considerable similarity in elimination characteristics. The main metabolite, formed by hydroxylation of the methyl side chain, is hydroxymethyl triprolidine. This compound may be obtained by microbial transformation of the antihistaminic drug triprolidine (Hansen et al., 1988). The fungus Cunninghamella elegans produces the hydroxymethyl derivative, but not the product of the next metabolic step, the corresponding carboxylic acid, which is formed in other species. Three further metabolites, which have been detected in mice (Deal et al., 1992) and beagle dogs (McNulty et al., 1992) are a pyrrolidinone derivative, a metabolite, in which

the pyrrolidine ring was opened with oxidation of the terminal carbon to a carboxylic acid, and a pyridine-ring hydroxylated derivative of triprolidine.

Interaction: An interaction of triprolidine and the opioid dipipanone was studied by Telekes et al. (1987) in healthy volunteers. While the drugs alone showed no sedating effects, the combination did cause statistically significant sedation.

Evaluation of studies: Triprolidine is rapidly absorbed with a lag time of about 15 min and a time at the peak level of less than 2 hr (Table 109, Figure 115). Peak concentrations and fictive initial concentrations show modest deviations, the elimination half lives are in good accordance.

Table 109: 2.5 mg Triprolidine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Cohen et al., 1985	+(BW825C (11M)	20-42	5	5.07(1!)	0.730(2!)	1.16(2!)	8.45(2!)	0.206(2!)	29.9(2!)
Simons et al., 1986	antihistaminic effect (7)		2.8	12.1(2!)	0.301(2!)	1.38(2!)	4.21(2!)	0.550(2!)	65.1(2!)
Miles et al., 1990	+(transdermal) syrup (6M)	18-35	2.5	6.13(1!)	0.556(2!)	2.86(2!)	4.99(2!)	0.146(2!)	84.8(2!)
Williams et al., 1984	tablet control (18)	18-40	2.5	3.78(1)	0.786(2!)	1.34(2!)	5.59(2!)	0.319(2!)	21.5(2!)
«	tablet +pseudoephedrine (17)	18-40	2.5	6.03(1)	0.651(2!)	3.85(2!)	5.64(2!)	0.216(2!)	84.8(2!)
«	syrup +pseudoephedrine (18)	18-40	2.5	6.47(1)	0.403(2!)	4.23(2!)	4.63 (2!)	0.217(2!)	96.5(2!)
	Mean ± SD			**6.54 ±2.69**	**1.16 ±0.26**	**0.267 ±0.133**	**0.1236 ±0.0227**	**0.264 ±0.104**	**63.1 ±31.1**
	Number of trials			6	6	6	6	6	6
	Number of observations			77	77	77	77	77	77

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Cohen et al., 1985	+(BW825C (11M)	6.50(1)	1.91(2)	62.6(1!)	56-83			
Simons et al., 1986	antihistaminic effect (7)	13.8(2)	2.00(2)	78.0(2!)	70			
Miles et al., 1990	+(transdermal) syrup (8M)	5.60(1)	2.00(2)	42.9(1!)				
Williams et al.,, 1984	tablet control (18)	5.50(1)	2.00(2)	37.1(1!)	60-90			
«	tablet +pseudoephedrine (17)	5.50(1)	1.49(2)	45.4(1!)	60-90			
«	syrup +pseudoephedrine (18)	6.00(1)	1.49(2)	40.6(1!)	60-90			
	Mean ± SD	**7.13 ±3.02**	**1.76 ±0.25**	**50.1 ±14.7**				
	Number of trials	6	6	6				
	Number of observations	77	77	77				

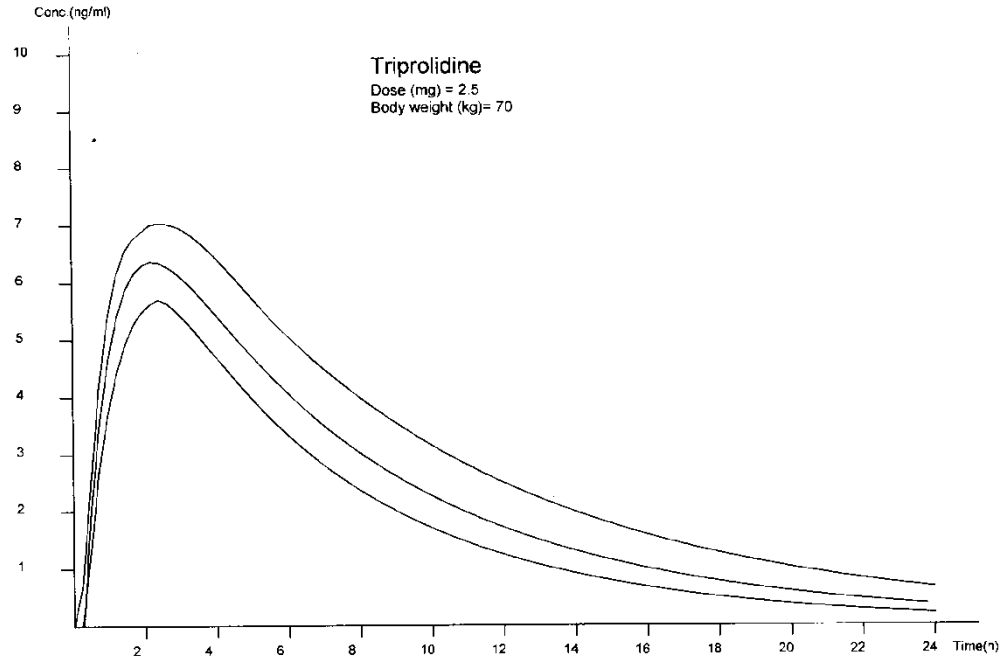


Figure 115: Plasma concentration-time curve of triprolidine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	6.54	±	2.69	ng/mL	
Ka:	1.16	±	0.26	h^{-1}	
α:	0.267	±	0.086	h^{-1}	
β:	0.1236	±	0.0227	h^{-1}	
t_0:	0.264	±	0.104	h	
V%:	63.1	±	31.1	%	
					derived from time-course of plasma concentrations
C_{max}:	7.13	±	3.02 ng/mL		5.21 (12.2-17.2) ng/mL
t_{max}:	1.76	±	0.25h	1.31	(1.91-2.88) h
AUC_{o-oo}:	50.1	±	14.7 ng*h/mL		290.9 (241.0.6-353.3) ng*h/mL
V_β/B:	80.0	±	7.6		75.7 ± 20.3
V_β/G:	1.11	±	0.30		0.995 ± 0.267 L/kg

7.5 Narcotics

7.5.1 Opiates

7.5.1.1 Morphine

Application: Morphine is the drug of choice in the treatment of moderate and severe pain, above all in patients with advanced cancer. It was detected as the first active alkaloid in opium, which is obtained from the latex of the plant opium poppy (papaver somniverum), by Friedrich Sertürner in the year 1803/04. Despite low bioavailability of about 25% (Table 114) in young healthy subjects, morphine is usually given orally either in solution of the hydrochloride or sulphate or in tablet form as a controlled release formulation. All routes of administration, except transdermal, occur readily. After intramuscular and subcutaneous administration, peak plasma levels are achieved within 15-20 min and are much higher than after oral intake, since oral morphine undergoes extensive first-pass metabolism (Glare & Walsh, 1991; Stuart-Harris et al., 2000). Peak levels and absorption rate constants after intravenous administration are dependent on the rate of drug infusing. The maximal concentrations are reached close after starting a bolus injection (Table 110 and Table 111). Further administration forms are sublingual, buccal (Osborne et al., 1990; Hoskin et al., 1989), by inhalation (Dershwitz et al., 2000), by snorting, rectal, epidural, and intrathecal. After absorption, morphine is rapidly and widely distributed and crosses the blood brain barrier.

Biotransformation: Glucuronidation, the main metabolic pathway of morphine, leads to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The major metabolite M3G posses opiate antagonist properties, whereas M6G is much more active than morphine. Due to the low bioavailability of morphine after oral intake, M6G plays a major part in the pharmacological effect of morphine than after parenteral administration. As further morphine conjugates in humans the 3,6-diglucuronide and morphine 3-ethereal sulfate were identified by Yeh et al. (1977). Chen et al. (2003) revealed a new metabolic pathway of morphine in cancer patients. They discovered the formation of morphine-3- and morphine-6-glucoside in the urine by three high-performance liquid chromatography systems. The amount of the 3-glucoside was higher than that of the 6-glucoside, similar to the M3G and M6G. The two O-glucuronides of normorphine, the morphine N-demethylation compound, were detected, too,

but in an opposite ratio. Normorphine is regarded as pharmacologically active, but is not usually found in plasma (Glare & Walsh, 1991).

Interaction: A comparison of the pharmacokinetics of morphine in young and elderly subjects (Baillie et al., 1989) showed a trend to a smaller volume of distribution and decreased clearance in the elderly group. This could be confirmed by calculation of the mean pharmacokinetic parameters after oral morphine intake (Table 114 and Table 115), which are elevated in elderly subjects, elimination half-life (3.70 vs. 2.38 hr), peak level (132.8 vs. 43.6 nmol/L), and AUC value (488 vs. 154 nmol*h/L). In similar way elimination half-life and AUC value after intravenous administration (Table 110 and Table 111) are increased in the elderly group. In cirrhotic patients compared with volunteers with normal liver function, the elimination half-life of morphine was enhanced and the bioavailability elevated due to an impaired biotransformation (Hasselström et al., 1990). Renal failure caused a statistically significant increase of areas under the concentration-time curves of morphine, M3G, and M6G. Particularly the AUC values of the glucuronides were considerably enlarged (Osborne et al., 1993). The observed morphine intoxications in renal failure has to be attributed primarily to an accumulation of the pharmacologically active metabolite M6G (Osborne et al., 1986; Davies et al., 1996). The isoform UGT2B7 of UDP- transferase catalyzes primarily the formation of morphine glucuronides (Coffman et al., 1997) with minor contribution of UGT1A3 (Green et al., 1998). Thus morphine pharmacokinetics was not altered in volunteers with Gilbert`s syndrome, which is caused by decreased capacity of UGT1A1 (Skarke et al., 2003).

Evaluation of studies: Morphine and the morphine glucuronides M3G and M6G show conformable courses of plasma concentrations with only slightly pronounced distribution phase. The elimination of the three substances occurs with similar rate so that a marked accumulation of the glucuronides after oral or intravenous administration of morphine in healthy subjects is not to be expected. Comparing the areas under the concentration-time curves of morphine, M3G, and M6G after injection of morphine (Table 110, Table 112 and Table 113), the ratio of M3G to morphine is 5.6, that of M6G to morphine 0.91. After oral administration (Table 114, Table 116 and Table 117), the ratios are by a factor of 4 to 5 higher (25.5 and 3.8), caused by the first-pass metabolism of morphine. Similar results are obtained using the peak concentrations of morphine, M3G, and M6G for calculating the ratios.

Table 110: 5 mg Morphine hydrochloride (sulphate) intravenous (absorption. distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}K_1$ (h)	$t_{½}K_2$ (h)	$t_{½}\beta$ (h)	V_1 (%)	V_2 (%)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	26-30	19.8	42.1(2!)	0.0306(2!)	0.0951(2!)	2.15(2!)	1.03(2!)	87.5(2!)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	13.2	50.7(2!)	0.043(2!)	0.66(2!)	2.31(2!)	6.25(2!)	49.9(2!)
Baillie et al., 1989	young + (elderly)(5M/3F)	26-30	26.4	23.4(2!)	0.0201(2!)	0.32(2!)	4.07(2!)	75(2!)	12.5(2!)
Dershwitz et al., 2000	+ (inhaled morphine) (10M/3F)	22-45	23.2	25.4(2!)	0.0116(2!)	0.156(2!)	1.81(2!)	3.13(2!)	21.1(2!)
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	26-40	26.4	-	-	-	1.90(2)	-	-
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	30.7(2!)	0.0632(2!)	0.126(2!)	2.21(2!)	49.8(2!)	98.4(2!)
Westerling et al., 2007	effects on salivation (6M/4F)	25-56	26.6	31.9(2!)	0.0120(2!)	0.284(2!)	2.49(2!)	50.0(2!)	12.1(2!)
	Mean			**34.3**	**0.0278**	**0.270**	**2.38**	**26.5**	**44.8**
	± SD			**±9.7**	**±0.0173**	**±0.194**	**±0.68**	**±28.2**	**±33.8**
	Number of trials			6	6	6	7	6	6
	Number of observations			59	59	59	65	59	59

Evaluated studies	Data from single dose studies	AUC_{o-oo} (nmol∗h/mL)	G (kg)	V_β (L/kg)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	355.2(2!)	71.0	4.51(2!)
Osborne et al., 1990	different routes of administration (7M/3F)	279,4(2!)	72.0	3.75(2!)
Baillie et al., 1989	young + (elderly)(5M/3F)	216.0(2!)	67.6±4.5	8.12(2!)
Dershwitz et al., 2000	+ (inhaled morphine) (10M/3F)	106.4(2!)	74.0	7.48(2!)
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	322.1(1)	-	-
Hasselström et al., 1989	metabolism (3M/4F)	101.8(2!)	65.0	6.19(2!)
Westerling et al., 2007	effects on salivation (6M/4F)	214.3(2!)	73.1±12.6	5.96(2!)
	Mean	**219.9**		**5.97**
	± SD	**±93.2**		**±1.55**
	Number of trials	7		6
	Number of observations	65		59

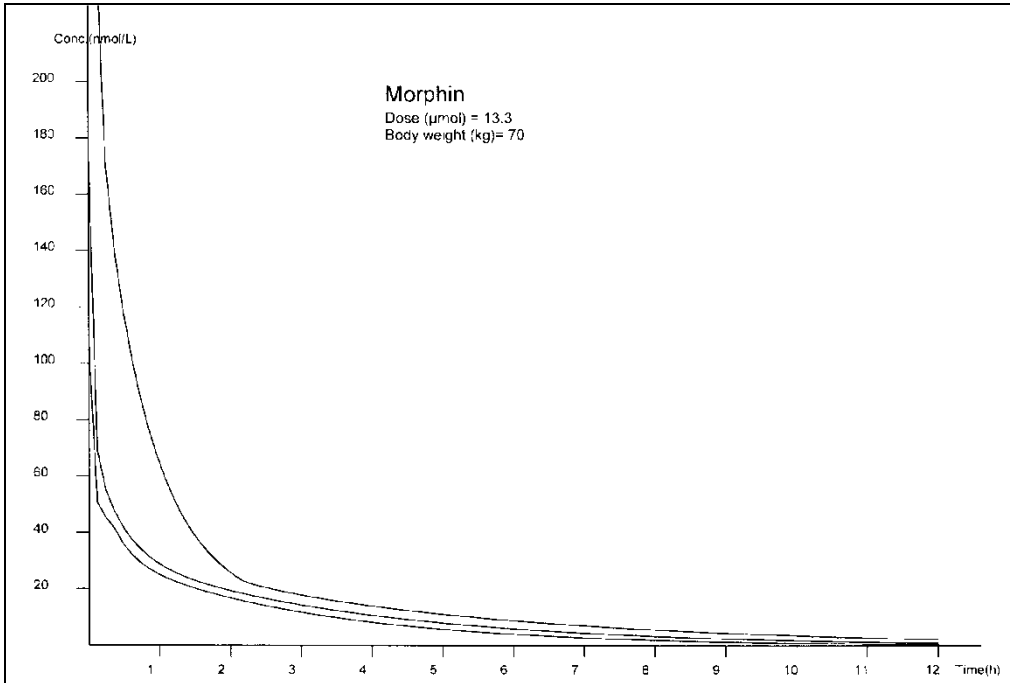


Figure 116: Plasma concentration-time curve of morphine after intravenous administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	34.3	±	9.7	nmol/L
K_1(rapid):	24.9	±	9.5	h^{-1}
V_1(rapid):	26.5	±	20	%
K_2(slow):	2.57	±	1.08	h^{-1}
V_2(slow):	44.8	±	33.8	%
β:	0.291	±	0.065	h^{-1}
V_β:	5.97	±	0.0655.54 ± 2.18L/kg	

derived from time-course of plasma concentrations

C_{max}: 174.6 (106.6-577.4) nmol/L
t_{max}: 0 (0-0) h
AUC_{o-oo}: 219.9 ± 93.2 ng∗h/mL 153.6 (114.7-328.7) nmol∗h/L

Table 111: 5 mg Morphine hydrochloride (sulphate) intravenous in elderly (absorption, distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}K_1$ (h)	$t_{½}K_2$ (h)	$t_{½}\beta$ (h)	V_1 (%)	V_2 (%)
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	79.7(2!)	0.0217(2!)	0.1086(2!)	3.28(2!)	4.40(2!)	75.0(2!)
Säwe et al., 1985	cancer patients (1M)	70	10.6	33.9(2!)	0.0200(2!)	0.136(2!)	2.10(2!)	1.17(2!)	66.6(2!)
Baillie et al., 1989	elderly + (young)(5M/4F)	66.4±4.5	26.4	32.2(2!)	0.0201(2!)	0.255(2!)	4.49(2!)	2.72(2!)	12.5(2!)
	Mean ± SD			**59.1 ±23.7**	**0.0210 ±0.008**	**0.167 ±0.071**	**3.70 ±0.68**	**3.60 ±0.97**	**50.2 ±30.6**
	Number of trials			3	3	3	3	3	3
	Number of observations			23	23	23	23	23	23

Evaluated studies	Data from single dose studies	AUC_{o-oo} (nmol*h/L)	G (kg)	V_β
Hand et al., 1987	radioimmunoassay (7M/6F)	433.3(2!)	63.4±2.8	2.38
Säwe et al., 1985	cancer patients (1)	221,4(2!)	54.0	5.60
Baillie et al., 1989	elderly + (young)(5M/4F)	297.2(2!)	66.4±3.2	5.90
	Mean ± SD	**370.8 ±73.6**		**3.90 ±1.75**
	Number of trials	3		3
	Number of observations	21		23

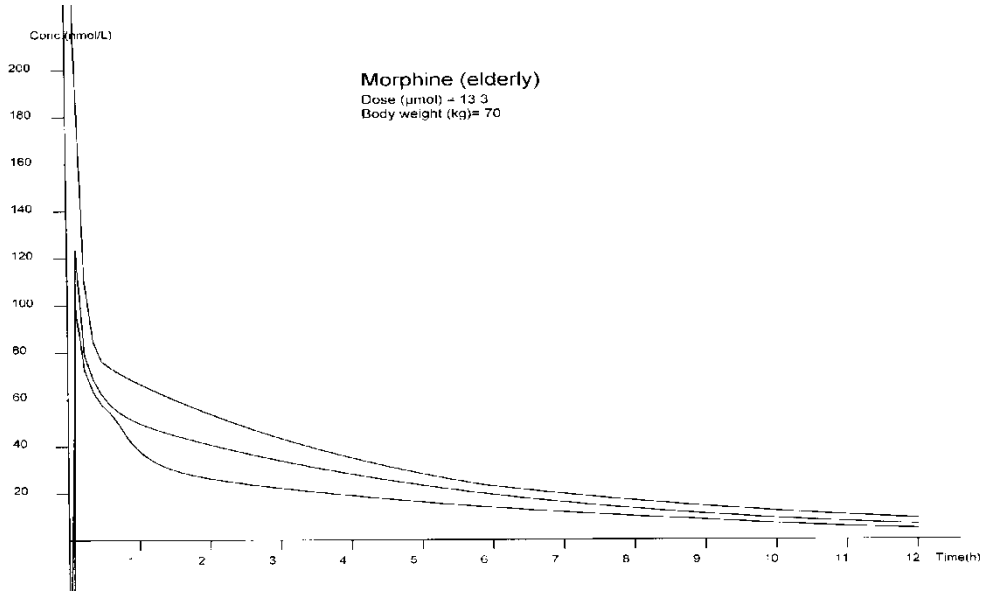


Figure 117: Plasma concentration-time curve of morphine after intravenous administration in elderly subjects.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	59.1	±	23.7	nmol/L
K_1(rapid):	33.0	±	9.1	h^{-1}
V_1(rapid):	3.6	±	0.97	%
K_2(slow):	4.15	±	1.24	h^{-1}
V_2(slow):	50.2	±	30.6	%
β:	0.187	±	0.029	h^{-1}

derived from time-course of plasma concentrations

V_β:	3.90 ± 1.75	3.21 ±	2.15L/kg
C_{max}:	1700 (1490-1831) nmol/L		
t_{max}:	0 (0-0) h		
AUC_{o-oo}:	370.8 ± 73.6 ng∗h/mL	562.5 (414.6-659.1) nmol∗h/L	

Table 112: Morphine-3-glucuronide from 5 mg Morphine hydrochloride (sulphate) intravenous (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	23-30	19.8	235.3(2!)	0.076(2!)	0.663(2!)	3.27 (2!)	0.039(2!)	65.1(2!)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	13.2	390.2(2!)	0.038(2!)	1.37(2!)	2.31(2!)	0.032(2!)	93.0(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	148.8(2!)	0.045(2!)	3.01(2!)	3.14(2!)	0.001(2!)	96.5(2!)
Säwe et al., 1985	cancer patients (1)	19-41	50	212.2(2!)	0.121(2!)	3.05(2!)	3.25(2!)	0.004(2!)	99.9(2!)
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	235.3(2!)	0.076(2!)	0.66(2!)	3.27 (2!)	0.039(2!)	65.1(2!)
	Mean			**257.2**	**0.0629**	**1.28**	**3.02**	**0.030**	**77.8**
	± SD			**±81.1**	**±0.0196**	**±0.90**	**±0.40**	**±0.014**	**±14.8**
	Number of trials			5	5	5	5	5	5
	Number of observations			42	42	42	42	42	42

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	295.2(2)	0.25(2)	1189(2!)	71.0			
Osborne et al., 1990	different routes of administration (7M/3F)	395.1(2)	0.25(2)	1709(2!)	72.0			
Hasselström et al., 1989	metabolism (3M/4F)	138.9(2)	0.33(2)	786(2!)	65.0			
Säwe et al., 1985	cancer patients (1)	171.2(2)	0.33(2!)	966(2!)	54.0			
Hand et al., 1987	radioimmunoassay (7M/6F)	295.2(2)	0.25(2)	1189(2!)	63.4±2.8			
	Mean	**290.0**	**0.27**	**1240**				
	± SD	**±82.9**	**±0.03**	**±302**				
	Number of trials	5	5	5				
	Number of observations	42	42	42				

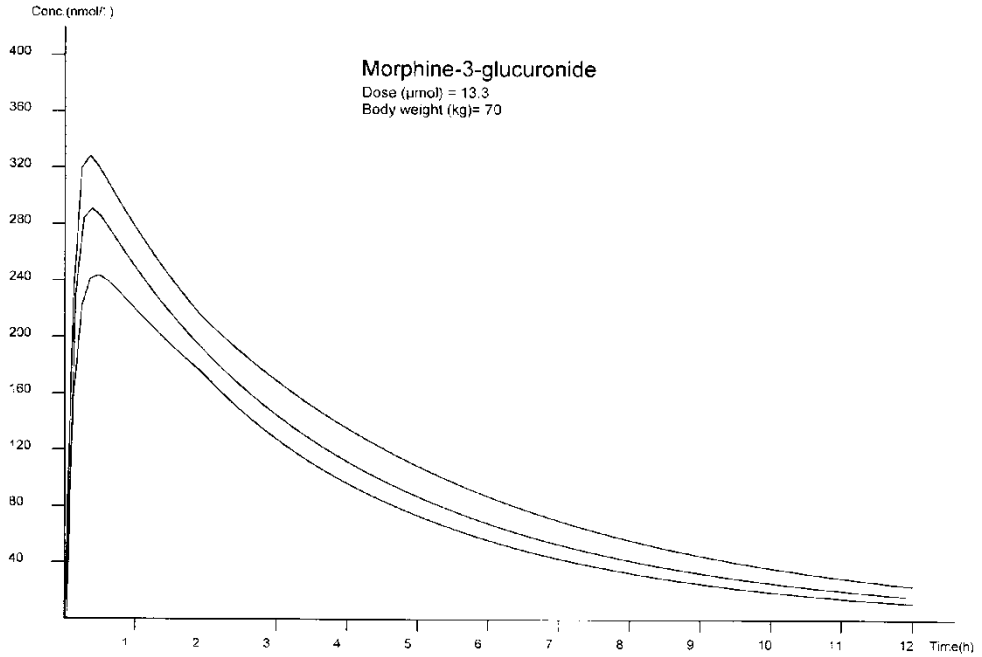


Figure 118: Plasma concentration-time curve of morphine-3-glucuronide after intravenous administration of morphine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	257.2	±	81.1	nmol/L
Ka:	11.0	±	2.6	h^{-1}
α:	0.54	±	0.22	h^{-1}
β:	0.230	±	0.027	h^{-1}
t_0:	0.030	±	0.014	h
V%:	77.8	±	14.8	%

				derived from time-course of plasma concentrations
C_{max}:	290.0	±	82.9	289.0 (243.7-328.2) nmol/L
t_{max}:	0.27	±	0.03	0.31 (0.31-0.48) h
AUC_{o-oo}:	1240	±	302	1220 (1032-1495) nmol*h/L

Table 113: Morphine-6-glucuronide from 5 mg Morphine hydrochloride (sulphate) intravenous (absorption, distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (µmol	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	23-30	19.8	54.9(2!)	0.183(2!)	4.42(2!)	2.66(2!)	0.050(2!)	96.1(2!)
Osborne et al., 1985	different routes of administration (7M/3F)	25-44	13.2	67.3(2!)	0.143(2!)	1.27(2!)	3.04(2!)	0.043(2!)	65.6(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	19.9(2!)	0.147(2!)	2.03(2!)	3.25(2!)	0.033(2!)	84.8(2!)
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	32.2(2!)	0.226(2!)	3.21(2!)	3.10(2!)	0.004(2!)	93.0(2!)
	Mean			**44.8**	**0.181**	**2.86**	**2.99**	**0.031**	**85.7**
	± SD			**±17.6**	**±0.035**	**±1.20**	**±0.21**	**±0.019**	**±12.1**
	Number of trials			4	4	4	4	4	4
	Number of observations			41	41	41	41	41	41

Evaluated studies	Data from single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol∗h/L)	G (kg)	B (%)	V_β/B (L)	V_β/G (L/kg)
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	48.1(2!)	0.50	210.0	71.0			
Osborne et al., 1985	different routes of administration (7M/3F)	83,3(2!)	0.75	337.4	72.0			
Hasselström et al., 1989	metabolism (3M/4F)	18.9(2!)	1.0	98.3	65.0			
Hand et al., 1987	radioimmunoassay (7M/6F)	26.6(1)	1.0	144.2	63.4±2.8			
	Mean	**44.9**	**0.80**	**201.1**				
	± SD	**±24.3**	**±0.21**	**±86.5**				
	Number of trials	4	4	4				
	Number of observations	41	41	41				

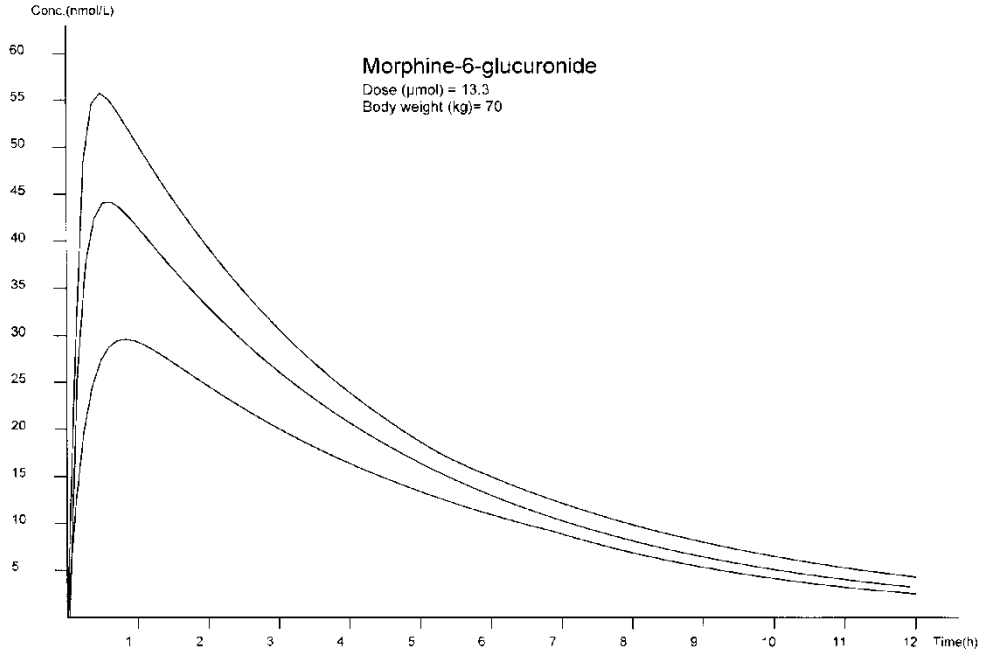


Figure 119: Plasma concentration-time curve of morphine-6-glucuronide after oral administration of morphine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	44.8	±	17.6	nmol/L
Ka:	6.19	±	2.40	h^{-1}
α:	0.242	±	0.071	h^{-}
β:	0.232	±	0.015	h^{-1}
t_0:	0.031	±	0.019	h
V%:	85.7	±	12.1	%

				derived from time-course of plasma concentrations
C_{max}:	44.9	±	24.3	44.2 (29.6-55.8) nmol/L
t_{max}:	0.80	±	0.21	0.59 (0.48-0.84) h
AUC_{o-oo}:	201.1	±	86.5	215.0 (162.9-263.5) nmol*h/L

Table 114: 20 mg Morphine hydrochloride (sulphate) oral (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	30.8	50.1(2!)	0.176(2!)	1.53(2!)	1.27(2!)	0.145(2!)	96.9(2!)
Baillie et al., 1989	young + (elderly)(5M/3F)	26-30	26.4	44.2(2!)	0.087(2!)	0.54(2!)	3.29(2!)	0.027(2!)	65.1(2!)
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	26-40	26.4	-	-	-	-	-	-
Hasselström et al., 1989	metabolism (3M/4F)	27-55	53.3	20.9(2!)	0.130(2!)	2.46(2!)	2.58(2!)	0.101(2!)	84.8(2!)
Westerling et al., 2007	effects on salivation (6M/4F)	25-56	26.6	26.8(2!)	0.171(2!)	0.65(2!)	4.01(2!)	0.030(2!)	32.6(2!)
Drake et al., 1996	Fasting + (fed) (24M) Oramorph	18-45	79.1	39.8(1!)	0.279(2!)	1.36(2!)	3.17 (2!)	0.132(2!)	84.8(2!)
“	Fasting + (fed) (24M) MST	18-45	79.1	29.7(1!)	0.301(2!)	1.42(2!)	4.06(2!)	0.139(2!)	85.8(2!)
Halbsguth et al., 2008	+ (oral diacetylmorphine (5M/3F)	21-42	48.4	56.4(2!)	0.064(2!)	0.890(2!)	1.80(2!)	0.012(2!)	93.0(2!)
	Mean ± SD			**38.1 ±11.4**	**0.214 ±0.086**	**1.29 ±0.48**	**3.13 ±0.94**	**0.102 ±0.051**	**79.6 ±18.2**
	Number of trials			7	7	7	7	7	7
	Number of observations			91	91	91	91	91	91

Data from comparative single dose studies	Evaluated studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)	B (%)
Osborne et al., 1990	different routes of administration (7M/3F)	39.0(2)	0.75(2)	81.8(2!)	72.0	19.6(2)
Baillie et al., 1989	young + (elderly)(5M/3F)	73.1(2)	0.70(2)	218.6(2!)	67.6±4.5	36±7(2)
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	74.3(1)	0.75(2)	155.6(1!)	-	23.8±4.9(2)
Hasselström et al., 1989	metabolism (3M/4F)	27.0(2)	0.50(2)	86.1(2!)	65.0	29.2±7.2(2)
Westerling et al., 2007	effects on salivation (6M/4F)	46.3(2)	0.75(2)	186.2(2!)	73.1±12.6	21.6(2)
Drake et al., 1996	Fasting + (fed) (24M) Oramorph	32.5(1)	1.99(2)	176.1(1!)	-	-
“	Fasting + (fed) (24M) MST	29.7(1)	1.93(2)	168.3(1!)	-	-
Halbsguth et al., 2008	+ (oral diacetylmorphine) (5M/3F)	57.1(2)	0.60(2)	146.1(2!)	76.0	23.9±10.6(2)
	Mean ± SD	**43.6 ±15.8**	**1.31 ±0.64**	**154.3 ±44.4**		**25.3 ±5.6**
	Number of trials	8	8	8		6
	Number of observations	97	97	97		49

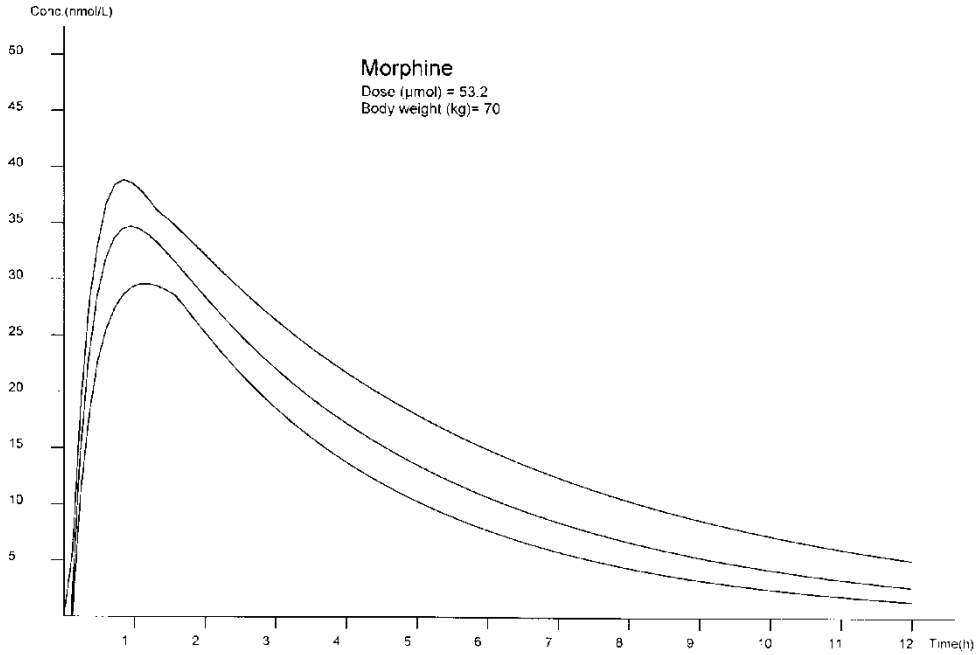


Figure 120: Plasma concentration-time curve of morphine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	38.1	±	11.4	nmol/L
Ka:	3.24	±	0.93	h^{-1}
α:	0.537	±	0.145	h^{-1}
β:	0.222	±	0.052	h^{-1}
t_0:	0.102	±	0.051	h
V%:	79.6	±	18.2	%
B:	25.3	±	5.6	%

				derived from time-course of plasma concentrations
C_{max}:	43.6	±	15.8	34.7 (29.6-38.8) nmol/L
t_{max}:	1.31	±	0.64	0.94 (0.84-1.20) h
AUC_{o-oo}:	154.3	±	44.4	174.8 (133.8-237.1) nmol*h/L
V_β:	5.42	±	2.31	

Table 115: 20 mg Morphine hydrochloride (sulphate) oral in elderly (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Säwe et al., 1985	cancer patients (1M)	70	53.2	44.5(2!)	0.361(2!)	0.53(2!)	4.86(2!)	0.283(2!)	11.5(2!)
Säwe et al., 1985	cancer patients (6M)	69.2±6.7	55.4	-	-	-	3.3(2)	-	-
Baillie et al., 1989	Elderly + (young)(5M/4F)	68-90	26.4	74.1(2!)	0.035(2!)	0.61(2!)	4.46(2!)	0.008(2!)	65.4(2!)
	Mean			**70.8**	**0.0712**	**0.601**	**4.02**	**0.039**	**59.4**
	± SD			**±9.6**	**±0.105**	**±0.026**	**±0.61**	**±0.089**	**±17.4**
	Number of trials			2	2	2	3	2	2
	Number of observations			10	10	10	16	10	10

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)	B (%)
Säwe et al., 1985	cancer patients (1M)	83.6(2)	0.75(2)	372.9(2!)	72.0	42.1(2!)
Säwe et al., 1985	cancer patients (6M)	-	-	-	60.7±5.6	
Baillie et al., 1989	Elderly + (young)(5M/4F)	139.0(2)	0.60(2)	502.0(2!)	67.6±4.5	48±12(2)
	Mean	**132.8**	**0.62**	**488**		**47.3**
	± SD	**±17.9**	**±0.05**	**±42**		**±1.9**
	Number of trials	2	2	2		2
	Number of observations	10	10	10		10

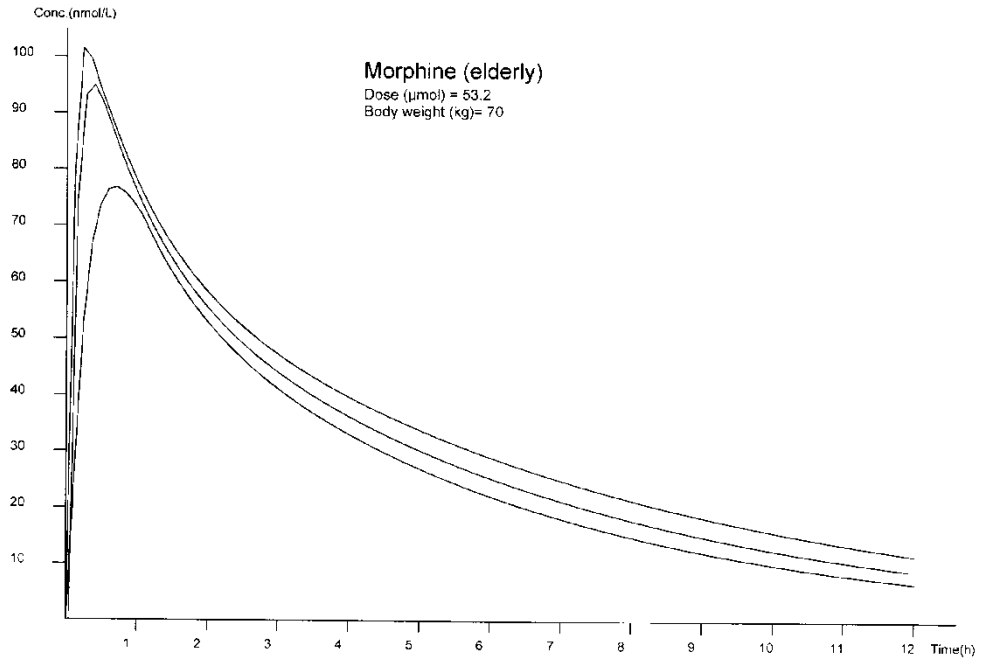


Figure 121: Plasma concentration-time curve of morphine after oral administration in elderly subjects.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	70.8	±	2.66	nmol/L
Ka:	9.74	±	5.81	h^{-1}
α:	1.153	±	0.045	h^{-}
β:	0.172	±	0.023	h^{-1}
t_0:	0.039	±	0.039	h
V%:	59.4	±	17.4	%
B:	47.3	±	1.9	%

					derived from time-course of plasma concentrations
C_{max}:	132.8	±	17.9		94.7 (76.8-102) nmol/L
t_{max}:	0.62	±	0.05		0.32 (0.24-0.72) h
AUC_{o-oo}:	488	±	42		439 (375-509) nmol∗h/L
V_β:	5.17	±	0.81	L/kg	

Table 116: Morphine-3-glucuronide from 20 mg Morphine hydrochloride (sulphate) oral (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	30.8	1000(2!)	0.369(2!)	2.21(2!)	2.74(2!)	0.166(2!)	86.1(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	53.3	1254(2!)	0.301(2!)	3.30(2!)	2.25(2!)	0.149(2!)	96.1(2!)
Halbsguth et al., 2008	+ (oral diacetylmorphine (5M/3F)	21-42	48.4	1318(1!)	0.246(2!)	1.85(2!)	2.20(2!)	0.071(2!)	96.5(2!)
Säwe et al., 1985	cancer patients (1M)	70	53.2	1944(1!)	0.477 (2!)	3.69(2!)	3.57 (2!)	0.338(2!)	98.4(2!)
	Mean ± SD			**1203 ±206**	**0.317 ±0.061**	**2.45 ±0.63**	**2.47 ±0.33**	**0.139 ±0.058**	**92.5 ±5.1**
	Number of trials			4	4	4	4	4	4
	Number of observations			26	26	26	26	26	26

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Osborne et al., 1990	different routes of administration (7M/3F)	849(2)	1.5(2)	3851(2!)	72.0
Hasselström et al., 1989	metabolism (3M/4F)	916(2)	1.0 (2)	3743(2!)	65.0
Halbsguth et al., 2008	+ (oral diacetylmorphine (5M/3F)	928(2)	1.0(2!)	3835(2!)	76.0
Säwe et al., 1985	cancer patients (1M)	1077(2)	2.0(2)	6979(2!)	54.0
	Mean ± SD	**900 ±51**	**1.23 ±0.29**	**3937 ±616**	
	Number of trials	4	4	4	
	Number of observations	26	26	26	

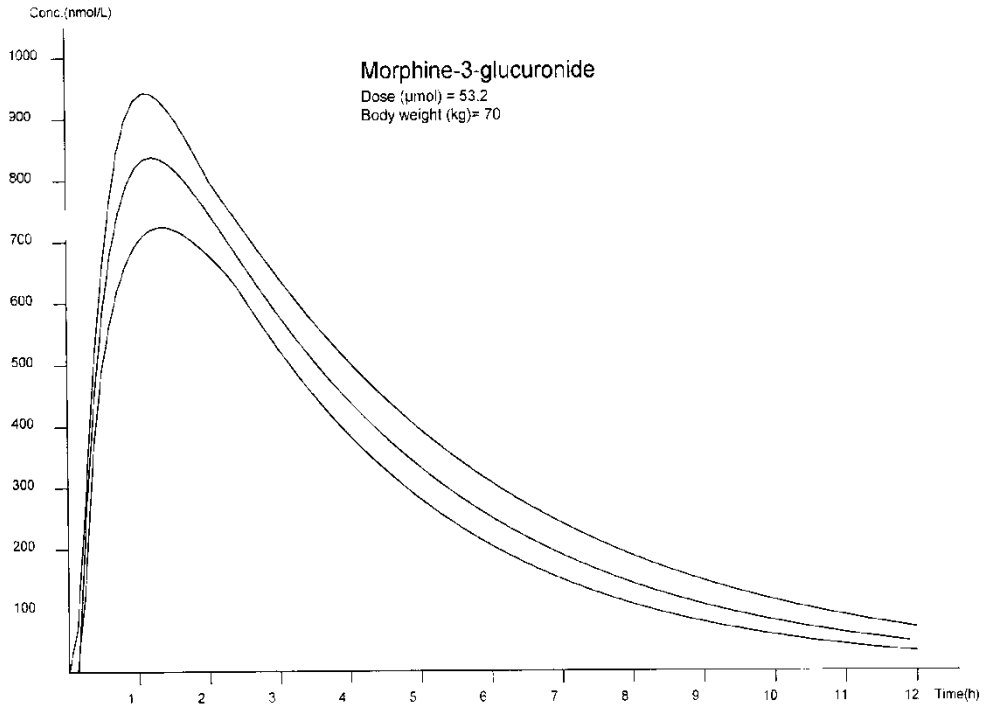


Figure 122: Plasma concentration-time curve of morphine-3-glucuronide after oral administration of morphine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	1203	±	206	nmol/L
Ka:	2.19	±	0.36	h^{-1}
α:	0.283	±	0.058	h^{-}
β:	0.281	±	0.033	h^{-1}
t_0:	0.139	±	0.058	h
V%:	92.5	±	5.1	%

				derived from time-course of plasma concentrations
C_{max}:	900	±	51	837 (724-942) nmol/L
t_{max}:	1.23	±	0.29	1.26 (1.08-1.32) h
AUC_{o-oo}:	3937	±	616	4027 (3391-4793) nmol*h/L

Table 117: Morphine-6-glucuronide from 20 mg Morphine hydrochloride (sulphate) oral (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	30.8	170.0(2!)	0.472(2!)	1.27(2!)	2.57(2!)	0.184(2!)	70.3(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	53.3	186.5(2!)	0.439(2!)	3.65(2!)	1.87(2!)	0.202(2!)	92.3(2!)
Halbsguth et al., 2008	+ (oral diacetylmorphine (5M/3F)	21-42	48.4	304.2(1!)	0.362(2!)	3.47(2!)	1.99(2!)	0.104(2!)	86.1(2!)
Säwe et al., 1985	cancer patients (1M)	70	53.2	134.5(1!)	0.414(2!)	2.27(2!)	3.57 (2!)	0.446(2!)	96.1(2!)
Hoskin et al., 1989	+ (intravenous & buccal) (2M/4F)	26-40	26.4	-	-	-	-	-	-
	Mean			**214.4**	**0.427**	**2.63**	**2.24**	**0.174**	**82.1**
	± SD			**±61.4**	**±0.047**	**±1.11**	**±0.41**	**±0.069**	**±9.8**
	Number of trials			4	4	4	4	4	4
	Number of observations			26	26	26	26	26	26

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol∗h/L)	G (kg)
Osborne et al., 1990	different routes of administration (7M/3F)	145.9(2)	1.5(2)	597.1(2!)	72.0
Hasselström et al., 1989	metabolism (3M/4F)	161.5(2)	1.0 (2)	456.9(2!)	65.0
Halbsguth et al., 2008	+ (oral diacetylmorphine (5M/3F)	174.4(2)	1.4(2!)	740.6(2!)	76.0
Säwe et al., 1985	cancer patients (1M)	92.8(2)	1.5(2)	575.0(2!)	54.0
Hoskin et al., 1989	+ (intravenous & buccal) (2M/4F)	-	-	418(1)	-
	Mean	**156.8**	**1.33**	**583.6**	
	± SD	**±17.6**	**±0.21**	**±117.5**	
	Number of trials	4	4	5	
	Number of observations	26	26	32	

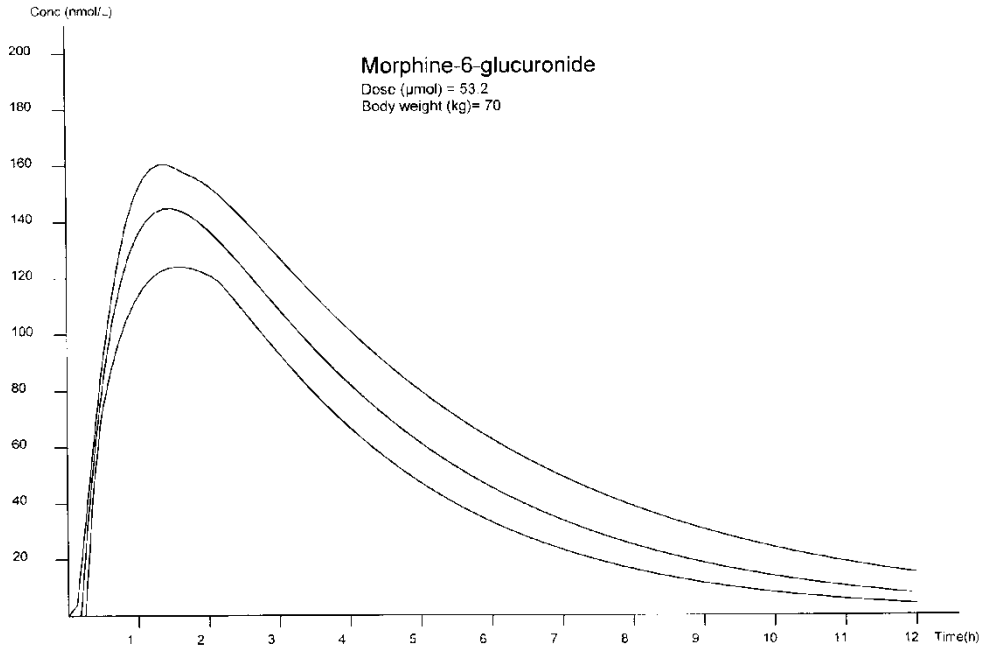


Figure 123: Plasma concentration-time curve of morphine-6-glucuronide after oral administration of morphine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	214.4	±	61.4	ng/mL
Ka:	1.62	±	0.16	h^{-1}
α:	0.264	±	0.079	h^{-}
β:	0.309	±	0.048	h^{-1}
t_0:	0.174	±	0.069	h
V%:	82.1	±	9.8	%

				derived from time-course of plasma concentrations
C_{max}:	156.8	±	17.6	145 (124-180) ng/mL
t_{max}:	1.33	±	0.21	1.43 (1.32-1.56) h
AUC_{o-oo}:	584	±	118	709 (558-921) nm*h/L

7.5.1.2 Codeine

Application: Codeine is like morphine a natural alkaloid found in opium poppy (papaver somniferum) and makes up 0.5% of opium Sindrup & Brøsen, 1995). It is gained by extraction, but most codeine is obtained by O-methylation of morphine in 3-position. It is widely used as analgesic, antitussive, and antidiarrhoeal drug. Early on it was supposed that the moderate analgesic effect of codeine, which is adequate to about 10% of that of morphine, is due to the biotransformation to morphine. This is supported by the low affinity of codeine, as in the case of other in 3-position substituted morphine derivatives, for the opiate receptor relative to that of morphine (Chen et al., 1991a; Mignat et al., 1995). Quiding et al. (1993) suggest some analgesic effect of codeine itself from experiments with 45 and 90 mg in patients unable to demethylate codeine to a detectable plasma concentration of morphine. Other authors look upon codeine with regard to its analgesic effect as a prodrug and accept that the analgesia is mediated by its metabolites morphine and morphine-6-glucuronide (M6G) (Osborne et al., 1988), the analgesic effect of which is shown to be 27-67 times higher than that of morphine in animal studies (Serrié, 1995). Also the effect of codeine on gastrointestinal activity was shown to be mediated like the analgesia by its metabolite morphine (Mikus et al., 1997).

Oral single dose of a codeine salt (e.g. phosphate or sulphate) is 30-60 mg up to 200 mg. Peak concentrations were not enhanced after multiple oral doses every six hours, but the C_{max} and AUC values of the active metabolites morphine and M6G accumulated about twofold resp. threefold (Guay et al., 1987). Further forms of codeine application are intramuscular and intra-rectal.

Biotransformation: The main step of codeine biotransformation is the glucuronidation to codeine-6-glucuronide (C6G), catalyzed by uridine diphosphate glucuronosyl transferase (UGT). In contrast to morphine glucuronidation, beside UGT2B7 another isoenzyme of UGT, UGT2B4, mediates the glucuronidation of codeine (Court et al., 2003). Minor pathways are O- and N-demethylation to morphine resp. norcodeine, which are glucuronidated, too. Starting from morphine, the same metabolic steps take place as are described in the morphine chapter (7.5.1.1). The O-demethylation is under the same polymorphic genetic control as the 4-hydroxylation of debrisoquine and catalyzed by the cytochrome P-450 isoenzyme CYP2D6 (Chen et al., 1988; Dayer et al., 1988; Yue et al., 1989). Thus the high interindividual variability of morphine concentration in plasma after codeine intake and as the consequence the analgesic effect is explainable. An ultra rapid metabolism of codeine leading to a life-

threatening opioid intoxication was observed by Gasche et al. (2004) in a patient, who had three or more functional alleles for Cyp2D6 and a transient reduction in renal function, The N-demethylation of codeine to norcodeine is mediated byCYP3A4, as in vitro experiments of Caraco et al. (1996) revealed using human liver microsomal preparations and specific inhibitors of CYP3A4 and CYP2D6.

Interaction: Interethnic differences in codeine metabolism were discovered by Yue et al. (1991b). Mean values of peak levels and areas under the curve (AUC) were statistically significant higher in Chinese than in Caucasian extensive metabolizers (EM). A lower efficiency in glucuronidation is supposed as cause for this ethnic influence. No statistically significant interaction of ethanol with codeine pharmacokinetics has been observed in a study of Bodd et al. (1987). Since UGT enzymes catalyze the conjugation of various endogemous and exogenous substances, interactions during the glucuronidation have been suggested Kiang et al., 2005). Takeda et al. (2006) published that the inhibition of morphine glucuronidation was potentiated by codeine. A noncompetitive inhibition of codeine-6-glucuronidation by diclofenac was observed by Ammon et al. (2000). On the other hand an interaction of codeine and ibuprofen was not found in a pharmacokinetic study of Kaltenbach et al. (1994). In vitro experiments with human liver microsomes revealed the influence of inhibitors on the O-demethylation of codeine (substrates of CYP2D6 such as thioridazine, amitriptyline, and metoprolol) and the N-demethylation (Yue & Säwe, 1997).

Evaluation of studies: Pharmacokinetic parameters of codeine itself showed no differences between extensive (EM) and poor metabolizers (PM) concerning the debrisoquine hydroxylation (Mikus et al., 1997; Caraco et al., 1996a; Yue et al., 1991a). Also the main codeine metabolite C6G showed no different AUC values in EMs and PMs (Caraco et al., 1996a; Yue et al., 1991a). Therefore a separate calculation of pharmacokinetic parameters relating codeine and C6G was not indicated. Against this the formation of morphine and morphine glucuronides was separately calculated and resulted in very different values of the pharmacokinetic parameters (Table 120, Table 121 and Figure 124, Figure 125). The mean areas under the curves (AUC) of morphine, M3G, and M6-G in poor metabolizers are diminished by a factor of about 14, 34, and 38 in comparison with extensive metabolizers. However, only a few data of PMs were available (14 resp. 6). Among codeine and the codeine metabolites C6G, morphine, M3G, and M6G, morphine-6-glucuronide possesses the longest elimination half-life and thus an accumulation of M3G is explainable. The ratios ofM3G to morphine and M6G to morphine after oral codeine administration are still higher than after morphine intake (42 and 6.2), but ratios of M3G to M6G in EMs and PMs are almost identical

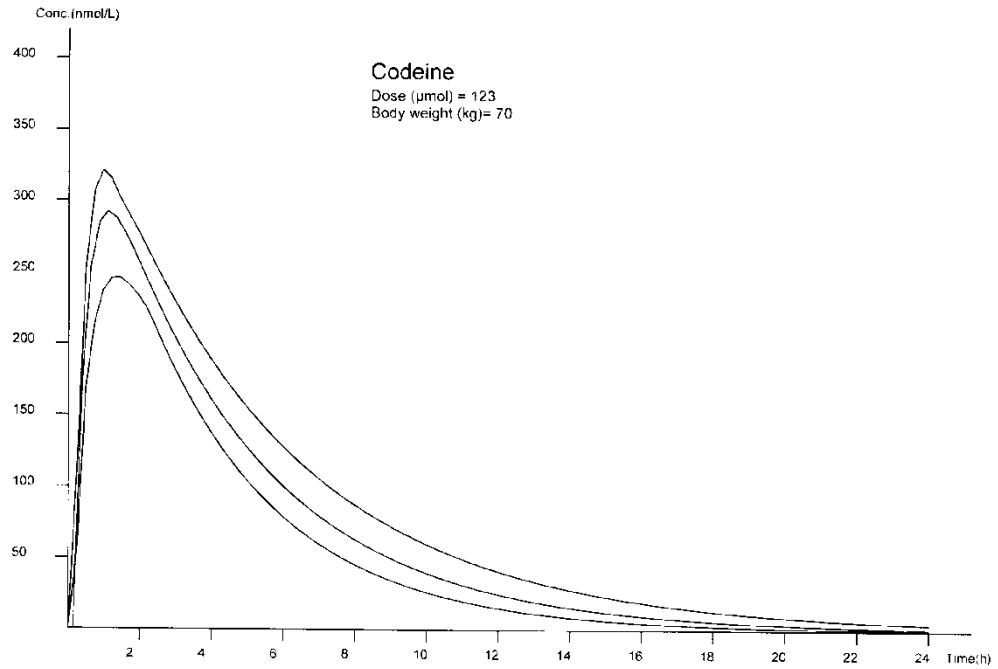
(6.8 and 6.1), just the same as those after intravenous and oral morphine administration (6.2 and 6.7).

Table 118: 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	29.7±3.2	418.4	-	-	-	3.9(2)	-	-
«	poor metabolizers (5M/4F)	34.6±4.6	418.4	-	-	-	3.8(2)	-	-
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	439(2!)	0.149(2!)	2.84(2!)	2.76(2!)	0.141(2!)	98.4(2!)
«	poor metabolizers (6M)	34.2±1.3	295.4	391(2!)	0.085(2!)	0.72(2!)	2.96(2!)	0.158(2!)	98.4(2!)
Guay et al., 1987	single + (multiple) dose (6M/4F)	27.8±3.7	172.2	187(2!)	0.137(2!)	1.14(2!)	4.38(2!)	0.142(2!)	32.8(2!)
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	222(2!)	0.188(2!)	2.44(2!)	3.32(2!)	0.102(2!)	65.1(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	275(2!)	0.270(2!)	1.22(2!)	3.61(2!)	0.093(2!)	65.1(2!)
«	poor metabolizers (2M/4F)	30±6	123	196(2!)	0.271(2!)	1.91(2!)	3.04(2!)	0.219(2!)	98.4(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	172(2!)	0.128(2!)	0.89(2!)	3.33(2!)	0.237(2!)	99.2(2!)
Chen et al., 1991	extensive metabolizers (7M/1F)	25-37	73.8	299(2!)	0.185(2!)	2.02(2!)	3.32(2!)	0.096(2!)	96.5(2!)
Findlay et al., 1978	+ (aspirin) (12M)	-	147	384(1!)	0.301(2!)	3.32(2!)	3.47(2!)	0.166(2!)	86.1(2!)
«	+ (acetaminophen) (20M)	-	147	315(1!)	0.268(2!)	2.37(2!)	3.75(2!)	0.163(2!)	65.1(2!)
Mikus et al., 1997	extensive metabolizers (5)	21-26	147	429(2!)	0.106(2!)	0.68(2!)	1.96(2!)	0.003(2!)	65.1(2!)
«	poor metabolizers (5)	24-29	147	332(2!)	0.223(2!)	1.53(2!)	2.33(2!)	0.004(2!)	63.6(2!)
Quiding et al., 1993	analgesic effect (25M)	20-39	111	486(1!)	0.420(2!)	2.79(2!)	1.99(2!)	(0.001)	93.8(2!)
«	after oral surgery (25M)	20-35	222	378(1!)	0.242(2!)	3.15(2!)	2.54(2!)	(0.001)	93.4(2!)
	Mean ± SD			**329 ± 101**	**0.246 ± 0.097**	**2.27 ± 0.85**	**3.08 ± 0.72**	**0.138 ± 0.059**	**82.0 ± 18.7**
	Number of trials			14	14	14	16	12	14
	Number of observations			154	154	154	172	104	154

Continuation of Table 118: 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	288(1)	-	1181(1)	-
«	poor metabolizers (5M/4F)	362(1)	-	1623(1)	-
Caraco et al., 1996	extensive metabolizers (10M)	339(2)	0.83(2)	1678(2!)	78.7±2.1
«	poor metabolizers (6M)	356(2)	0.58(2)	1623(2!)	87.3±2.1
Guay et al., 1987	single + (multiple) dose (6M/4F)	447(2)	0.60(2)	1669(2!)	73.1±11.6
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	341(2)	1.10(2)	1377(2!)	76.9±10.8
Yue et al., 1991a	extensive metabolizers (3M/5F)	275(2)	1.0(2)	828(2!)	66±10
«	poor metabolizers (2M/4F)	266(2)	0.86(2)	788(2!)	69±11
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	146(2)	0.88(2)	792(2!)	66±10
Chen et al., 1991	extensive metabolizers (7M/1F)	294(2)	0.97(2)	1381(2!)	67.9±11.9
Findlay et al., 1978	+ (aspirin) (12M)	442(1)	1.0(2)	2015(1!)	-
«	+ (acetaminophen) (20M)	381(1)	1.1(2)	2083(1!)	-
Mikus et al., 1997	extensive metabolizers (5)	601(2)	0.54(2)	1325	76±9
«	poor metabolizers (5)	505(2)	0.62(2)	1365	80.4±7
Quiding et al., 1993	analgesic effect (25M)	266(1)	1.0(2)	1167	-
«	after oral surgery (25M)	268(1)	1.0(2)	1362	-
	Mean ± SD	**336 ± 99**	**0.92 ± 0.17**	**1400 ± 382**	
	Number of trials	16	14	16	



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	329	±	101	nmol/L
Ka:	2.82	±	0.80	h^{-1}
α:	0.305	±	0.030	h^{-1}
β:	0.225	±	0.043	h^{-1}
t_0:	0.138	±	0.059	h
V%:	82.0	±	18.7	%
B:	90 %			

derived from time-course of plasma concentrations

C_{max}:	336	±	99	292 (246-321) nmol/L
t_{max}:	0.92	±	0.17	1.12 (0.96-1.44) h
AUC_{o-oo}:	1400	±	382	1555 (1244-1957) nmol*h/L

Figure 124: Plasma concentration-time curve of codeine after oral administration.

Table 119: Codeine-6-glucuronide from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	5378(2!)	0.408(2!)	1.86(2!)	2.93(2!)	0.129(2!)	93.0(2!)
«	poor metabolizers (6M)	34.2±1.3	295.4	5649(2!)	0.315(2!)	1.63(2!)	3.04(2!)	0.155(2!)	99.6(2!)
Guay et al., 1987	single + (multiple) dose (6M/4F)	27.8±3.7	172.2	-	-	-	-	-	-
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	4520(2!)	0.368(2!)	1.52(2!)	3.13(2!)	0.275(2!)	65.4(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	2771(2!)	0.485(2!)	0.80(2!)	3.52(2!)	0.307(2!)	36.9(2!)
«	poor metabolizers (2M/4F)	30±6	123	4260(2!)	0.333(2!)	2.14(2!)	2.98(2!)	0.173(2!)	84.8(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	4770(2!)	0.402(2!)	2.47(2!)	2.97(2!)	0.141(2!)	86.1(2!)
Chen et al., 1991	extensive metabolizers (7M/1F)	25-37	73.8	5725(2!)	0.275(2!)	4.28(2!)	3.17(2!)	0.137(2!)	98.1(2!)
	Mean ± SD			**4740 ± 980**	**0.374 ± 0.066**	**2.13 ± 1.05**	**3.11 ± 0.20**	**0.184 ± 0.068**	**80.7 ± 21.2**
	Number of trials			7	7	7	7	7	7
	Number of observations			52	52	52	52	52	52

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Caraco et al., 1996	extensive metabolizers (10M)	3585(2)	1.8(2)	20361(2!)	78.7±2.1
«	poor metabolizers (6M)	4137(2)	1.5 (2)	22219(2!)	87.3±2.1
Guay et al., 1987	single + (multiple) dose (6M/4F)	5113(2)	1.0(2)	-	73.1±11.6
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	4435(2)	1.4(2)	21848(2!)	76.9±10.8
Yue et al., 1991a	extensive metabolizers (3M/5F)	2669(2)	1.5(2)	12970(2!)	66±10
«	poor metabolizers (2M/4F)	3495(2)	1.3(2)	18450(2!)	69±11
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	3862(2)	1.0(2)	19877(2!)	66±10
Chen et al., 1991	extensive metabolizers (7M/1F)	4899(2)	1.3(2)	24499(2!)	67.9±11.9
	Mean ± SD	**4046 ± 781**	**1.35 ± 0.27**	**19952 ± 3478**	
	Number of trials	8	8	7	
	Number of observations	62	62	52	

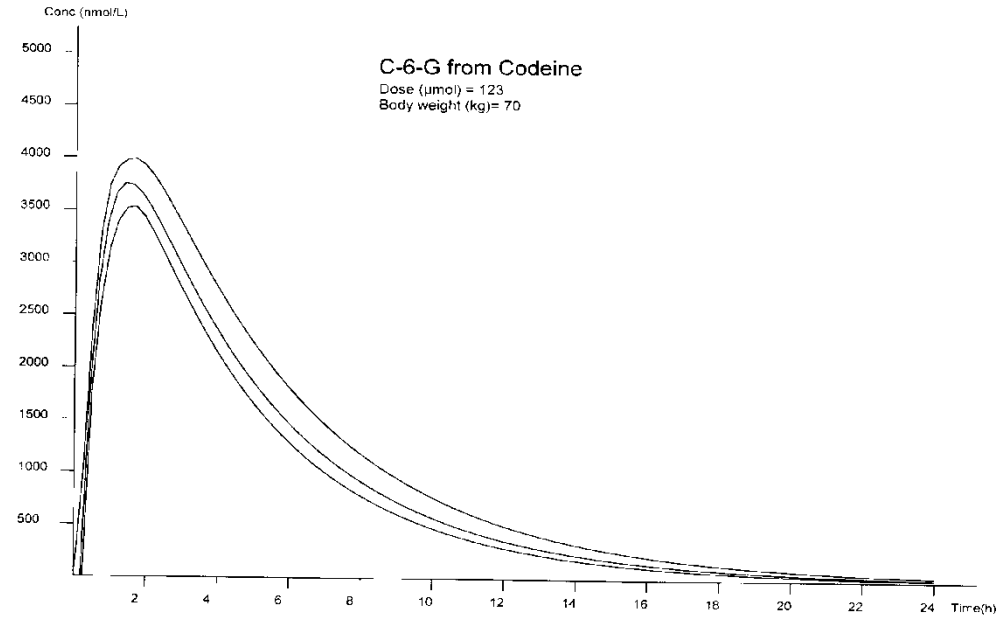


Figure 125: Plasma concentration-time curve of codeine-6-glucuronide after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	4740	±	980	nmol/L
Ka:	1.85	±	0.28	h^{-1}
α:	0.325	±	0.107	h^{-1}
β:	0.223	±	0.014	h^{-1}
t_0:	0.184	±	0.068	h
V%:	80.7	±	21.2	%

				derived from time-course of plasma concentrations
C_{max}:	4046	±	781	3756 (3531-3989) nmol/L
t_{max}:	1.35	±	0.27	1.38 (1.38-1.68) h
AUC_{0-oo}:	19952	±	3478	21498 (19097-25828) nmol*h/L

Table 120: Morphine from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) in extensive metabolizers (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$T_{½}Ka$ (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	29.7±3.2	418.4	8.61(1!)	0.038(2!)	0.99(2!)	3.01(2!)	0.028(2!)	84.8(2!)
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	6.84(2!)	0.068(2!)	0.71(2!)	3.32(2!)	0.133(2!)	65.1(2!)
Guay et al., 1987	single + (multiple) dose (6M/4F)	27.8±3.7	172.2	20.6(2!)	0.150(2!)	4.42(2!)	(10.0)	0.097(2!)	92.3(2!)
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	8.04(1!)	0.163(2!)	3.37(2!)	2.05(2!)	0.094(2!)	93.0(2!)
Findlay et al., 1978	+ (aspirin) (12M)	-	147	17.7(1!)	0.357(2!)	2.70(2!)	(7.2)	0.156(2!)	84.8(2!)
«	+ (acetaminophen) (20M)	-	147	22.2(1!)	0.282(2!)	2.06(2!)	(5.77)	0.157(2!)	86.1(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	9.67(2!)	0.290(2!)	4.62(2!)	1.52(2!)	0.149(2!)	98.4(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	11.0(2!)	0.291(2!)	3.71(2!)	1.82(2!)	0.168(2!)	98.4(2!)
Mikus et al., 1997	extensive metabolizers (5)	21-26	147	3.77(2!)	0.120(2!)	0.39(2!)	3.27(2!)	(0.002)	16.4(2!)
Quiding et al., 1993	analgesic effect (25M)	20-39	111	15.7(1!)	0.517(2!)	5.33(2!)	1.27(2!)	(0.001)	87.3(2!)
«	after oral surgery (25M)	20-35	222	7.94(1!)	0.089(2!)	3.17(2!)	2.23(2!)	(0.001)	100(2!)
	Mean ± SD			**12.9 ± 5.9**	**0.245 ± 0.161**	**3.15 ± 1.53**	**2.12 ± 0.72**	**0.128 ± 0.043**	**86.8 ± 16.3**
	Number of trials			11	11	11	8	8	11
	Number of observations			138	138	138	96	83	138

Continuation of Table 120: Morphine from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) in extensive metabolizers (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	11.2(1)	0.75(2)	38.7(1!)	-
Caraco et al., 1996	extensive metabolizers (10M)	9.37(2)	0.50(2)	35.3(2!)	78.7±2.1
Guay et al., 1987	single + (multiple) dose (6M/4F)	20.6(2)	1.3(2!)	(305)	73.1±11.6
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	8.35(2)	1.0(2)	24.6(2!)	76.9±10.8
Findlay et al., 1978	+ (aspirin) (12M)	18.9(1)	1.5(2)	(185)	-
«	+ (acetaminophen) (20M)	20.6(1)	1.5(2)	(181)	-
Yue et al., 1991a	extensive metabolizers (3M/5F)	6.31(2)	1.0(2)	18.1(2!)	66±10
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	7.86(2)	1.0(2)	25.4(2!)	66±10
Mikus et al., 1997	extensive metabolizers (5)	12.6(2)	0.54(2)	24.3(2!)	76±9
Quiding et al., 1993	analgesic effect (25M)	5.2(1)	-	33.2(1!)	-
«	after oral surgery (25M)	4.11(1)	-	24.5(1!)	-
	Mean ± SD	**10.9 ± 6.2**	**1.11 ± 0.37**	**28.1 ± 6.2**	
	Number of trials	11	9	8	
	Number of observations	138	88	6.2	

Table 121: Morphine from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) in poor metabolizers (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Eckhardt et al., 1998	poor metabolizers (5M/4F)	34.6±4.6	418.4	0.51(1!)	0.032(2!)	3.17(2!)	2.19 (2!)	0.008(2!)	99.1(2!)
Mikus et al., 1997	poor metabolizers (5)	24-29	147	0.18(2!)	0.221(2!)	0.61(2!)	5.28 (2!)	(0.004)	8.2(2!)
	Mean ± SD			**0.34 ± 0.17**	**0.100 ± 0.092**	**2.26 ± 1.25**	**3.29 ± 1.51**	**0.008**	**66.6 ± 44.4**
	Number of trials			2	2	2	2	1	2
	Number of observations			14	14	14	14	9	14

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Eckhardt et al., 1998	poor metabolizers (5M/4F)	0.59(1)	0.37(2)	1.6(1!)	-
Mikus et al., 1997	poor metabolizers (5)	0.65(2)	0.62(2)	2.42(2!)	80.4±7
	Mean ± SD	**0.62 ± 0.03**	**0.46 ± 0.12**	**2.03 ± 0.42**	
	Number of trials	2	2	2	
	Number of observations	14	14	14	

Table 122: Morphine-3-glucuronide from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) in extensive and poor metabolizers (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	151.2(2!)	0.352(2!)	3.21(2!)	3.64(2!)	0.131(2!)	98.4(2!)
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	135.2(2!)	0.401(2!)	2.06(2!)	6.63(2!)	0.148(2!)	64.6(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	216.6(2!)	0.438(2!)	0.94(2!)	3.04(2!)	0.208(2!)	69.2(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	181.8(2!)	0.596(2!)	2.14(2!)	7.05(2!)	0.118(2!)	64.6(2!)
	Mean ± SD			**172 ± 30**	**0.444 ± 0.094**	**2.16 ± 0.85**	**4.90 ± 1.77**	**0.150 ± 0.035**	**76.3 ± 15.1**
	Number of trials			4	4	4	4	4	4
	Number of observations			32	32	32	32	32	32
Yue et al., 1991a	poor metabolizers (2M/4F)	30±6	123	7.82	0.467	3.63	2.98	0.126	93.4

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol∗h/L)	G (kg)
Caraco et al., 1996	extensive metabolizers (10M)	105(2)	1.5(2)	726(2!)	78.7±2.1
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	160*(2)*	1.3(2)	1389(2!)	76.9±10.8
Yue et al., 1991a	extensive metabolizers (3M/5F)	175(2)	1.5(2)	883(2!)	66±10
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	182(2)	1.5(2)	1876(2!)	66±10
	Mean ± SD	**152 ± 33**	**1.46 ± 0.08**	**1177 ± 468**	
	Number of trials	4	4	4	
	Number of observations	32	32	32	
Yue et al., 1991a	poor metabolizers (2M/4F)	5.19	1.5	30.9	69±11

Table 123: Morphine-6-glucuronide from 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) in extensive and poor metabolizers (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (µmol)	Cp0 (nmol/L)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	32.0(2!)	0.385(2!)	1.58(2!)	4.03(2!)	0.146(2!)	86.1(2!)
Guay et al., 1987	single + (multiple) dose (6M/4F)	27.8±3.7	172.2	-	-	-	-	-	-
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	23.4(2!)	0.525(2!)	1.07(2!)	5.79(2!)	0.268(2!)	35.2(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	65.5(2!)	0.447(2!)	1.06(2!)	1.98(2!)	0.356(2!)	84.8(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	53.3(1!)	0.792(2!)	3.50(2!)	2.41(2!)	0.239(2!)	84.8(2!)
	Mean ± SD			**44.1 ± 16.3**	**0.529 ± 0.161**	**1.83 ± 0.99**	**3.44 ± 1.40**	**0.245 ± 0.080**	**75.9 ± 19.7**
	Number of trials			4	4	4	4	4	4
	Number of observations			32	32	32	32	32	32
Yue et al., 1991a	poor metabolizers (2M/4F)	30±6	123	1.64	0.389	2.83	2.35	0.126	93.0

Evaluated studies	Data from comparative single dose studies	C_{max} (nmol/L)	t_{max} (h)	AUC_{o-oo} (nmol*h/L)	G (kg)
Caraco et al., 1996	extensive metabolizers (10M)	25.1(2)	1.5(2)	177(2!)	78.7±2.1
Guay et al., 1987	single + (multiple) dose (6M/4F)	71.9(2)	1.9(2)	-	73.1±11.6
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	30.0(2)	2.0(2)	211(2!)	76.9±10.8
Yue et al., 1991a	extensive metabolizers (3M/5F)	39.8(2)	1.5(2)	155(2!)	66±10
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	29.2(2)	1.75(2)	162(2!)	66±10
	Mean ± SD	**40.5 ± 18.3**	**1.71 ± 0.20**	**174 ± 20**	
	Number of trials	5	5	4	
	Number of observations	42	42	32	
Yue et al., 1991a	poor metabolizers (2M/4F)	1.12	1.5	5.07	69±11

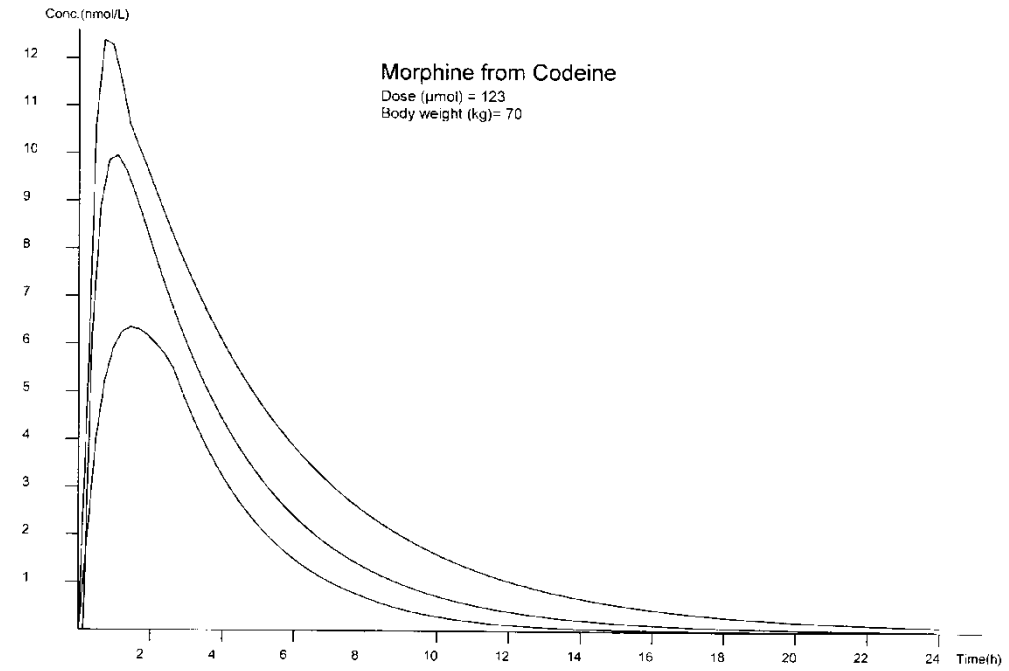


Figure 126: Plasma concentration-time curve of morphine in extensive metabolizers after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	12.8	±	5.9	nmol/L
Ka:	2.83	±	1.12	h^{-1}
α:	0.220	±	0.072	h^{-1}
β:	0.327	±	0.083	h^{-1}
t_0:	0.128	±	0.043	h
V%:	86.8	±	16.3	%

				derived from time-course of plasma concentrations
C_{max}:	10.9	±	6.2	9.98 (6.3-12.4) nmole/L
t_{max}:	1.11	±	0.37	1.03 (0.72-1.44) h
AUC_{o-oo}:	28.1	±	6.2	42.5 (27.7-62.6) nmol*h/L

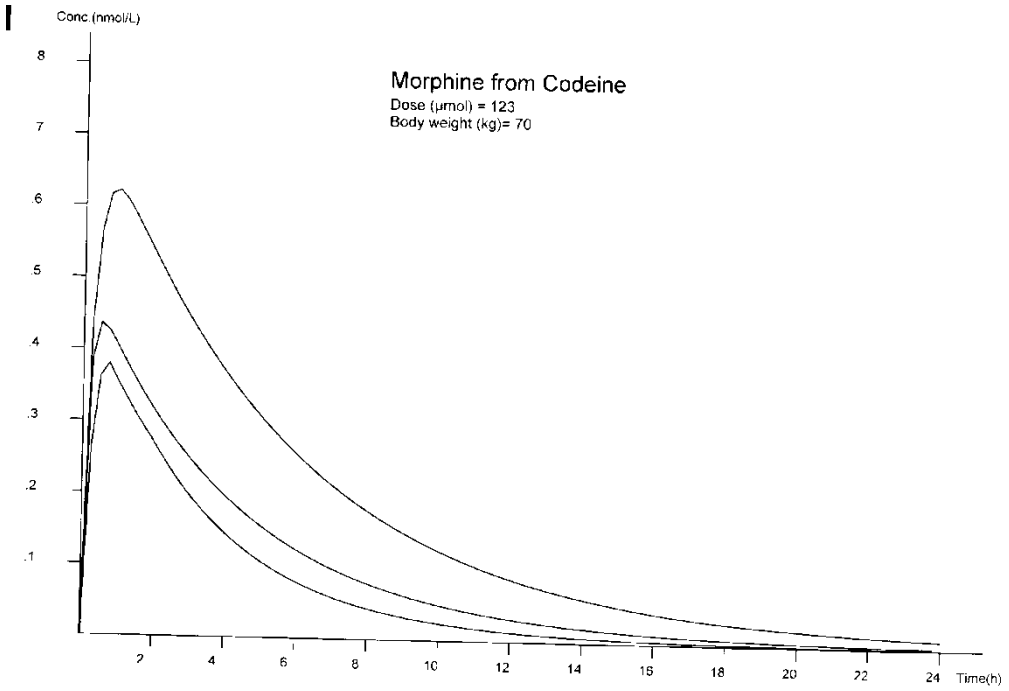


Figure 127: Plasma concentration-time curve of morphine in poor metabolizers after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	0.34	±	0.17	nmole/L
Ka:	6.93	±	3.32	h^{-1}
α:	0.307	±	0.110	h^{-}
β:	0.211	±	0.067	h^{-1}
t_0:	0.008			h
V%:	66.6	±	44.4	%

				derived from time-course of plasma concentrations
C_{max}:	0.62	±	0.03	0.43 (0.38-0.62) nmole/L
t_{max}:	0.46	±	0.12	0.61 (0.61-0.96) h
AUC_{o-oo}:	2.03	±	0.42	2.07 (1.49-4.04) nmole∗h/L

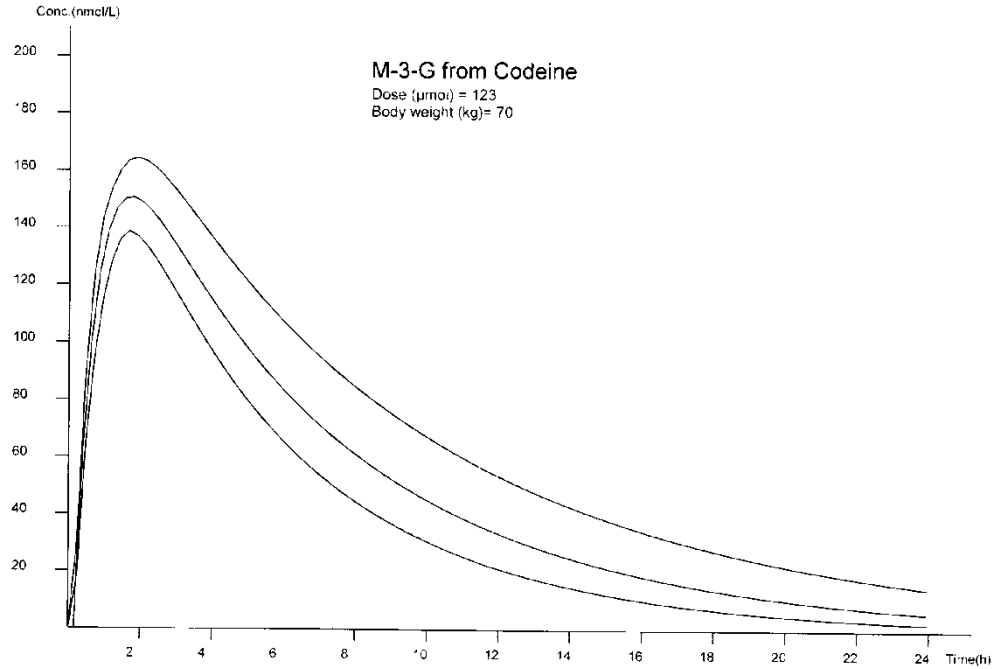
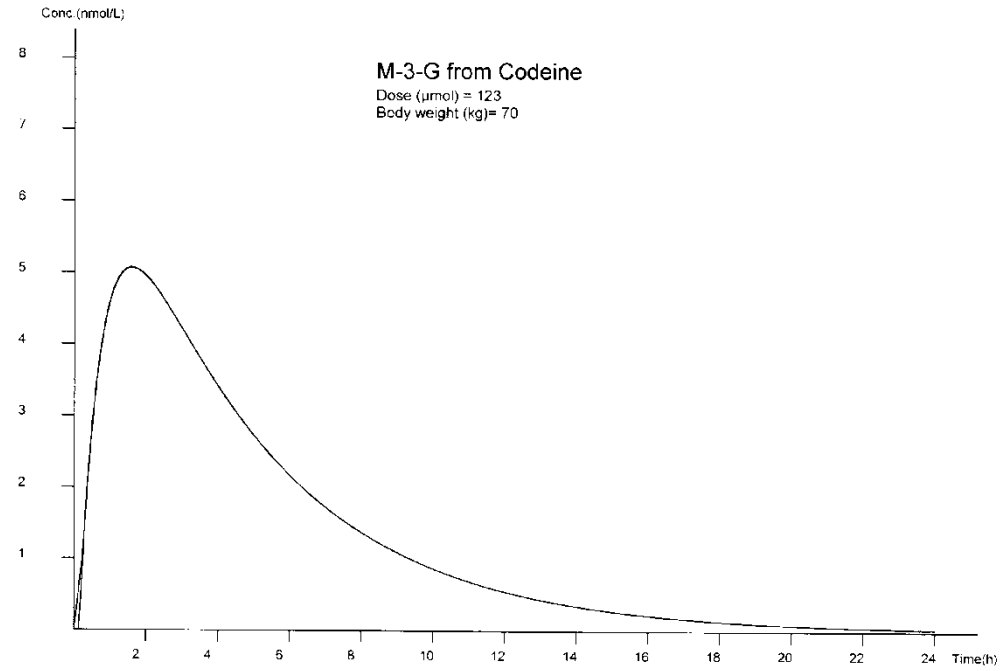


Figure 128: Plasma concentration-time curve of morphine-3-glucuronide in extensive metabolizers after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	172	±	30	nmole/L
Ka:	1.56	±	0.27	h^{-1}
α:	0.321	±	0.091	h^{-}
β:	0.141	±	0.035	h^{-1}
t_0:	0.150			h
V%:	76.3	±	15.1	%

				derived from time-course of plasma concentrations
C_{max}:	152	±	33	151 (139-164) nmole/L
t_{max}:	1.46	±	0.02	1.65 (1.65-1.92) h
AUC_{o-oo}:	1177	±	468	1239 (942-1748) nmole*h/L



Pharmacokinetic parameters derived from evaluation of one pharmacokinetic study

Cp0:	7.82	nmole/L
Ka:	1.56	h^{-1}
α:	0.321	h^{-}
β:	0.141	h^{-1}
t_0:	0.126	h
V%:	93.4	%

		derived from time-course of plasma concentrations
C_{max}:	5.19	5.07 nmole/L
t_{max}:	1.50	1.57 h
AUC_{o-oo}:	30.9	30.9 nmole*h/L

Figure 129: Plasma concentration-time curve of morphine3-glucronide in poor metabolizers after oral administration of codeine.

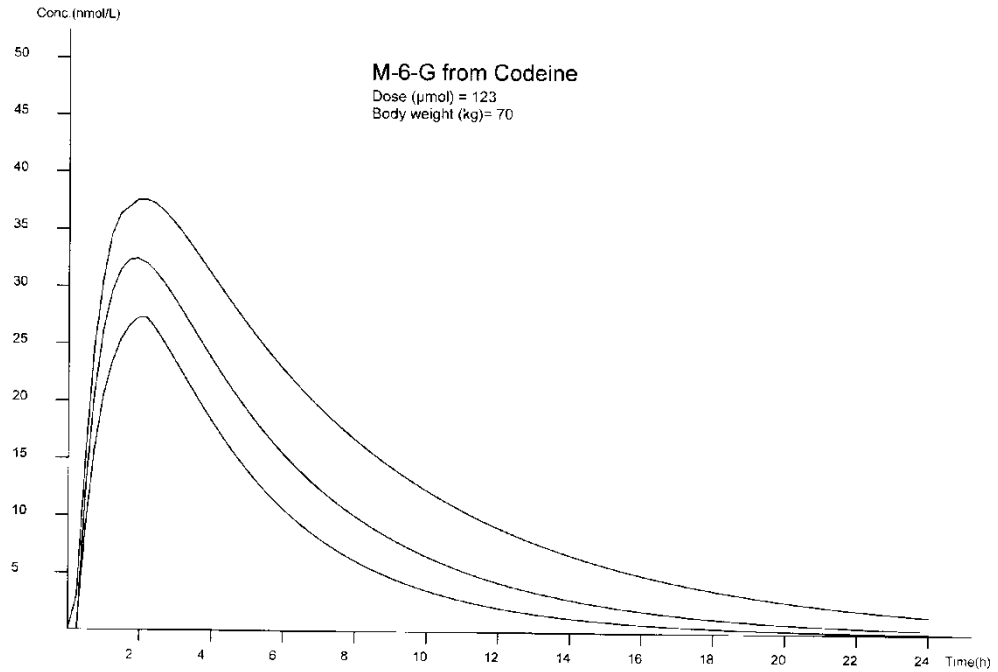


Figure 130: Plasma concentration-time curve of morphine-6-glucuronide in extensive metabolizers after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	44.1	±	16.3	nmole/L
Ka:	1.31	±	0.31	h^{-1}
α:	0.379	±	0.133	h^{-}
β:	0.201	±	0.069	h^{-1}
t_0:	0.245	±	19.7	h
V%:	75.9	±	44.4	%

				derived from time-course of plasma concentrations
C_{max}:	40.5	±	18.3	32.4 (27.3-37.6) nmole/L
t_{max}:	1.71	±	0.20	1.75 (1.75-2.16) h
AUC_{o-oo}:	174	±	20	212 (148-326) nmole*h/L

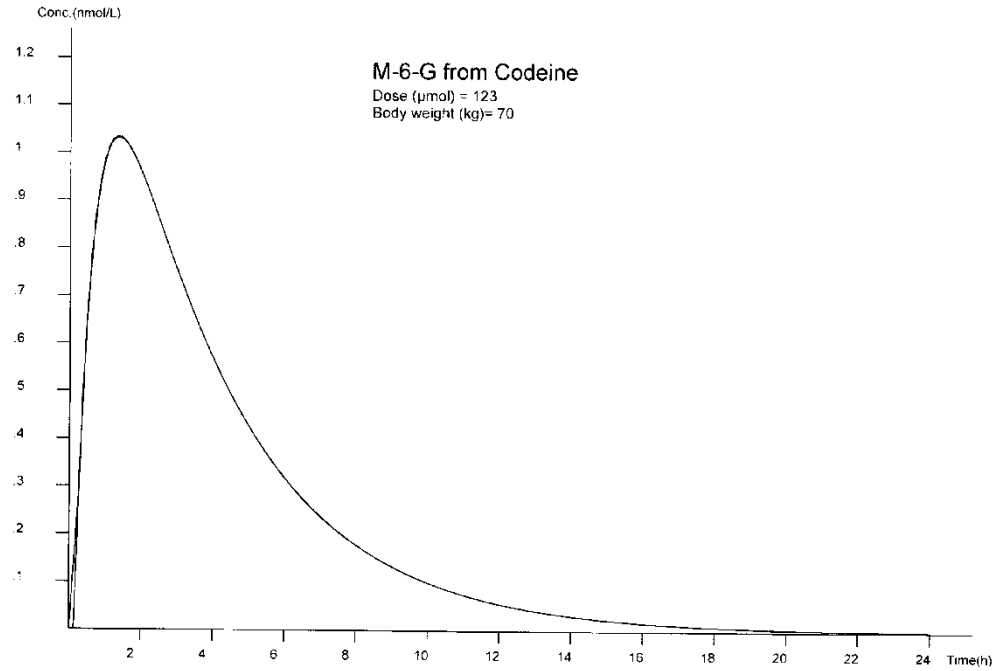


Figure 131: Plasma concentration-time curve of morphine-6-glucronide in poor metabolizers after oral administration of codeine.

Pharmacokinetic parameters derived from evaluation of one pharmacokinetic study

Cp0:	1.64	nmole/L
Ka:	1.78	h^{-1}
α:	0.245	h^{-}
β:	0.295	h^{-1}
t_0:	0.126	h
V%:	93.0	%

		derived from time-course of plasma concentrations
C_{max}:	1.12	1.03 nmole/L
t_{max}:	1.50	1.33 h
AUC_{o-oo}:	5.07	5.05 nmole*h/L

7.5.2 Cannabinoides

7.5.2.1 Smoking of Δ^9-tetrahydrocannabinol

Application: Δ^9-tetrahydrocannabinol (THC) is the primary psychoactive constituent of marijuana, the dried parts of the annual, dioecious, flowering plant hemp (Cannabis sativa varia indica), predominantly leaves and flowers of the female plant. The THC content of marijuana is 2 to 20%, that of hashish, the resin of female plants, 5 to 15%. Hash oil is also produced from the plant with a THC content of up to 50%.The main administration form is smoking with an average efficious dose of 15 mg THC. A high absorption rate constant leads to formation of high peak concentrations already during the smoking time and a subsequent pronounced distribution phase in the first hour after smoking. Estimation of the absolute bioavailability has been made possible by studies with intravenous administration of THC (Hollister et al., 1981; Lindgren et al., 1981). Evaluation of these studies by Sticht & Käferstein (1995, 1998) resulted in mean pharmacokinetic parameters such as a distribution volume of 236 ± 67 L resp. a distribution factor of 3.37 L/kg at a body weight of 70 kg. Using this value for calculation of the THC time course in plasma after smoking, an absolute bioavailability of about 18% was determined, which is in good conformance with the average of 17% from pharmacokinetic studies (Table 124, Figure 132).

The oral intake of THC is the rule with medicinal use of dronabinol/Marinol® in Germany and other countries. It is questionable whether THC and cannabis can generally be regarded as “illegal” drugs nowadays. The study of Hollister et al. (1981) demonstrated that after oral intake THC is absorbed with a lag time of about 25 min and comparatively low plasma levels. From this study pharmacokinetic parameters have been calculated (Sticht & Käferstein, 1998), in particular with 300 an absolute bioavailability of only 6%.

Biotransformation: The mean degradation pathway of THC is oxidation to non-active 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) via the psychoactive 11-hydroxy derivative 11-hydroxy-Δ^9-tetrahydrocannabinol (11-hydroxy-THC). Huestis et al. (1992) observed substantially lower mean peak levels of 11-hydroxy-THC than of THC levels immediately after the end of smoking. The ascent of THCCOOH concentration proceeded more slowly with mean peak time of 113 min. Further metabolites are generated by hydroxylation in 8- or 3’-position of THC and 11-hydroxy-THC yielding α- and β-8-hydroxy-Δ^9-tetrahydrocannabinol (Van der Schyf et al., 1988), α- and β-8,11-dihydroxy-Δ^9- Δ^9-tetrahydrocannabinol (Kemp et al., 1995), and 3’-hydroxy- and 3’,11-dihydroxy-THC

(Handrick et al., 1982). Some of these metabolites have been shown to possess pharmacological activity, but with different intensity. The excretion of the metabolites in the urine, particularly that of THCCOOH, occurs to a high degree as conjugates, mainly as glucuronides.

Interaction: A study of Watanabe et al. (2007) demonstrated that 11-hydroxylation is mediated by an isoenzyme of cytochrome P450, CYP2C9, because the reaction was inhibited by sulfaphenazole, a selective inhibitor of CYP2C enzymes, whereas hydroxylation of the 8-position is catalyzed by CYP3A4, which is inhibited by ketozonazole. An influence of the genetic polymorphisms of CYP2C9 on Δ^9-tetrahydrocannabinol pharmacokinetics was investigated by Sachse-Seeboth et al. (2009). The mean area of THC was threefold higher and that of THCCOOH was 70% lower in CYP2C9*3/*3 homozygotes than in CYP2C9*1/*1 homozygotes.

Evaluation of studies: For calculating the mean pharmacokinetic parameters after THC smoking, 14 trials with 48 to 152 single observations were used, which are about twice as many as had been available in an earlier investigation (Sticht & Käferstein, 1998). However the values have not been altered statistically significant. The calculated standard deviation of V% is too high. A value of 8.0 instead of 10.5 was chosen. Thus minimal and maximal curves are formed being conformable with the C_{max} and AUC values so far as possible.

Table 124: Pharmacokinetic parameters after smoking of 15 mg THC (absorption, distribution and elimination).

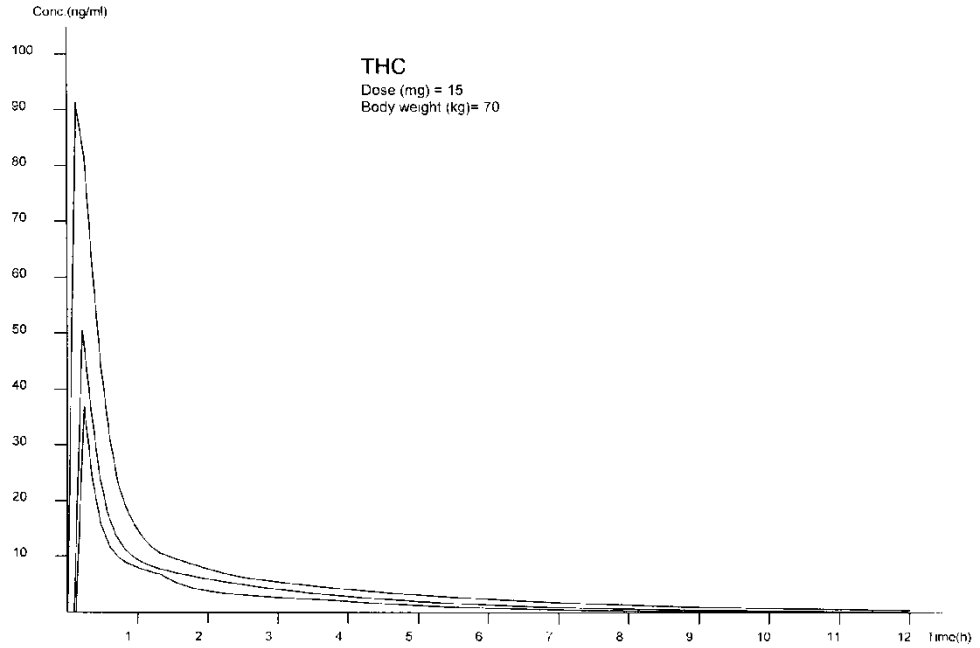
Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Hollister et al., 1981	Degree of intoxication (11)		19	8.23(1!)	-	0.0737(2!)	1.40(2!)	-	9.23(2!)
Lindgren et al., 1981	Heavy and light (9)		12.7	10.4(1!)	-	0.0917(2!)	1.74(2)	0.025(2!)	6.20(2!)
„	users (9)		13.4	15.0(1!)	-	0.0821(2!)	1.21(2!)	0.617(2!)	10.9(2!)
Perez-Reyes et al., 1982	Marijuana effect (6) (2.54 %)		24	12.8(1!)	0.0266(2!)	0.189(2!)	2.13(2!)	0.003(2!)	8.79(2!)
“	(6) (1.97 %)		17	11.7(1!)	0.0272(2!)	0.230(2!)	3.02(2!)	0.003(2!)	8.79(2!)
“	(6) (1.32 %)		12	12.4(1!)	0.0297(2!)	0.177(2!)	3.41(2!)	0.004(2!)	6.25(2!)
Chiang & Barnett, 1984	Marijuana effect (6) (2.5 %)		24	15.0(1!)	0.0363(2!)	0.148(2!)	1.81(2!)	0.003(2!)	8.78(2!)
„	(6) (2.0 %)		19.2	-	0.0403(2)	0.158(2)	2.63(2)	0.005(2!)	-
„	(6) (1.3 %)		12.5	-	0.0243(2)	0.213(2)	3.32(2)	0.010(2!)	-
Heishman et al., 1990	Acute and (1)		20	23.0(1!)	-	0.852(2!)	2.74(2!)	-	43.8(2!)
„	residual effects (1)		20	19.4(1!)	-	0.275(2!	2.60(2!)	-	10.9(2!)
„	(1)		20	10.1(1!)	-	0.660(2!	2.72(2!)	-	21.7(2!)
Huestis et al., 1992	Formation of (1)		33.8	1.73(2!)	0.0506(2!)	0.154(2!)	4.18(2!)	0.01(2!)	1.17(2!)
“	metabolites (1)		33.8	3.71(2!)	0.0546(2!)	0.139(2!)	3.00(2!)	0.01(2!)	2.19(2!)
“	(1)		33.8	2.77(2!)	0.0499(2!)	0.102(2!)	1.90(2!)	0.02(2!)	2.34(2!)
“	(1)		33.8	5.53(2!)	0.0611(2!)	0.125(2!)	2.37(2!)	0.023(2!)	1.36(2!)
“	(1)		33.8	17.5(2!)	0.0539(2!)	0.0934(2!)	0.96(2!)	0.016(2!)	3.12(2!)
“	(1)		33.8	6.13(2!)	0.0361(2!)	0.116(2!)	2.20(2!)	0.0024(2!)	6.06(2!)
“	(1)		15.8	4.56(2!)	0.0513(2!)	0.105(2!)	2.09(2!)	0.014(2!)	1.17(2!)
“	(1)		15.8	5.88(2!)	0.0420(2!)	0.138(2!)	1.28(2!)	0.019(2!)	5.47(2!)
“	(1)		15.8	14.5(2!)	0.0774(2!)	0.101(2!)	0.845(2!)	0.01(2!)	2.92(2!)
“	(1)		15.8	8.70(2!)	0.0723(2!)	0.118(2!)	1.60(2!)	0.025(2!)	1.46(2!)
“	(1)		15.8	17.4(2!)	0.0611(2!)	0.105(2!)	0.75(2!)	0.013(2!)	4.68(2!)
“	(1)		15.8	17.6 (2!)	0.0624(2!)	0.116(2!)	0.89(2!)	0.006(2!)	5.68(2!)
Wachtel et al., 2002	Marijuana (7M/6F)	19-26	8.4	16.4(2!)	-	0.173(2!)	1.92(2!)	-	23.4(2!)

"	Marijuana (7M/6F)	19-26	16.9	22.7(2!)	-	0.119(2!)	1.40(2!)	-	37.5(2!)
Huestis & Cone, 2004	+ (oral fluid) (6M)	-	33.8	7.30(1!)	-	0.139(2!)	1.27(2!)	-	3.13(2!)
Ramaekers et al., 2006	Limits of impairment (14M/6F)	19-29	17.5	4.42(1!)	-	0.0861(2!)	1.70(2!)	-	4.69(2!)
"	Limits of impairment (14M/6F)	19-29	35	4.06(1!)	-	0.0869(2!)	1.73(2!)	-	5.47(2!)
	Mean ± SD			**11.9 ±6.6**	**0.0371 ±0.0133**	**0.134 ±0.087**	**1.90 ±0.65**	**0.093 ±0.210**	**11.3 ±10.5**
	Number of trials			8	10	7	15	7	7
	Number of observations			44	54	30	101	30	30

Continuation of Table 124: Pharmacokinetic parameters after smoking of 15 mg THC (absorption, distribution and elimination).

Evaluated studies	**Data from comparative single dose studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{o-oo} (ng*h/mL)**	**G (kg)**	**B (%)**
Hollister et al. 1981	degree of intoxication (11)	-	-	22.7(1!)	-	12.9(1!)
Lindgren et al. 1981	Heavy and light (9)	-	-	-	-	16.3(1!)
„	users (9)	-	-	-	-	23.5(1!)
Perez-Reyes et al., 1982	Marijuana effect (6) (2.54 %)	96.9(1)	0.117(2)	67.3(1!)	-	34.3(1!)
"	(6) (1.97 %)	94.8(1)	0.117(2)	83.8(1!)	-	18.4(1!)
"	(6) (1.32 %)	117.9(1)	0.117(2)	96.9(1!)	-	19.9(1!)
Chiang & Barnett, 1984	Marijuana effect (6)	91.5(1)	0.100(2)	60.1(1!)	-	23.6(1)
Heishman et al., 1990	Acute and (1)	-	-	123.5(1!)	-	35.9(1!)
„	residual effects (1)	-	-	127.4(1!)	-	30.3(1!)
„	(1)	-	-	74.2(1!)	-	15.8(1!)
Huestis et al., 1992	Formation of (1)	55.9(2)	0.221(2)	30.0(2!)	77.6	2.70(1!)
"	metabolites (1)	55.9(2)	0.166(2)	34.2(2!)	"	5.70(2!)
"	(1)	32.8(2)	0.139(2)	14.8(2!)	"	4.23(2!)
"	(1)	116.2(2)	0.147(2)	51.7(2!)	"	8.44(2!)
"	(1)	118.4(2)	0.105(2)	49.4(2!)	"	25.8(2!)

“	(1)	45.2(2)	0.088(2)	28.1(2!)	“	9.44(2!)
“	(1)	108.2(2)	0.125(2)	39.0(2!)	“	6.96(2!)
“	(1)	43.7(2)	0.146(2)	22.8(2!)	“	8.91(2!)
“	(1)	60.8(2)	0.153(2)	30.5(2!)	“	20.6(2!)
“	(1)	123.0(2)	0.173(2)	54.0(2!)	“	13.0(2!)
“	(1)	74.0(2)	0.171(2)	34.7(2!)	“	24.7(2!)
“	(1)	73.2(2)	0.134(2)	40.9(2!)	“	25.6(2!)
Wachtel et al.2002	Marijuana (7M/6F)	-	-	56.8(2!)	65.3(2!)	25.8(2!)
-	Marijuana (7M/6F)	-	-	50.6(2!)	65.3(2!)	35.7(2!)
Huestis & Cone 2004	+ (oral fluid) (6M)	-	-	48.0(1!)	-	11.5(1!)
Ramaekers et al. 2006	Limits of impairment (14M/6F)	-	-	17.9(2!)	70	7.0(2!)
“	Limits of impairment (14M/6F)	-	-	15.6(2!)	70	6.4(2!)
	Mean **± SD**	**87.9** **±26.5**	**0.124** **±0.026**	**30.5** **±23.9**		**16.9** **±10.7**
	Number of trials	5	5	12		14
	Number of observations	36	36	122		140



Pharmacokinetic parameters derived from evaluation of one pharmacokinetic study

Cp0:	11.9	±	5.9	ng/mL
Ka:	18.7	±	5.0	h^{-1}
α:	5.17	±	2.03	h^{-1}
β:	0.365	±	0.093	h^{-1}
t_0:	0.093	±	0.093	h
V%:	11.3	±	8.0	%

				derived from time-course of plasma concentrations
C_{max}:	87.9	±	26.5ng/mL	48.9 (36.8-91.3) ng/mL
t_{max}:	0.124	±	0.026h	0.23 (0.12-0.24) h
AUC_{o-oo}:	30.5	±	23.9ng*h/mL	42.9 (29.2-80.1) ng*h/mL
B:	16.9	±	10.7%	18.4 ± 10.7%

Figure 132: Plasma concentration-time curve of Δ^9-tetrahydrocannabinol (THC) after smoking of 15 mg THC.

7.6 Stimulants

7.6.1 Cocaine

Application: Cocaine is obtained from the leaves of the coca plant and is a worldwide-spread drug with strong stimulating effect and a high addiction potential. It found the firat medical application as topical anesthetic but was replaced by synthetic substances as Lidocaine, Tetracaine and others, derived from the chemical structure of cocaine but with fewer side effects. Its pharmacological action is inhibiting the reuptake of neurotransmitters as dopamine, noradrenaline, and serotonin into the presynaptic vesicles. Peripher effects beside local anesthetic and vasodilatation are cardiovascular stimulation leading to increase of blood pressure and pulse rate, and dilation of pupils. The influence on the CNS is dependent on the bioavailability and absorption rate, which are determined by the ways of drug incorporation.

Routes of cocaine administration are compaired by numerous authors as Cone (1995) injection, intrasal, and smoked, Wilkinson et al. (1980) intranasal and oral kinetics, Jevaid et al. (1983) intravenous and intranasal administration and many others. Fattinger et al. (2000) pointed out that after nasal administration a part of the dose is swallowed and thereafter absorbed gastrointestinally. Only 1 % of the cocaine was recovered after heating cocaine hydrochloride to 800° C, in contrast to 16 %, when the free base was heated (Cook et al., 1994). Not more than 6 % of the free base was gained when it was smoked in a tobacco cigarette, but a clearly higher amount (about 44 %) could be recovered, when the free base was heated in a glass pipe at 265°C (Perez-Reyes et al., 1982) and 57±19 % (Jeffcoat et al., 1989). A variety of pyrolysis products are formed under different conditions of heating such as temperature, added components and the surrounding atmosphere (Cook, 1991). Low bioavailability after oral administration of cocaine, 33 % (Fattinger et al., 2000) and 50 % (Herbst et al., 2011), are caused by first-pass metabolism.

Biotransformation: Three functional groups of the cocaine structure are susceptible to biotransformation (Inaba, 1989), resulting in benzoylecgonine or ecgoninemethylester by hydrolysis of one of the ester groups and by demethylation of the N-methyl group leading to norcocaine, the only pharmacologically active metabolite up to now without attendance of ethanol (Hawks et al., 1974). The main metabolite benzoylecgonine is formed by spontaneous cleavage or by involvement of liver carboxyesterases, the hydrolysis of cocaine to ecgoninemethylester is catalysed by plasma and liver esterases. By addition of fluoride to blood samples, the hydrolysis of cocaine is inhibited. A complete cleavage of the ester groups

leads to the well water soluble amphoteric ecgonine. An extensive review of the metabolism of cocaine with and without coadministration of ethanol is given bei Cami et al. (1998).

Interaction: Numerous clinical trials in healthy volunteers were performed, where cocaine and ethanol were coadministered (Farré et al., 1993, 1997; McCance-Katz et al., 1998). This interaction affects pharmacokinetic and pharmacodynamic levels. The biosynthesis of the active metabolites cocaethylene and norcocaethylene is induced. The enhanced cocaine and norcocaine plasma concentrations can explain the greater euphoria and increased perception of well-being relative to cocaine alone (Cami et al., 1998; McCance-Katz et al., 1998). On the other hand C_{max} and AUC values of benzoylecgonine and ecgoninemethylester are decreased, perhaps by inhibition of enzymes.

Lukas et al. (1994) proved the influence of marihuana on the pharmacokinetics of intranasal administered cocaine. Pretreatment with a high-dose marihuana, a cigarette containing 2.53% Δ^9-THC, resulted in a significant increase of cocaine levels and AUC values. The authors concluded that the absorption of cocaine was enhanced by a partial attenuation of the vasoconstrictive effect of cocaine.

Evaluation of studies: Comparing the courses of the plasma concentration-time curves after intravenous (Figure 133), intranasal (Figure 135), smoked (Figure 139), and oral administration of cocaine (Figure 141), it becomes obvious, that plasma concentrations are subject of pronounced variation. The evaluation of pharmacokinetic parameters of metabolites of cocaine were performed after intravenous (Figure 134), intranasal (Figure 136), and smoked administration (Figure 140) those of benzoylecgonine and after nasal administration additionally those of ecgoninemethylester (Figure 137) and of cocaethylene after coadministration of ethanol (Figure 138).

Table 125: Intravenous administration of 50 mg/70 kg body weight cocaine hydrochloride (absorption. distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}K_1$ (h)	$t_{½}K_2$ (h)	$t_{½}\beta$ (h)	V_1 (%)	V_2 (%)
Kogan et al., 1977	Gas-liquid `chromatography (1)		100	362(2!)	0.0473(2!)	0.456(2!)	1.49(2!)	49.6(2!)	72.1(2!)
"	of cocaine and Benzoylecgonine (1)		100	385(2!)	0.0510(2!)	0.284(2!)	1.14(2!)	49.6(2!)	49.6(2!)
"	(1)		100	355(2!)	0.0247(2!)	0.478(2!)	1.25(2!)	37.5(2!)	49.9(2!)
Javaid et al., 1978	Relation to physiological and (5)		16	635(1!)	0.0171(2!)	0.272(2!)	0.585(2!)	16.2 (2!)	98.4(1!)
"	subjective effects (+ intranasal administration) (10)		32	400(1!)	0.0268(2!)	0.272(2!)	0.800(2!)	46.9 (2!)	86.1(2!)
Barnett et al., 1981	Comparison with (1M)		100	170(2!)	0.180(2!)	0.844(2!)	1.11(2!)	49.9(2!)	43.6(2!)
«	published data after nasal and (1M)		100	332(2!)	0.0735(2!)	0.398(2!)	0.723(2!)	49.6(2!)	86.8(2!)
«	gastrointestinal absorption (1M)		100	536(2!)	0.120(2!)	0.630(2!)	0.764(2!)	99.6(2!)	99.9(2!)
«	(1M)		200	501(2!)	0.0164(2!)	0.256(2!)	1.36(2!)	18.8(2!)	49.8(2!)
«	(1M)		200	501(2!)	0.0170(2!)	0.680(2!)	1.36(2!)	5.47(2!)	72.1(2!)
Javaid et al., 1983	Comparison with (1)		32	1020(1)			0.32(2)	-	-
«	intranasal administration (1)		32	181(1)	-	-	1.07(2)	-	-
«	(1)		32	407(1)	-	-	0.78(2)	-	-
«	(1)		32	390(1)	-	-	0.69(2)	-	-
Cone et al., 1988	Correlation of saliva cocaine (5M)	26-38	15	297(1!)	0.0792(2!)	0.162(2!)	0.782(2!)	70.3(2!)	49.8(2!)
«	levels with plasma levels (5M)	26-38	40	278(1!)	0.0399(2!)	0.362(2!)	0.938(2!)	93.8(2!)	49.8(2!)
Jeffcoat et al., 1989	+(nasal insufflation and smoking) (4M)	24.3±0.9	25	137(2!)	0.167(2!)	1.267(2!)	1.57(2!)	32.8(2!)	74.4(2!)
Perez-Reyes et al., 1994	Comparison of cocaine and cocaethylene (6M)	28.3±1.4	26.6	309(2!)	0.0363(2!)	0.894(2!)	1.43(2!)	49.6(2!)	86.1(2!)

Continuation of Table 125: Intravenous administration of 50 mg/70 kg body weight cocaine hydrochloride (absorption. distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	t½K1 (h)	t½K2 (h)	t½β (h)	V1 (%)	V2 (%)
Cone, 1995	Comparison of three routes of (1M)	39	25	215(2!)	0.221(2!)	0.647(2!)	1.13(2!)	49.8(2!)	74.7(2!)
	Cocaine administration, (1M)	43	25	146(2!)	0.0598(2!)	0.710(2!)	1.47(2!)	18.8(2!)	74.7(2!)
«	intravenous, intranasal (1M)	34	25	291(2!)	0.0939(2!)	0.374(2!)	1.03(2!)	49.9(2!)	70.3(2!)
«	and smoked route (1M)	30	25	127(2!)	0.183(2!)	0.550(2!)	(6.31)	49.9(2!)	49.8(2!)
«	(1M)	35	25	336(2!)	0.0831(2!)	0.286(2!)	1.04(2!)	49.9(2!)	99.6(2!)
«	(1M)	35	25	71(2!)	0.150(2!)	0.802(2!)	(8.19)	49.8(2!)	49.8(2!)
Jenkins et al., 1995	Comparison of heroin and (1)		44.8	183(1!)	0.0285(2!)	0.272(2!)	0.915(2!)	98.4(2!)	99.6(2!)
«	cocaine concentrations in (1)		44.8	441(1!)	0.0285(2!)	0.272(2!)	0.756(2!)	98.4(2!)	93.0(2!)
«	saliva with concentrations (1)		44.8	112(1!)	0.0255(2!)	0.488(2!)	1.19(2!)	25.0(2!)	70.0(2!)
«	In blood and plasma (1)		44.8	335(1!)	0.0285(2!)	0.294(2!)	1.01(2!)	99.2(2!)	99.6(2!)
«	(1)		44.8	287(1!)	0.0314(2!)	0.0595(2!)	1.55(2!)	50.0(2!)	9.23(2!)
«	(1)		44.8	198(1!)	0.0371(2!)	0.174(2!)	1.53(2!)	99.8(2!)	87.3(2!)
«	(1)		44.8	88(1!)	0.0389(2!)	0.295(2!)	1.21(2!)	43.1(2!)	99.9(2!)
	Mean ± SD			**323 ±158**	**0.0500 ±0.0443**	**0.471 ±0.320**	**1.02 ±0.33**	**52.2 ±25.1**	**76.3 ±17.7**
	Number of trials			11	10	10	11	10	10
	Number of observations			60	56	56	60	56	56

Evaluated studies	**Data from single dose studies**	**AUC_{o-oo} (ng*h/mL)**	**G (kg)**	**V_d (L)**	**V_β (L/kg)**
Kogan et al., 1977	Gas-liquid `chromatography (1)	903(2!)	61	107.3	1.76(2!)
“	of cocaine and Benzoylecgonine (1)	831(2!)	100	165.7	1.66(2!)
"	(1)	920(2!)	54	97.0	1.80(2!)
Javaid et al., 1978	Relation to physiological and (5)	695(1!)		70.2	

“	subjective effects (+ intranasal administration) (10)	548(1!)		55.8	
Barnett et al., 1989	Comparison with (1M)	591(2!)	68	255	3.74(2!)
«	published data after nasal and (1M)	415(2!)	95	182	1.92(2!)
«	gastrointestinal absorption (1M)	595(2!)	58	69	1.19(2!)
«	(1M)	1255(2!)	68	86	1.27(2!)
«	(1M)	1885(2!)			1.01(2!)
Javaid et al., 1983	Comparison with (1)	381(1)	74.0	49	-
«	intranasal administration (1)	245(1)	-	276	-
«	(1)	432(1)	-	123	-
«	(1)	363(1)	-	144	-
Cone et al., 1988	Correlation of saliva cocaine (5M)	423(1!)	63.5-73.1	168	2.41(1!)
	levels with plasma levels (5M)	527(1!)	63.5-73.1	180	2.57(1!)
Jeffcoat et al., 1989	+(nasal insufflation and smoking) (4M)	472(2!)	75.7±2.1	352	4.65(2!)
Perez-Reyes et al., 1994	Comparison of cocaine and cocaethylene (6M)	728(2!)	66.7±1.4	137	2.06(2!)
Cone, 1995	Comparison of three routes of cocaine, (1M)	490(2!)	72.6	215	2.96(2!)
«	administration: intravenous, intranasal (1M)	422(2!)	74.8	328	4.38 (2!)
«	and smoked route (1M)	543(2!)	65.8	144	2.19(2!)
«	(1M)	1301(2!)	65.8	329	5.00(2!)
«	(1M)	566(2!)	97.5	185	1.90(2!)
«	(1M)	928(2!)	68.0	228	3.36(2!)
Jenkins et al., 1995	Comparison of heroin and cocaine (1)	243(1!)	-	244	-
«	concentrations in saliva with (1)	497(1!)	-	101	-
«	concentrations in blood and plasma (1)	241(1!)	-	398	-
«	(1)	489(1!)	-	133	-
«	(1)	945(1!)	-	156	-
«	(1)	447(1!)	-	225	-

«	(1)	527(1!)	-	155	-
	Mean	**608**			**2.67**
	± SD	**±280**			**±1.17**
	Number of trials	11			7
	Number of observations	60			34

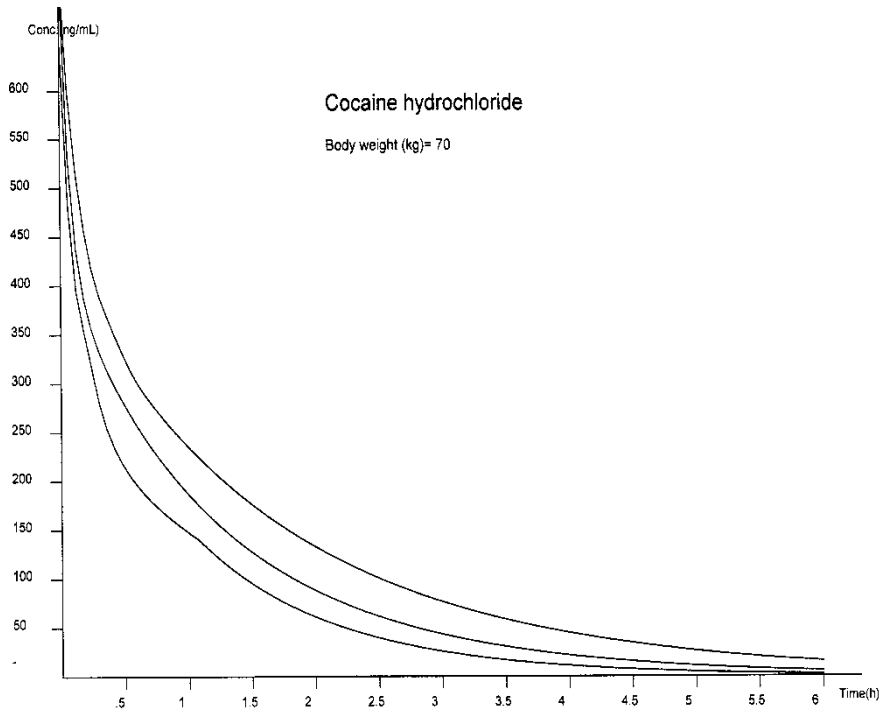


Figure 133: Plasma concentration-time curve of cocaine after intravenous administration of 50 mg/70 kg body weight cocaine hydrochloride

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	323	±	158	ng/mL
K_1(rapid):	13.9	±	6.6	h^{-1}
V_1(rapid):	52.2	±	25.1	%
K_2(slow):	1.47	±	0.59	h^{-1}
V_2(slow):	76.3	±	17.7	%
β:	0.680	±	0.167	h^{-1}
B:	100%			

derived from time-course of plasma concentrations

V_β:	2.67	±	1.17	1.97	±	1.89	L/kg
AUC_∞:	608	±	280	596 (447-808)			ng*h/mL

Table 126: Benzoylecgonine from intravenous administration of 50 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Kogan et al., 1977	Gas-liquid `chromatography (1)	23-30	100	814.(2!)	1.01(2!)	8.56(2!)	6.83(2!)	0.041(2!)	86.1(2!)
„	of cocaine and Benzoylecgonine (1)		100	414(2!)	0.243(2!)	6.13(2!)	10.65(2!)	0.008(2!)	99.6(2!)
„	(1)		100	300(2!)	0.368(2!)	9.37(2!)	7.00(2!)	0.032(2!)	84.8(2!)
Jeffcoat et al., 1989	+(nasal insufflation and smoking) (4M)	28.3±1.4	25	269(2!)	0.468(2!)	6.13(2!)	7.52(2!)	0.012(2!)	99.6(2!)
Cone, 1995	Comparison of three routes of (1M)	39	25	485(2!)	0.745(2!)	7.37(2!)	4.01(2!)	0.028(2!)	98.4(2!)
«	administration: intravenous, intranasal (1M)	43	25	409(2!)	0.772(2!)	6.13(2!)	4.28(2!)	0.008(2!)	99.6(2!)
«	and smoked route (1M)	65:8	25	437(2!)	0.296(2!)	6.36(2!)	4.14 (2!)	0.012(2!)	99.8(2!)
«	(1M)	30	25	315(2!)	0.591(2!)	6.36(2!)	4.50(2!)	0.043(2!)	99.2(2!)
«	(1M)	35	25	461(2!)	0.737(2!)	2.47(2!)	5.96(2!)	0.059(2!)	99.2(2!)
«	(1M)	35	25	170(2!)	0.579(2!)	6.13(2!)	7.13 (2!)	0.037(2!)	99.6(2!)
Jenkins et al., 1995	Comparison of heroin and cocaine (1)		44.8	528(1!)	0.738(2!)	6.13(2!)	4.00(2!)	0.017(2!)	99.6(2!)
«	concentrations in saliva with (1)		44.8	342(1!)	0.768(2!)	6.13(2!)	4.51 (2!)	0.039(2!)	99.2(2!)
«	concentrations in blood and plasma (1)		44.8	446(1!)	0.800(2!)	4.01(2!)	4.84 (2!)	0.014(2!)	98.4(2!)
«	(1)		44.8	394(1!)	1.07(2!)	7.37(2!)	3.85 (2!)	0.007(2!)	98.4(2!)
«	(1)		44.8	372(1!)	0.749(2!)	6.08(2!)	7.12 (2!)	0.008(2!)	92.3(2!)
«	(1)		44.8	393(1!)	1.46(2!)	4.72(2!)	3.87(2!)	0.008(2!)	93.4(2!)
«	(1)		44.8	567(1!)	1.88(2!)	6.30(2!)	5.64(2!)	0.018(2!)	69.2(2!)
	Mean ± SD			**388 ±146**	**0.734 ±0.388**	**6.21 ±1.42**	**5.92 ±1.82**	**0.021 ±0.015**	**95.8 ±7.6**
	Number of trials			4	4	4	4	4	4
	Number of observations			20	20	20	20	20	20

Continuation of Table 126: Benzoylecgonine from intravenous administration of 50 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Kogan et al., 1977	Gas-liquid `chromatography (1)	675(2)	4.0(2)	8262(2!)	61
"	of cocaine and Benzoylecgonine (1)	363(2)	0.75(2)	6206(2!)	100
"	(1)	366(2)	1.0(2)	3568(2!)	54
Jeffcoat et al., 1989	+(nasal insufflation and smoking) (4M)	269(2)	4.0(2)	2735(2!)	75.7±2.1
Cone, 1995	Comparison of three routes of (1M)	270(2)	0.33(2)	2357(2!)	72.6
«	administration: intravenous, (1M)	212(2)	4.0(2)	2085(2!)	74.8
«	intranasal (1M)	320(2)	4.0(2)	2427(2!)	65.8
«	and smoked route (1M)	201(2)	4.0(2)	1795(2!)	65.8
«	(1M)	281(2)	4.0(2)	3474(2!)	97.5
«	(1M)	113(2)	4.0(2)	1608(2!)	68.0
Jenkins et al., 1995	Comparison of heroin and cocaine (1)	282(1)	2.0(2!)	2491(1!)	
"	concentrations in saliva with (1)	176(1)	2.0(2)	1863(1!)	
"	concentrations in blood and plasma (1)	240(1)	1.0(2)	2628(1!)	
"	(1)	153(1)	2.0(2)	1634(1!)	
"	(1)	267(1)	2.0(2)	3660(1!)	
"	(1)	141(1)	4.0(2)	1896(1!)	
"	(1)	355(1)	8.0(2)	4679(1!)	
	Mean ± SD	**284 ±122**	**3.2 ±1.8**	**3177 ±1725**	
	Number of trials	4	4	4	
	Number of observations	20	20	20	

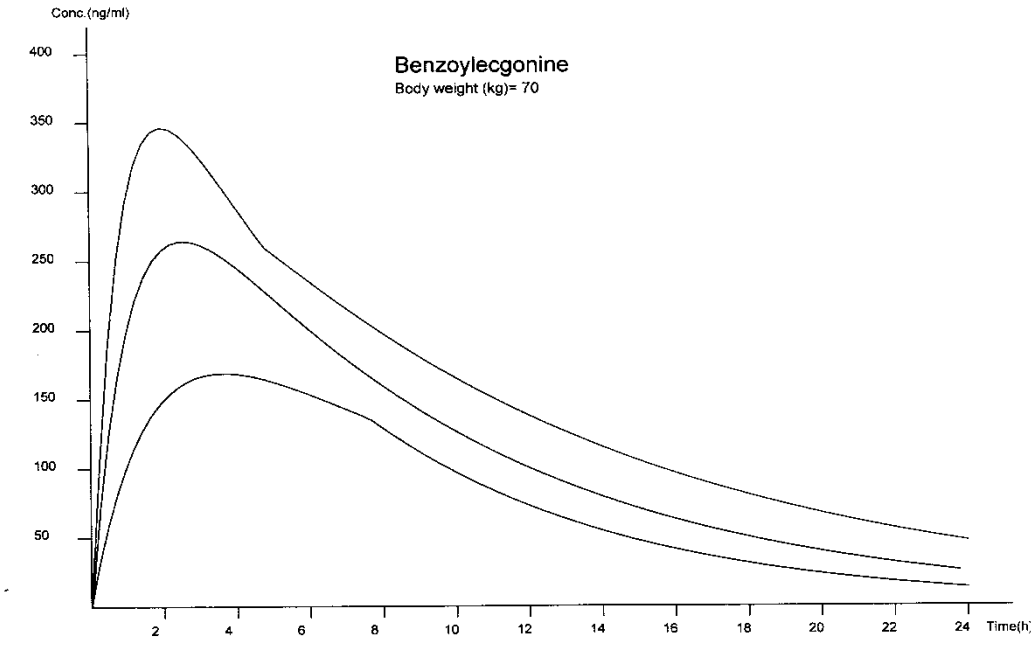


Figure 134: Plasma concentration-time curve of benzoylecgonine after intravenous injection of 50 mg/70 kg body weight cocaine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	388	±	146	ng/mL
Ka:	0.944	±	0.326	h^{-1}
α:	0.112	±	0.021	h^{-1}
β:	0.234	±	0.028	h^{-1}
t_0:	0.117	±	0.027	h
V%:	95.8	±	7.6	%
B:	(100%)			

					derived from time-course of plasma concentrations
C_{max}:	284	±	122	ng/mL	264 (169-346) ng/mL
t_{max}:	3.2	±	1.8	h	2.4 (1.9-3.6) h
AUC_{o-oo}:	3177	±	1725	ng*h/mL	3036 (2019-4292) ng*h/mL

Table 127: Intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Javaid et al., 1978	Relation of cocaine plasma concentrations to physiological and (2)		96	266(1!)	0.139(2!)	2.01(2!)	1.69(2!)	0.004(2!)	96.5(2!)
„	subjective effects (6)		64	372(1!)	0.156(2!)	4.68(2!)	0.673(2!)	0.029(2!)	96.5(2!)
„	(+ injection of cocaine) (5)		16	1120(1!)	0.321(2!)	7.70(2!)	0.579(2!)	0.087(2!)	93.6(2!)
Van Dyke et al., 1978	Plasma cocaine concentrations and central effects (4M)	25-32	2 mg/kg	187(2!)	0.296(2!)	5.92(2!)	1.39(2!)	0.170(2!)	96.9(2!)
Wilkinson et al., 1980	+ (oral cocaine kinetics) Cocaine hydrochloride solution (4M)		0.19 mg/kg	179(2)	-	-	-	-	-
„	„ (7M)		0.38 mg/kg	148(2)	-	-	1.21 (2)	-	-
„	Cristalline cocaine hydrochloride (3M)		0.38 mg/kg	221(2)	-	-	-	-	-
„	Cocaine hydrochloride solution (4M)		0.75 mg/kg	118(2)	-	-	-	-	-
„	„ (4M)		1.5 mg/kg	125(2)	-	-	-	-	-
„	„ (5M)		2.0 mg/kg	119(2)	-	-	-	-	-
„	Volunteers after several (2)		-	-	-	-	1.19 (2)	-	-
„	single doses: 0.19, 0.38, 0.75, 1.5, (2)		-	-	-	-	1.46 (2)	-	-
„	or 2.0 mg/kg (5)		-	-	-	-	1.56 (2)	-	-
„	(5)		-	-	-	-	1.00 (2)	-	-
„	(5)		-	-	-	--	0.95 (2)	-	-
„	(2)		-	-	-	--	1.30 (2)	-	-
„	(4)		-	-	-	--	1.24 (2)	-	-
Javaid et al., 1983	Comparison of intranasal and (1)		64	-	0.163(2)	-	0.495 (2)	-	-
„	intravenous administration (1)		64	-	0.453(2)	-	1.20 (2)	-	-
„	(1)		64	-	0.110(2)	-	1.69 (2)	-	-
„	(1)		64	-	0.333(2)	-	0.485 (2)	-	-
„	(1)		96	-	0.189(2)	-	1. 36. (2)	-	-
„	(1)		96	-	0.202(2)	-	1.69 (2)	-	-
„	(1)		96	-	0.350(2)	-	1.51 (2)	-	-

„	(1)		96	-	0.122(2)	-	0.56 (2)	-	-
Jeffcoat et al., 1989	+(intravenous injection and smoking) (6M)	24.3±0.9	106	279(2!)	0.154(2)	3.19(2!)	1.98 (2!)	0.002(2!)	93.0(2!)
Farré et al., 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	22-30	100	371(2!)	0.304(2)	6.13(2!)	1.47 (2!)	0.001(2!)	98.4(2!)
Perez-Reyes, 1994	Interaction between coaine and ethanol (6M)	24.7±1.1	1.25 mg/kg	205(2!)	0.270(2)	8.56(2!)	2.23 (2!)	0.035(2!)	96.5(2!)
“	(6M)	24.7±1.1	1.9 mg/kg	293(2!)	0.169(2)	6.36(2!)	1.81 (2!)	0.003(2!)	99.6(2!)
Lukas et al., 1994	Marihuana smoking increases plasma cocaine levels (5M)	21-35	0.9 mg/kg	284(2!)	0.066(2)	6.36(2!)	1.33 (2!)	0.002(2!)	98.8(2!)
McCance et al., 1996	+(intranasal administration of cocaethylene (8M)	34.5±3.4	0.92 mg/kg	292(2!)	0.210(2)	6.13(2!)	1.86 (2!)	0.006(2!)	99.2(2!)
Kosten et al., 1994	Gender differences in response to intranasal cocaine (23M)	30±5	2 mg/kg	-	-	-	-	-	-
“	administration in humans (11F)	32±10	2 mg/kg	-	-	-	-	-	-
Cone. 1995	Comparison of three routes (1M)	39	32	238(2!)	0.171(2!)	10.8(2!)	2.75 (2!)	0.017(2!)	96.1(2!)
“	of Cocaine administration, (1M)	43	32	190(2!)	0.096(2!)	0.81(2!)	4.04 (2!)	0.001(2!)	95.4(2!)
“	intravenous, intranasal (1M)	34	32	260(2!)	0.064(2!)	2.86(2!)	4.04 (2!)	0.002(2!)	93.0(2!)
“	and smoked route (1M)	30	32	187(2!)	0.075(2!)	0.94(2!)	(8.08)	0.001(2!)	65.4(2!)
“	(1M)	35	32	262(2!)	0.192(2!)	6.13(2!)	1.58 (2!)	0.045(2!)	92.3(2!)
“	(1M)	35	32	135(2!)	0.117(2!)	3.03(2!)	6.57 (2!)	0.002(2!)	93.0(2!)
Farré et al., 1997	Alcohol and coaine interactions in humans, 0.8 g/kg (9M)	25-30	100	394(2!)	0.182(2!)	6.13(2!)	1.52 (2!)	0.001(2!)	98.2(2!)
	Mean ± SD			**276 ±168**	**0.207 ±0.082**	**5.81 ±1.82**	**1.48 ±0.58**	**0.023 ±0.043**	**96.6 ±4.3**
	Number of trials			18	13	12	21	12	12
	Number of observations			101	80	72	105	72	72

Continuation of Table 127: Intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)	B (%)
Javaid et al., 1978	Relation of cocaine plasma concentrations to physiological and (2)	215(1)	0.5 (2)	621(1!)	-	-
„	subjective effects (6)	180(1)	0.5(2)	362(1!)	-	-
„	(+ injection of cocaine) (5)	331(1)	1.0(2)	1227(1!)	-	-
Van Dyke et al., 1978	Plasma cocaine concentrations and central effects (4M)	115(2)	1.0(2)	443(2!)	-	-
Wilkinson et al., 1980	+ (oral cocaine kinetics) Cocaine hydrochloride solution (4M)	179(2)	0.69(2)	278(2)	70.3	-
„	„ (7M)	148(2)	0.79(2)	308(2!)	80.1	-
„	Cristalline cocaine hydrochloride (3M)	221(2)	0.58(2)	384(2!	70.0	-
„	Cocaine hydrochloride solution (4M)	118(2)	0.88(2)	214(2)	70.3	-
„	„ (4M)	125(2)	1.08(2)	221(2)	70.3	-
„	„ (5M)	119(2)	1.51(2)	277(2)	81.7	-
„	Volunteers after several (2)	-	-	-	99	-
„	single doses: 0.19, 0.38, 0.75, 1.5, (2)	-	-	-	120	-
„	or 2.0 mg/kg (5)	-	-	-	74	-
„	(5)	-	-	-	72	-
„	(5)	-	-	-	64	-
„	(2)	-	-	-	61	-
„	(4)	-	-	-	71	-
Javaid et al., 1983	Comparison of intranasal and (1)	-	-	214(1)	-	28(2)
„	intravenous administration (1)	-	-	118(1)	-	24(2)
„	(1)	-	-	356(1)	-	41(2)
„	(1)	-	-	137(1)	-	19(2)
„	(1)	-	-	511(1)	-	67(2)
„	(1)	-	-	316(1)	-	64(2)
„	(1)	-	-	594(1)	-	69(2)

„	(1)	-	-	216(1)	-	30(2)
Jeffcoat et al., 1989	+(intravenous injection and smoking) (6M)	224(2)	0.63(2)	825(2!)	75.7±11.2	80±13(2)
Farré et al., 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	184(2)	0.95(2)	674(2!)	66.6	-
Perez-Reyes, 1994	Interaction between coaine and ethanol (6M)	149(2)	1.0(2)	666(2!)	69.2±2.3	-
“	(6M)	207(2)	0.5(2)	705(2!)	69.2±2.3	-
Lukas et al., 1994	Marihuana smoking increases plasma cocaine levels (5M)	212(2)	0.58(2)	546(2!)	76.15±9.92	-
McCance et al., 1995	+(intranasal administration of cocaethylene (8M)	224(2)	1.06(2)	714(2!)	-	-
Cone, 1995	Comparison of three routes of (1M)	204(2)	1.5(2)	1030(2!)	72.6	105(2!)
“	Cocaine administration, (1M)	180(2)	1.0(2)	1057(2!)	74.8	125(2!)
“	intravenous, intranasal (1M)	267(2)	0.5(2)	1564(2!)	65.8	144(2!)
“	and smoked route (1M)	250(2)	0.5(2)	(2275)	65.8	87.4(2!)
“	(1M)	222(2)	1.0(2)	711(2!)	97.5	62.8(2!)
“	(1M)	143(2)	1.0(2)	(1299)	65.0	69.9(2!)
Kosten et al., 1996	Gender differences in response to intranasal cocaine (23M)	-	-	459(2!)	78±18	-
“	administration in humans (11F)	-	-	299(2!)	68±19	-
Farré et al., 1997	Alcohol and coaine interactions in humans, 0.8 g/kg (9M)humans, 0.8 g/kg (9M)	269(2)	0.75(2)	817(2!)	69.6	-
	Mean ± SD	**191 ±52**	**0.84 ±0.26**	**526 ±246**		**70.8 ±31.7**
	Number of trials	18	18	21		3
37	Number of observations	101	101	139		19

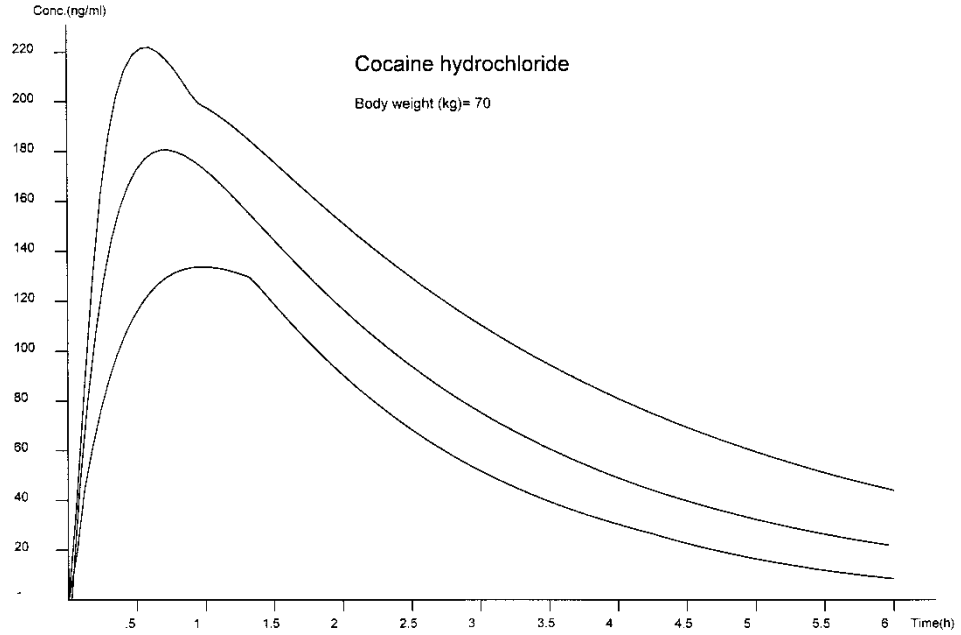


Figure 135: Plasma concentration-time curve of cocaine after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	276	±	168	ng/mL
Ka:	3.35	±	0.95	h^{-1}
α:	0.119	±	0.028	h^{-1}
β:	0.468	±	0.137	h^{-1}
t_0:	0.023	±	0.023	h
V%:	96.6	±	4.3	%

					derivedfromtime-courseof plasmaconcentrations	
C_{max}:	191	±	52	ng/mL	179 (135-219)	ng/mL
t_{max}:	0.84	±	0.26	h	0.74 (0.48-0.96)	h
AUC_{o-oo}:	526	±	246	ng*h/mL	581 (370-893)	n*h/mL
Vβ	:2.67	±	1.17	L/kg		
B:	70.8	±	31.7		49.8	%

Table 128 :Benzoylecgonine from intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Jeffcoat et al., 1989	+(intravenous injection and smoking) (6M)	24.3±0.9	106	877(2!)	1.19(2)	5.98(2!)	8.33 (2!)	0.116(2!)	86.1(2!)
Farré et al., 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	22-30	100	945(2!)	0.861(2)	5.06(2!)	6.19 (2!)	0.340(2!)	93.0(2!)
Cone. 1995	Comparison of three routes (1M)	39	32	688(2!)	0.789(2!)	1.05(2!)	5.53 (2!)	0.393(2!)	86.1(2!)
"	of Cocaine administration, (1M)	43	32	690(2!)	0.681(2!)	6.13(2!)	5.63 (2!)	0.526(2!)	99.6(2!)
"	intravenous, intranasal (1M)	34	32	739(2!)	0.975(2!)	8.45(2!)	5.60 (2!)	0.323(2!)	86.8(2!)
"	and smoked route (1M)	30	32	770(2!)	1.12(2!)	7.37(2!)	4.81(2!)	0.180(2!)	93.0(2!)
"	(1M)	35	32	-	-	-	-	-	-
"	(1M)	35	32	376(2!)	0.400(2!)	6.36(2!)	7.20 (2!)	0.432(2!)	99.6(2!)
Farré et al., 1997	Alcohol and coaine interactions in humans, 0.8 g/kg (8M)	25-30	100	833(2!)	0.776(2!)	1.22(2!)	7.21 (2!)	0.300(2!)	93.0(2!)
	Mean ± SD			**846 ±118**	**0.895 ±0.191**	**4.31 ±2.82**	**6.86 ±0.99**	**0.286 ±0.105**	**91.5 ±3.8**
	Number of trials			5	5	5	5	5	5
	Number of observations			29	29	29	29	29	29

Continuation of Table 128 :Benzoylecgonine from intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)
Jeffcoat et al., 1989	+(intravenous injection and smoking) (6M)	623(2)	3.0(2)	10356(2!)	75.7±11.2
Farré et al., 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	740(2)	3.6(2)	7689(2!)	66.6
Cone, 1995	Comparison of three routes of (1M)	447(2)	3.0(2)	4745(2!)	72.6
"	Cocaine administration, (1M)	447(2)	2.0(2)	4944(2!)	74.8

“	intravenous, intranasal (1M)	508(2)	3.0(2)	6148(2!)	65.8
“	and smoked route (1M)	417(2)	4.0(2)	4624(2!)	65.8
“	(1M)	535(2)	2.0(2)	-	97.5
“	(1M)	304(2)	2.0(2)	3703(2!)	65.0
Farré et al., 1997	Alcohol and coaine interactions in humans, 0.8 g/kg (9M)humans, 0.8 g/kg (8M)	675(2)	2.3(2)	8762(2!)	69.6
	Mean ± SD	**625 ±145**	**2.9 ±0.6**	**8057 ±1829**	
	Number of trials	5	5	5	
	Number of observations	30	30	29	

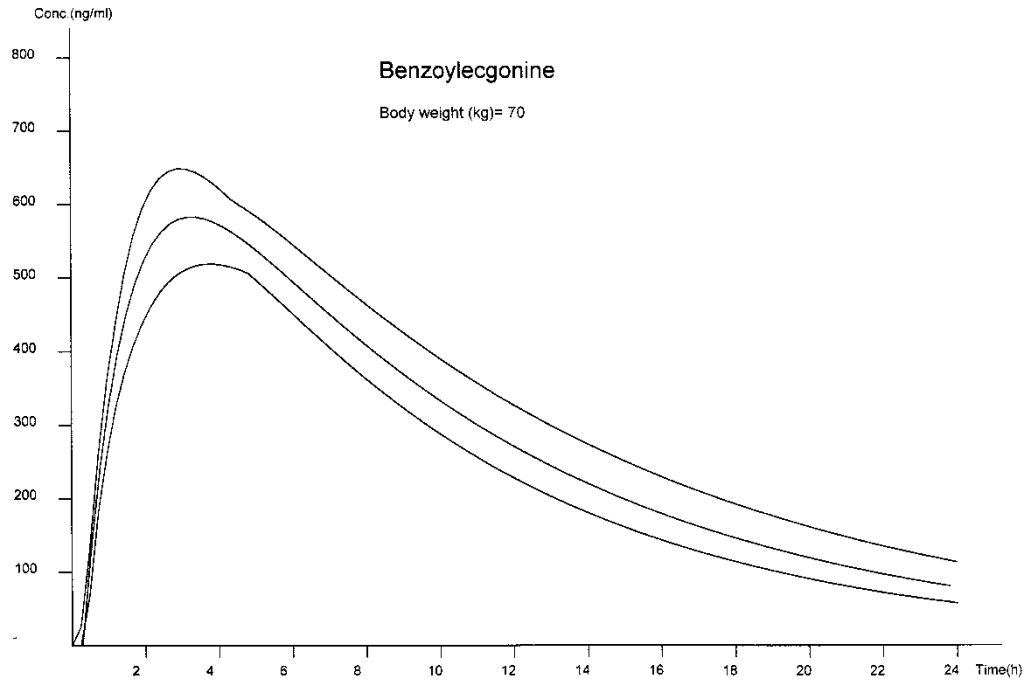


Figure 136: Plasma concentration-time curve of Benzoylecgonine after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	846	±	118	ng/mL	
Ka:	0.775	±	0.137	h^{-1}	
α:	0.161	±	0.064	h^{-1}	
β:	0.101	±	0.013	h^{-1}	
t_0:	0.286	±	0.105	h	
V%:	91.5	±	3.8	%	
B:	(100 %)				
					derivedfromtime-courseof plasmaconcentrations
C_{max}:	625	±	145	ng/mL	583 (519-648) ng/mL
t_{max}:	2.9	±	0.6	h	3.3 (2.9-3.8) h
AUC_{o-oo}:	8057	±	1857	ng*h/mL	7666 (6410-9371) n*h/mL
Vβ	:1.73	±	0.28	L/kg	

Table 129: Ecgoninemethylester after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination)

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Farré et al. 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	22-30	100	179.0 (2!)	0.832(2!)	2.40(2!)	3.57(2!)	0.481(2!)	84.8(2!)
Farré et al. 1997	Alcohol and coaine interactions in humans, 0.8 g/kg *(8M)*	25-30	100	137.9 (2!)	0.666(2!)	6.94(2!)	4.12(2!)	0.435(2!)	98.4(2!)
	Mean			**159.7**	**0.931**	**4.54**	**3.83**	**0.459**	**91.2**
	± SD			**±20.8**	**±0.105**	**±2.30**	**±0.28**	**±0.032**	**±6.9**
	Number of trials			2	2	2	2	2	2
	Number of observations			17	17	17	17	17	17

Continuation of Table 129: Ecgoninemethylester after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination)

Evaluated studies	Data from comparative single dose studies	Cmax (ng/mL)	Tmax (h)	AUCo-oo (ng*h/mL)	G (kg)
Farré et al. 1993	Alcohol and coaine interactions in humans, 1.0 g/kg (9M)	111.5 (2!)	2.0 (2)	780.3(2!)	66.6
Farré et al. 1997	Alcohol and coaine interactions in humans , 0.8 g/kg *(8M)*	91.5 (2!)	2.5(2)	704.6(2!)	69.6
	Mean	**102.1**	**2.24**	**744.6**	
	± SD	**±10.1**	**±0.25**	**±38.3**	
	Number of trials	2	2	2	
	Number of observations	17	17	17	

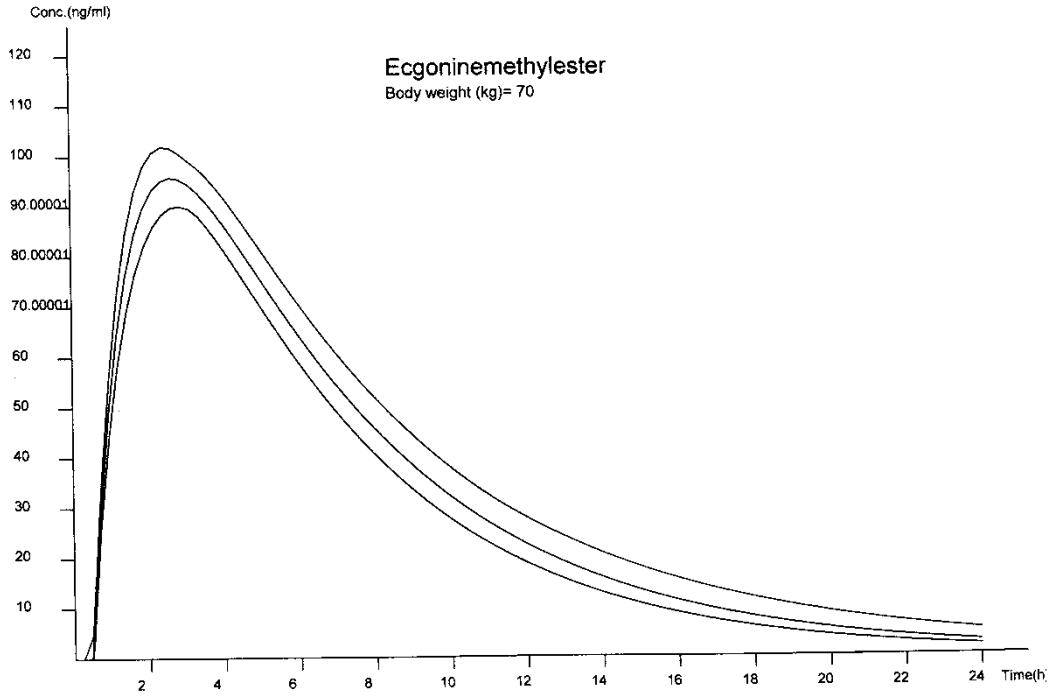


Figure 137: Plasma concentration-time curve of ecgoninemethylester after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	159.7	±	20.8	ng/mL
Ka:	0.931	±	0.105	h^{-1}
α:	0.153	±	0.052	h^{-1}
β:	0.181	±	0.012	h^{-1}
t_0:	0.459	±	0.023	h
V%:	91.2	±	6.9	%

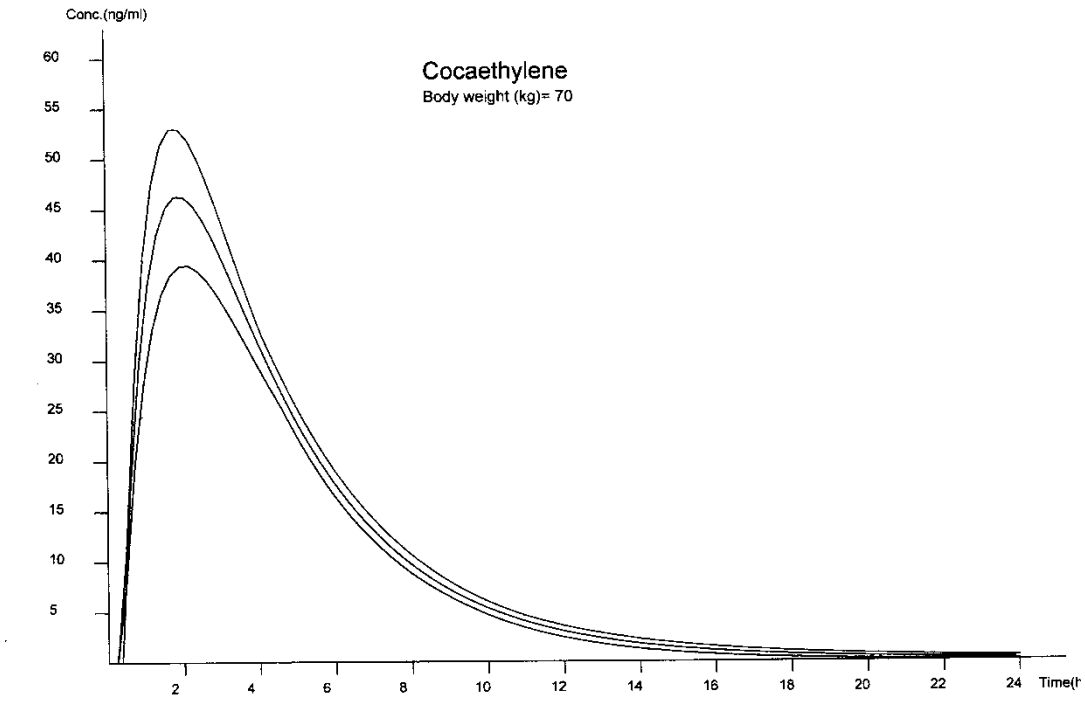
				derived from time-course of plasma concentrations
C_{max}:	102.1	±	10.1 ng/mL	95.6 (90.0-101.7) ng/mL
t_{max}:	2.24	±	0.25 h	2.6 (2.4-3.9) h
AUC_{o-oo}:	744.6	±	38.3 ng*h/mL	794 (704-833) ng*h/mL

Table 130: Cocaethylene after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride and ethanol intake of 1.0 resp. 0.8 g/kg/ body weight (absorption, distribution and elimination)

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Farré et al. 1993	Acute alcohol intoxication 1.0 g/kg (9M)	22-30	100	113.9 (2!)	0.680(2!)	6.19(2!)	2.03(2!)	0.344(2!)	96.5(2!)
Farré et al. 1997	Acute alcohol intoxication 0.8 g/kg *(8M)*	25-30	100	89.9 (2!)	0.520(2!)	7.15(2!)	2.21(2!)	0.381(2!)	99.8(2!)
Perez-Reyes et al. 1994	Comparison of intravenously injected Cocaethylene and Cocaine								
	Mean			**102.6**	**0.605**	**6.64**	**2.15**	**0.361**	**98.1**
	± SD			**±12.2**	**±0.081**	**±0.49**	**±0.091**	**±0.019**	**±1.7**
	Number of trials			2	2	2	2	2	2
	Number of observations			17	17	17	17	17	17

Continuation of Table 130: Cocaethylene after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride and ethanol intake of 1.0 resp. 0.8 g/kg/ body weight (absorption, distribution and elimination)

Evaluated studies	Data from comparative single dose studies	Cmax (ng/mL)	Tmax (h)	AUCo-oo (ng*h/mL)	G (kg)
Farré et al. 1993	Acute alcohol intoxication 1.0 g/kg (9M)	49.2 (2!)	2.0 (2)	255.0(2!)	66.6
Farré et al. 1997	Acute alcohol intoxication 0.8 g/kg *(8M)*	47.1 (2!)	2.0(2)	221.0(2!)	69.6
Perez-Reyes et al. 1994	Comparison of intravenously injected Cocaethylene and Cocaine				
	Mean	**48.2**	**2.0**	**239.0**	
	± SD	**±1.06**	**±0.0**	**±17.2**	
	Number of trials	2	2	2	
	Number of observations	17	17	17	



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	102.6	±	12.2	ng/mL
Ka:	1.15	±	0.14	h^{-1}
α:	0.104	±	0.007	h^{-1}
β:	0.322	±	0.013	h^{-1}
t_0:	0.361	±	0.019	h
V%:	98.1 %	±	1.7	

				derived from time-course of plasma concentrations
C_{max}:	48.2	±	1.06 ng/mL	46.4 (39.4-53.0) ng/mL
t_{max}:	2.0	±	0.0 h	1.9 (1.7-2.2) h
AUC_{o-oo}:	239.0	±	17.2 ng*h/mL	246 (215-278) ng*h/mL

Figure 138: Plasma concentration-time curve of cocaethylene after intranasal administration of 100 mg/70 kg body weight cocaine hydrochloride and ethanol intake of 1.0 resp. 0.8 g/kg body weight

Table 131: Smoking of 44.6 mg/70 kg body weight cocaine base corresponding to 50 mg cocaine hydrochloride (absorption. distribution and elimination).

Evaluated studies	Data from single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}K_1$ (h)	$t_{½}K_2$ (h)	$t_{½}\beta$ (h)	V_1 (%)	V_2 (%)
Paly et al., 1982	(4)	20-25	225	146(1!)	0.0299(2!)	0.153(2!)	0.613(2!)	24.3(2!)	86.1(2!)
"	(4)	20-25	225	180(1!)	0.0272(2!)	0.290(2!)	0.625(2!)	50.0(2!)	84.8(2!)
Jeffcoat et al., 1989	+(intravenous injection and nasal insufflation) (6M)	24.3±0.9	39.5	173(2!)	0.0237(2!)	0.415(2!)	1.18(2!)	19.2(2!)	86.8(2!)
Cone, 1995	Comparison of three routes of (1M)	39	42	(10)(1!)	0.0432(2!)	0.324(2!)	1.75(2!)	21.5 (2!)	48.4(1!)
"	Cocaine administration, (1M)	43	42	41(2!)	0.118(2!)	0.592(2!)	(6.78)	18.5 (2!)	18.8(2!)
«	intravenous, intranasal (1M)	34	42	26(2!)	0.0688(2!)	0.617(2!)	(9.48)	24.9(2!)	25.0(2!)
«	and smoked route (1M)	30	100	56(2!)	0.425(2!)	0.665(2!)	(6.86)	35.2(2!)	93.8(2!)
«	(1M)	35	42	121(2!)	0.0724(2!)	0.824(2!)	2.01(2!)	49.6(2!)	49.6(2!)
«	(1M)	35	42	35(2!)	0.0509(2!)	1.27(2!)	(8.09)	16.4(2!)	46.1(2!)
Jenkins et al., 1995	Comparison of heroin and (1)		40	102(2!)	0.0285(2!)	0.272(2!)	0.893(2!)	99.2(2!)	99.6(2!)
«	cocaine concentrations in (1)		40	68(1)	0.0285(2!)	0.272(2!)	0.921(2!)	99.6(2!)	99.8(2!)
«	saliva with concentrations (1)		40	112(1)	0.0334(2!)	0.350(2!)	1.19(2!)	25.0(2!)	65.6(2!)
«	in blood and plasma (1)		40	47(1)	0.0456(2!)	0.272(2!)	0.627(2!)	84.8(2!)	99.2(2!)
«	(1)		40	215(1)	0.0067(2!)	0.691(2!)	0.525(2!)	18.8(2!)	87.2(2!)
«	(1)		40	143(1!)	0.0452(2!)	0.271(2!)	0.585(2!)	73.8(2!)	99.6(2!)
«	(1)		40	87(1!)	0.0281(2!)	0.268(2!)	0.890(2!)	17.6(2!)	74.7(2!)
	Mean ± SD			**127 ±58**	**0.0506 ±0.0771**	**0.406 ±0.243**	**0.931 ±0.391**	**36.9 ±25.2**	**78.2 ±21.5**
	Number of trials			11	10	10	11	10	10
	Number of observations			60	56	56	60	56	56

Evaluated studies	Data from single dose studies	AUC_{o-oo} (ng_*h/mL)	G (kg)
Paly et al., 1982	(4)	121.7(2!)	-

“	(4)	157.2(2!)	-
Jeffcoat et al., 1989	+(intravenous injection and nasal insufflation) (6M)	354.4(2!)	75.7±2.1
Cone, 1995	Comparison of three routes of (1M)	-	72.6
“	Cocaine administration, (1M)	588(2!)	74.8
«	intravenous, intranasal (1M)	437(2!)	65.8
«	and smoked route (1M)	-	65.8
«	(1M)	515(2!)	97.5
«	(1M)	498(2!)	68.0
Jenkins et al., 1995	Comparison of heroin and cocaine (1)	132.5(1!)	-
«	concentrations in saliva with (1)	90.9(1!)	-
«	concentrations in blood and plasma (1)	236(1!)	-
«	(1)	43.2(1!)	-
«	(1)	207(1!)	-
«	(1)	140(1!)	
«	(1)	159(1!)	
	Mean	**269**	
	± SD	**±153**	
	Number of trials	11	
	Number of observations	60	

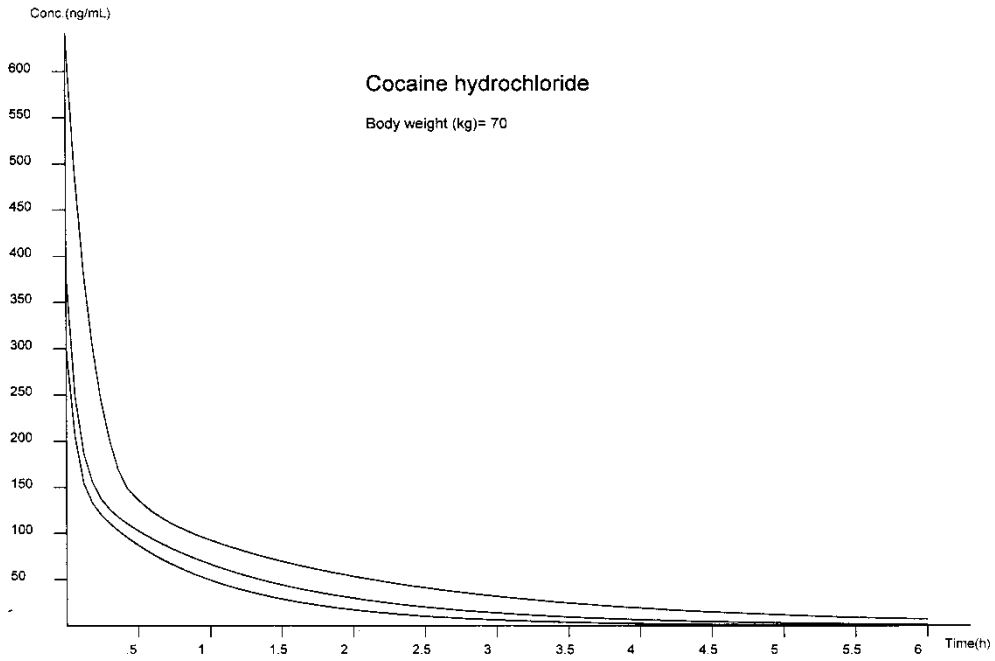


Figure 139: Plasma concentration-time curve of cocaine after smoking of 44.6 mg/70 kg cocaine base corresponding to 50 mg cocaine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	127	±	58	ng/mL
K_1(rapid):	13.7	±	9.5	h^{-1}
V_1(rapid):	36.9	±	25.2	%
K_2(slow):	1.17	±	0.73	h^{-1}
V_2(slow):	78.2	±	21.5	%
β:	0.745	±	0.263	h^{-1}

			derived from time-course of plasma concentrations			
V_β:	2.67	± 1.17	2.67	±	2.25	L/kg
B:			53.2 %			
$AUC_{o\text{-}oo}$:	269	± 153	224 (188-394)			ng_*h/mL

Table 132: Benzoylecgonine from smoking 44.6 mg/70 kg body weight cocaine corresponding to 50 mg cocain hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Jeffcoat et al., 1989	+(intravenous injection and nasal insufflation) (6M)	24.3±0.9	39.5	152(2!)	0.470(2!)	6.13(2!)	7.52 (2!)	0.012(2!)	99.6(2!)
Cone. 1995	Comparison of three routes (1M)	39	42	-	-	-	-	-	-
"	of cocaine administration, (1M)	43	42	169(2!)	0.600(2!)	6.13(2!)	5.77 (2!)	0.103(2!)	99.2(2!)
"	intravenous, intranasal (1M)	34	42	166(2!)	0.818(2!)	6.13(2!)	1.90 (2!)	0.004(2!)	99.6(2!)
"	and smoked route (1M)	30	42	93.4(2!)	1.48(2!)	6.13(2!)	3.73 (2!)	0.027(2!)	99.2(2!)
"	(1M)	35	42	250(2!)	1.08(2!)	7.37(2!)	6.42(2!)	0.029(2!)	98.4(2!)
"	(1M)	35	42	83.0(2!)	1.91(2!)	6.13(2!)	6.52(2!)	0.068(2!)	99.2(2!)
Jenkins et al., 1995	Comparison of heroin and cocaine (1)	-	40	141(1!)	0.432(2!)	6.13(2!)	5.05 (2!)	0.037(2!)	99.6(2!)
"	cocaine concentrations in (1)	-	40	107(1!)	0.480(2!)	6.13(2!)	4.33 (2!)	0.039(2!)	96.0(2!)
"	concentrations in blood and plasma (1)	-	40	161(1!)	0.315(2!)	3.98(2!)	7.14(2!)	0.070(2!)	98.2(2!)
"	(1)	-	40	38.4(1!)	0.363(2!)	0.155(2!)	5.07(2!)	0.003(2!)	92.3(2!)
"	(1)	-	40	134(1!)	0.666(2!)	9.90(2!)	2.69(2!)	0.028(2!)	93.0(2!)
"	(1)	-	40	141(1!)	1.08(2!)	6.54(2!)	5.11(2!)	0.127(2!)	93.0(2!)
"	(1)	-	40	107(1!)	0.192(2!)	6.13(2!)	4.54(2!)	0.083(2!)	95.2(2!)
	Mean ± SD			**144 ±43**	**0.680 ±0.437**	**5.98 ±1.79**	**5.74 ±1.77**	**0.038 ±0.036**	**97.8 ±2.6**
	Number of trials			3	3	3	3	3	3
	Number of observations			18	18	18	18	18	18

Continuation of Table 132: Benzoylecgonine from smoking 44.6 mg/70 kg body weight cocaine corresponding to 50 mg cocain hydrochloride (absorption, distribution, and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	G (kg)
Jeffcoat et al., 1989	+(nasal insufflation and smoking) (6M)	184.5(2)	1.5(2)	1545(2!)	75.7±2.1
Cone, 1995	Comparison of three routes of (1M)	-	-	-	72.6
«	administration: intravenous, (1M)	113(2)	2.35(2)	1263(2!)	74.8
«	intranasal (1M)	46.6(2)	1.27(2)	263(2!)	65.8
«	and smoked route (1M)	57.3(2)	1.39(2)	444.3(2!)	65.8
«	(1M)	250(2)	2.52(2)	3004(2!)	97.5
«	(1M)	63.4(2)	1.68(2)	743(2!)	68.0
Jenkins et al., 1995	Comparison of heroin and cocaine (1)	101.5(1)	1.0(2!)	940(1!)	
“	concentrations in saliva with (1)	66.9(1)	1.0(2)	596(1!)	
“	concentrations in blood and plasma (1)	132.7(1)	2.0(2)	1602(1!)	
“	(1)	34.6(1)	1.0(2)	295.2(1!)	
“	(1)	80.3(1)	2.0(2)	527(1!)	
“	(1)	79.2(1)	4.0(2)	904(1!)	
“	(1)	83.7(1)	1.0(2)	672(1!)	
	Mean	**133**	**1.7**	**1225**	
	± SD	**±65**	**±0.7**	**±694**	
	Number of trials	3	3	3	
	Number of observations	18	18	18	

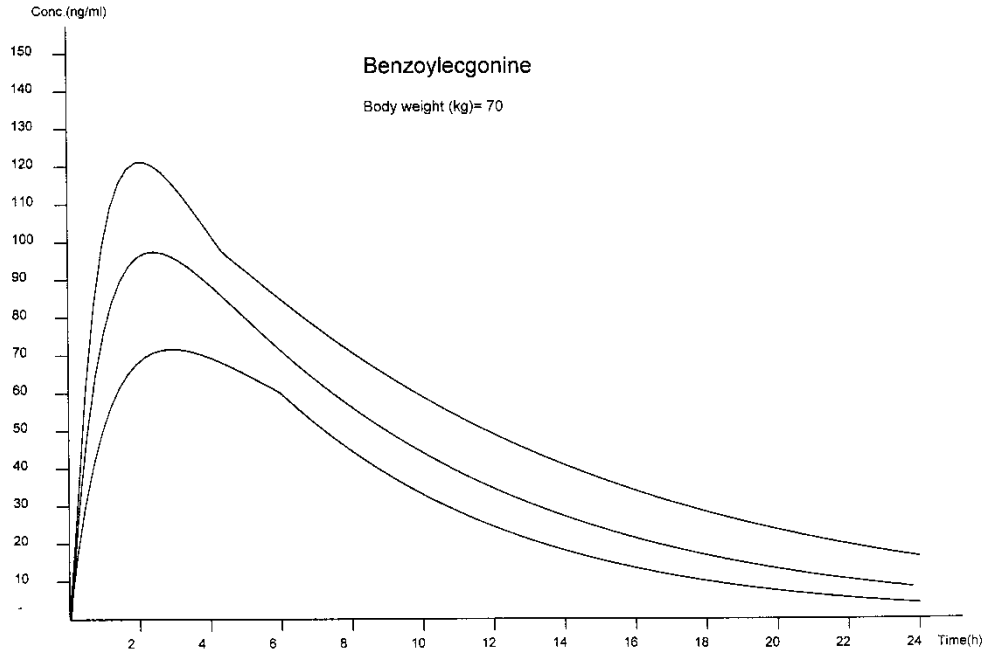


Figure 140: Plasma concentration-time curve of benzoylecgonine after smoking of 44.6 mg//70 kg body weight cocaine corresponding to 50 mg cocain hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	144	±	43	ng/mL
Ka:	1.02	±	0.17	h^{-1}
α:	0.116	±	0.027	h^{-1}
β:	0.121	±	0.029	h^{-1}
t_0:	0.038	±	0.036	h
V%:	97.8	±	2.6	%
B:	(100) %			

				derived from time-course of plasma concentrations	
C_{max}:	133	±	65	97 (72-121)	ng/mL
t_{max}:	1.7	±	0.7	2.4 (2.2-2.9)	h
AUC_{o-oo}:	1225	±	694	1072 (763-1511)	ng*h/mL
			V_β:	5.02 ± 2.14	L/kg

Table 133: Cocaine after oral administration of 140 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg/kg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Van Dyke et al., 1978	Plasma concentrations of cocaine and centrat effects (4M)	25-32	2	237(2!)	0.126(2!)	0.997(2!)	1.14(2)	0.449(2!)	84.8(2!)
Wilkinson et al., 1980	Comparison of intranasal and (4M)	24-33	2	-	-	-	-	-	-
«	Oral cocaine kinetics (1M)	-	2	433(2)	0.0581(2)	-	0.875(2)	0.470(2)	100(2)
«	(1M)	-	2	268(2)	0.167(2)	-	0.695(2)	0.440(2)	100(2)
«	(1M)	-	3	274(2)	0.420(2)	-	0.695(2)	0.485(2)	100(2)
“	(1M)	-	2	375(2)	0.250(2)	-	0.797(2)	0.473(2)	100(2)
“	(1M)	-	2	149(2)	0.135(2)	-	0.790(2)	1.00(2)	100(2)
Fattinger et al., 2000	Nasal mucosal versus gastrointestinal absorption of nasally administration (12M/5F)	22-28	2	440(2!)	0.294(2!)	4.42(2!)	1.23(2!)	0.247(2!)	99.6(2)
Herbst et al., 2011	Cocaethylene formation following ethanol and cocaine administration by different routes (5M/1F)	21-45	3	584(2!)	0.639(2!)	4.39(2!)	1.49(2!)	0.416(2!)	93.0(2!)
	Mean ± SD	-		**420 ± 116**	**0.324 ± 0.170**	**3.91 ± 1.22**	**1.20 ± 0.22**	0.355 **± 0.152**	**96.6 ± 5.2**
	Number of trials			4	4	3	4	4	4
	Number of observations			32	32	27	32	32	32

Continuation of Table 133: Cocaine after oral administration of 140 mg/70 kg body weight cocaine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng_*h/mL)	B (%)	G (kg)
Van Dyke et al., 1978	Plasma concentrations of cocaine and centrat effects (4M)	210(2)	1.0(2!)	397(2!)		-
Wilkinson et al., 1980	Comparison of intranasal and (4M)	242(2)	1.1(2!)	372(2)		61-120
«	oral cocaine kinetics (1M)	-	-	-		120
«	(1M)	-	-	-		74
«	(1M)	127(2)	1.0 (2)	279(2)		74
“	(1M)	-	-	-		61
“	(1M)	-	-	-		71
Fattinger et al., 2000	Nasal mucosal versus gastrointestinal absorption of nasally administration (12M/5F)	256(2)	1.0(2)	606(2!)	33(2)	69±11
Herbst et al., 2011	Cocaethylene formation following ethanol and cocaine administration by different routes (5M/1F)	302(2)	1.25(2)	736(2!)	50(2)	76±9
	Mean	**253**	**1.1**	**565**	**37.4**	
	± SD	**± 35**	**± 0.1**	**± 132**	**± 7.5**	
	Number of trials	4	4	4		
	Number of observations	32	32	32		

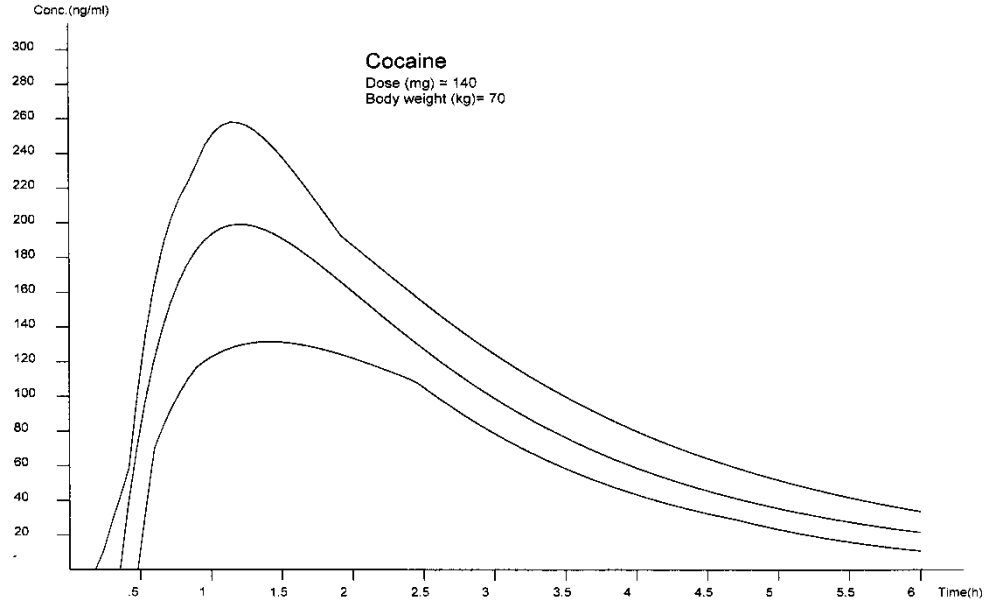


Figure 141: Plasma concentration-time curve of cocaine after oral administration.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	420	±	116	ng/mL
Ka:	2.14	±	0.74	h^{-1}
α:	0.177	±	0.042	h^{-1}
β:	0.578	±	0.090	h^{-1}
t_0:	0.355	±	0.152	h
V%:	96.6	±	5.2	%

derived from time-course of plasma concentrations

C_{max}:	253	±	35	199 (-258)	ng/mL
t_{max}:	1.1	±	0.1	1.26 (1.14-1.44)	h
$AUC_{o\text{-}oo}$:	565	±	132	602 (396-842)	ng*h/mL
B:	41	±	7	37.4 ± 7.5	%
V_β:				2.67 ± 1.02	L/kg

7.6.2 Khat alkaloids

Application: The stimulating effect when chewing leaves of the Khat plant (Catha edulis Forsk.) is used particularly in East Africa and on the Arabian Peninsula, but it must be assumed that migrants from these areas maintain their habits (Nencini et al., 1986, 1989). The subjective effects from Khat chewing were studied in 14 male Somali. Euphoria, improved intellectual efficiency and alertness were observed in 10 of these subjects, but 4 volunteers felt only dysphoria and mild sedation. Blood pressure and pulse rate were increased in all the subjects studied (Nencini et al., 1986). The first from khat isolated and identified alkaloid was d-norpseudoephedrine (cathine) (Wolfes, 1930), and for a long time the effect of khat leaves was attributed to this agent, but could not be satisfactorily explained. Hodgkinson (1962) stated that no effect of khat is decribed which cannot be attributed to an amphetamine-like drug. The real principle of the fresh khat plant, S-(-)-α-aminopropiophenone (cathinone), was isolated at the United Nations Narcotics Laboratory (Szendrei, 1980) and is regarded since then as potent psychostimulant and a natural amphetamine producing amphetamine-like sympathomimetic subjective and objective effects (Kalix 1992).

Biotransformation: This was confirmed by Brenneisen et al. (1990) using through stereospecific synthesis obtained cathinone in a pharmacokinetic experiment. 6 healthy volunteers received 0.5 mg per kg body weight in gelatin capsules as hydrochloride. The observed increases of blood pressure and heart rate were concomitant with the course of cathinone levels in blood plasma. Additionally concentrations of the metabolite norephedrine were determined. Reduction of the keto group to an alcohol is the main step in the biotransformation of cathinone resulting in two diastereomeric phenylpropanolamines, R,S-(-)-norephedrine and S,S-(+)-norpseudoephedrine (Schorn and Steinegger, 1979). These substances are already present in the plant and are additionally formed in the body by a rapid biotransformation shown by two pharmacokinetic experiments with khat leaves, the content of which in terms of the quantities of the three active agents had been determined before (Widler et al., 1994; Toennes et al., 2003).

Evaluation of studies: From Table 134 it is apparent that the elimination half-life in the evaluated studies is averaged to less than 2 hours. The course of the plasma concentration-time curve can be explained by an one-compartment-model, because V% is above 90%. However, the absorption rate constant, lag time and t_{max} from the data of Brenneisen et al.(1990) were not included in the evaluation, since an ingestion of cathinone as a pure substance is accompanied with a significantly faster absorption than chewing of khat leaves. In the phenylpropanolamine

diastereomers (Figure 142 and Figure 143) overlap absorption and formation by enzymatic reduction of cathinone. Thus the increase in plasma curve is slowed comparing with a pure absorption phase and after 8 hours in the study of Brenneisen et al. (1990).the elimination phase is not yet reached. The pharmacokinetic data were therefore excluded from averaging. The elimination of cathinone metabolites is much slower than that of the parent compound (8-9 hours versus about 2 hours).

Table 134: Cathinone after chewing of khat leaves containing 50 mg cathinone/70 kg body weight (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg/70 kg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Brenneisen et al., 1990	Amphetamine-like effects in humans of the khat alkaloid cathinone (6M)	32±2.1	35	456(2!)	(0.465)	12.2(2!)	1.13(2!))	(0.071)	98.3(2!)
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	30±5	56	397(2!)	0.769(2!)	4.85(2!)	1.30(2!))	0.328(2!)	93.0(2!)
Halket et al., 1995	Plasma cathinone levels following chewing khat leaves (3M/2F)	21-30	56-70	102(1!)	0.568(2!)	5.13(2!)	3.22(2!)	0.407(2!)	96.1(2!)
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	26-57	44.2	153(2!)	0.805(2!)	3.85(2!)	1.95(2!)	0.714(2!)	99.2(2!)
	Mean ± SD			**324 ± 145**	**0.712 ± 0.104**	**6.83 ± 4.47**	**1.83 ± 0.84**	**0.457 ± 0.161**	**96.4 ± 2.4**
	Number of trials			4	3	4	4	3	4
	Number of observations			21	15	21	21	15	21

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Brenneisen et al., 1990	Amphetamine-like effectsin humans of the khat alkaloid cathinone (6M)	151(2)	(1.0)	574(2!))	-
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	99.0(2)	2.33(2)	481(2!))	-
Halket et al., 1995	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	67.0(1)	1.5(2)	417(1!)	50-75
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	61.6(2)	2.4 (2)	292(2!)	71.5±17.3
	Mean ± SD	**103 ± 37**	**2.07 ± 0.41**	**462 ± 105**	

Number of trials	4	3	4
Number of observations	21	15	21

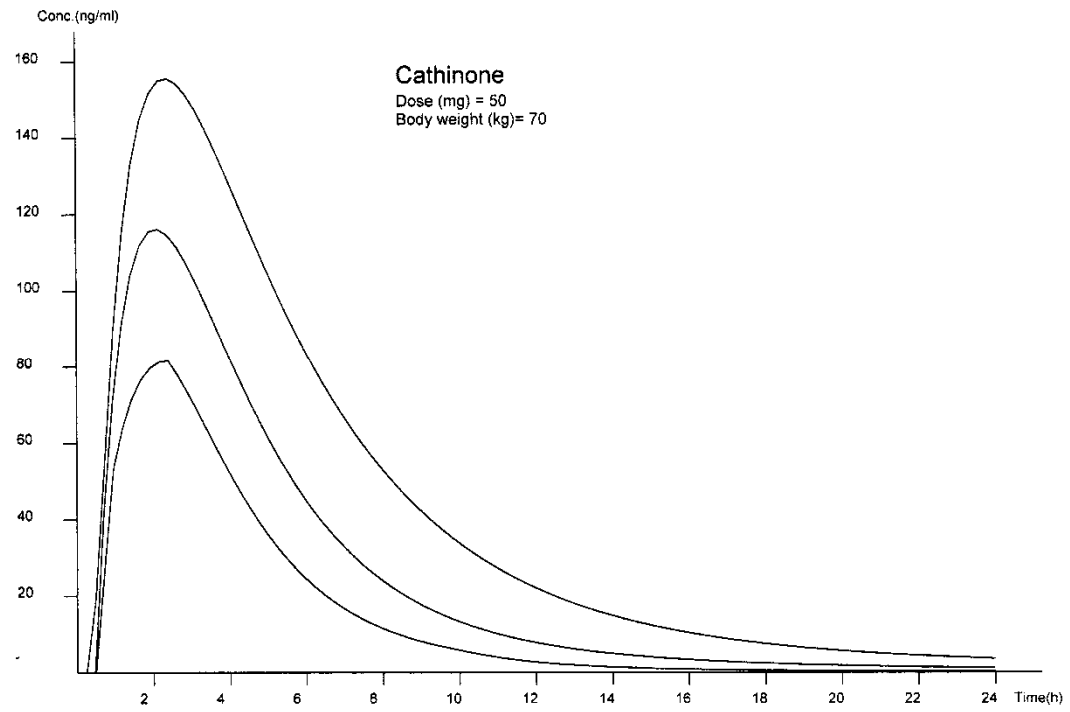


Figure 142: Plasma concentration-time curve of cathinone after chewing of khat leaves containing 50mg/70 kg body weight cathinone.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	324	±	145	ng/mL
Ka:	0.974	±	0.125	h^{-1}
α:	0.102	±	0.041	h^{-1}
β:	0.379	±	0.119	h^{-1}
t_0:	0.457	±	0.161	h
V%:	96.4	±	2.4	%

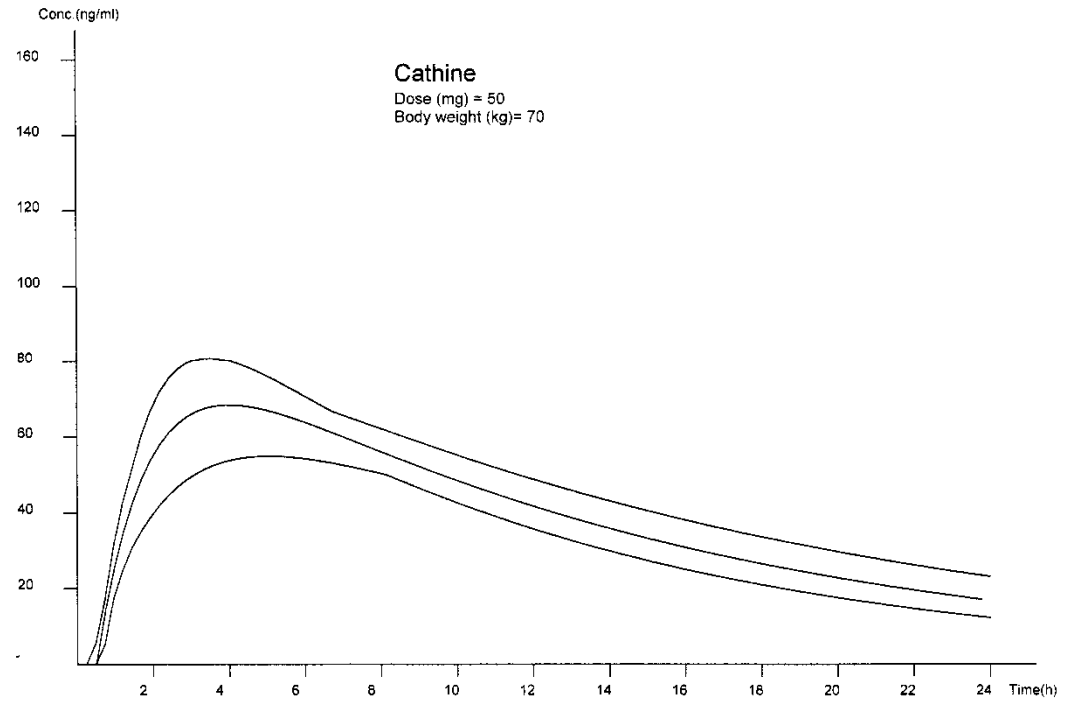
derived from time-course of plasma concentrations

C_{max}:	103	±	37	116 (82-156) ng/mL
t_{max}:	2.07	±	0.41	1.96 (-2.4) h
AUC_{o-oo}:	462	±	105	627 (370-1102) ng∗h/mL

Table 135: Cathine after chewing of khat leaves containing 50 mg cathinone and 36-42mg cathine/ 70 kg body weight (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg/70 kg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	30±5	56	79.4(2!)	0.650(2!)	8.77(2!)	10.4(2!))	0.629(2!)	96.1(2!)
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	26-57	44.2	114(2!)	1.45(2!)	3.81(2!)	6.09(2!))	0.291(2!)	90.0(2!)
	Mean ± SD			**93.2 ± 17.4**	**0.97 ± 0.40**	**6.8 ± 2.5**	**9.32 ± 1.93**	**0.494 ± 0.170**	**93.1 ± 3.1**
	Number of trials			2	2	2	2	2	2
	Number of observations			10	10	10	22	3	4

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	79.5(2)	2.67(2)	1156(2!))	-
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	80.6(2)	2.62(2)	900(2!))	71.5±17.3
	Mean ± SD	**79.9 ± 0.5**	**2.65 ± 0.03**	**1054 ± 129**	
	Number of trials (observations)	2 (10)	2 (10)	2 (10)	



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	93.2	±	17.4	ng/mL
Ka:	0.715	±	0.209	h^{-1}
α:	0.102	±	0.028	h^{-1}
β:	0.0744	±	0.0128	h^{-1}
t_0:	0.494	±	0.170	h
V%:	93.1	±	3.2	%

derived from time-course of plasma concentrations

C_{max}:	79.9	±	0.5	68.5 (54.9-80.9) ng/mL
t_{max}:	2.65	±	0.03	4.09 (3.36-5.04) h
AUC_{o-oo}:	1054	±	129	1179 (921-1509) ng*h/mL

Figure 143: Plasma concentration-time curve of cathine after chewing of khat leaves containing 50 mg cathinone and 36-42mg cathine /70kg body weight

Table 136: Norephedrine after chewing of khat leaves containing 50 mg cathinone and 18-23mg norephedrine/70 kg body weight (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg/70 kg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Brenneisen et al., 1990	Amphetamine-like effects in humans of the khat alkaloid cathinone (6M)	32±4.1	35 (HCl)	(136)	(0.307)	(6.93)	26.9(2!))	0.059(2!)	(99.2)
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	30±5	56	105(2!)	0.750(2!)	6.93(2!)	10.85(2!))	0.232(2!)	93.0(2!)
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	26-57	44.2	182(2!)	1.23(2!)	6.67(2!)	4.74(1!)	0.685(2!)	99.2(2!)
	Mean ± SD			**136 ± 39**	**0.942 ± 0.241**	**6.83 ± 0.13**	**8.4 ± 3.1**	**0.413 ± 0.228**	**96.8 ± 3.1**
	Number of trials								
	Number of observations			2	2	2	2	2	2
				10	10	10	10	10	10

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Brenneisen et al., 1990	Amphetamine-like effects in humans of the khat alkaloid cathinone (6M)	(133)	(2.0)	(5184)	-
Widler et al., 1994	Pharmacodynamics and pharmacokinetics of khat (6M)	98.2(2)	2.33(2)	1453(2!))	-
Toennes et al., 2003	Pharmacokinetics of cathinone, cathine and norephedrine after chewing of khat leaves (2M/2F)	81.7(2)	2.84(2)	803(2!))	71.5±17.3
	Mean ± SD	**91.6 ± 8.3**	**2.53 ± 0.26**	**1391 ± 327**	
	Number of trials	2	2	2	
	Number of observations	10	10	10	

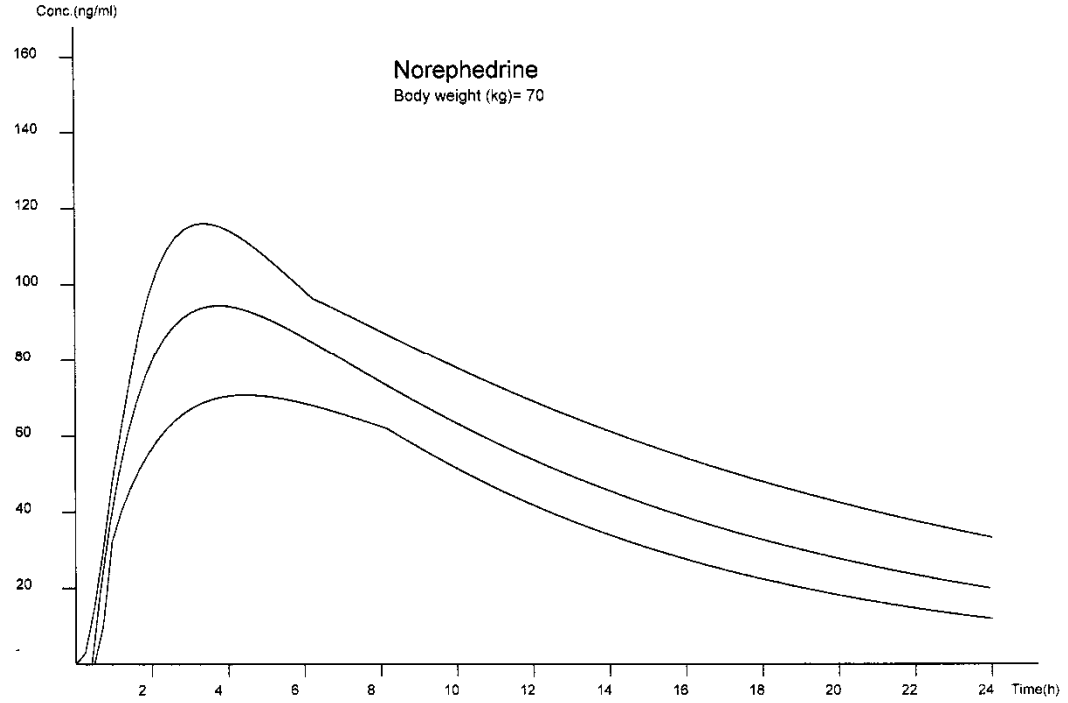


Figure 144: Plasma concentration-time curve of norephedrine after chewing khat leaves containing 50mg cathinone and 18-23mg norephedrine/70 kg body weight /kg body weight.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	136	±	39	ng/mL
Ka:	0.736	±	0.150	h^{-1}
α:	0.102	±	0.002	h^{-1}
β:	0.0825	±	0.0222	h^{-1}
t_0:	0.413	±	0.228	h
V%:	96.8	±	3.1	%

				derived from time-course of plasma concentrations
C_{max}:	91.6	±	8.3	94.4 (71-116) nmol/L
t_{max}:	2.53	±	0.26	3.7 (3.4-4.6) h
AUC_{o-oo}:	1193	±	327	1500 (1063-2167) nmol*h/L

7.6.3 3,4-Methylendioxy-methamphetamine (MDMA, ecstasy)

Application: MDMA is a widely used recreational drug and structurally similar to methamphetamine and mescaline. Thus stimulating effects are associated with entactogen properties such as euphoria, friendliness, closeness, and empathy (Cami et al., 2000). After single oral doses of 75 and 125 mg in eight men with experience in recreational use of MDMA, significantly increases of blood pressure, heart rate, and pupillary diameter were observed (Mas et al., 1999). At similar dosage of MDMA (1 and 1.6 mg/kg body weight) no significant effects on body temperature, respiratory rate, or oxygen saturation were found (Kolbrich et al., 2008). The authors suppose that temperature effects may result from interaction with environmental and subjective factors. The biochemical effectof MDMA consists in an altering of the neurotransmission in the brain by inducing serotonin, norepinephrine, and dopamine release and inhibiting the re-uptake of these neurotransmitters (White et al., 1996).

Biotransformation: The main biotransformation steps of MDMA are N-demethylation to 3,4-methylendioxy-amphetamine (MDA) and demethylenation to 3,4-dihydroxy-methamphetamine (HHMA). Demethylenation of MDA leads to 3,4-dihydroxy-amphetamine (HHA). Further metabolites are generated by O-methylation of the dihydroxy derivatives to the 3-methoxy-4-hydroxy compounds HMMA and HMA. Metabolites with phenolic groups are present in plasma and urine predominantly as glucuronides. The elimination rate is primarily dependent on the activity of the demethylenating system and not on that of N-demethylation. Only 8 to 9% of the MDMA appeared in plasma in form of MDA (Mas et al., 1999).

Different P450 isoenzymes catalyse the metabolism of MDMA, CYP3A4 N-demethylation and CYP2D6 demethylenation (de la Torre et al., 2004). CYP2D6 is highly polymorphic and the variable activity is the cause of different metabolizing rates. 7 to 10 % of European Caucasians are poor metabolizers with regard to this metabolic deficiency (de la Torre et al., 2005). Non-linear pharmacokinetics was detected, when de la Torre et al. (2000) compared maximal concentrations and AUC values after different doses of MDMA. Higher doses resulted in overproportionated C_{max} and AUC values. This effect was attributed to saturation or an inhibition of the demethylenation step, supported by the observation that concentrations of the metabolite HMMA did not increase at higher dosage (de la Torre et al., 2000). A controlled clinical trial of O´Mathúna et al. (2008) proved the theory in 15 male subjects, who received a dose of 1.5 mg/kg MDMA. The urinaty ratio of dextromethorphan and dextrorphan increased

almost 100-fold. CYP2D6 activity recovered after 10 days with a recovery half-life of 46.6 hours.

Fallon et al. (1999) investigated the enantioselective disposition of MDMA and its demethylated metabolite MDA. After oral administration of 40 mg racemic MDMA, the elimination half-life of R-MDMA was significantly longer than that of the S-enatiomer. Thus plasma concentrations and AUC values of the R-enatiomer exceeded those of the S-MDMA by far (5.8±2.2 h versus 3.6±0.9 h). Meyer et al. (2008) concluded from in vitro experiments with cytrochrome P450 isoenzymes, that the different pharmacokinetic properties of the MDMA enantiomers was caused by enantioselective metabolism by CYP2C19 and CYP2D6.

Interaction: The frequent combined consume of alcohol and MDMA gave cause to a study, in which 9 male healthy volunteers received oral doses of 100 mg MDMA + 0.8 g/kg ethanol and MDMA and ethanol alone. The MDMA-alcohol combination showed a 13% increase of plasma levels of MDMA, a 9-15% decrease of ethanol concentrations in blood, and induced longer lasting of euphoria than MDMA or alcohol alone (Hernández-Lopez et al., 2002). A pretreatment of volunteers with paroxetine, a selective serotonin reuptake inhibitor, revealed a significant influence on pharmacokinetics and pharmacodynamics of MDMA (Farré et al., 2007).

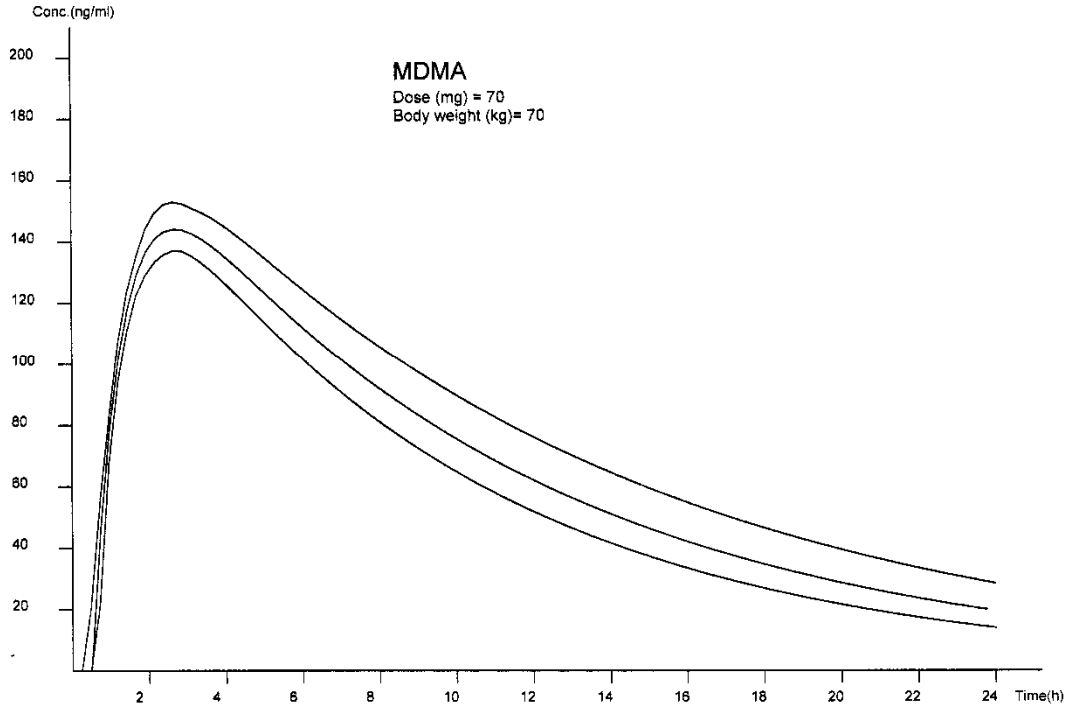
Evaluation of studies: Resulting from the non-linear pharmacokinetics of MDMA (de la Torre et al., 2000), two different plasma concentration-time curves (Table 137 & Table 138, Figure 145 & Figure 146) with doses of 1 and 1.6 mg/kg body weight were evaluated. Comparing the pharmacokinetics at these doses, an increase of the elimination half-life and above all an overproportional enlargement of the area under the plasma concentration-time curve is found. The maximal concentration of the demethylated metabolite MDA after oral intake of 1.6 mg/kg body weight MDMA amounts only to about 5% of the value of the parent substance and the ratio of the AUC values is 10 to 1. This means that MDA only negligably contributed to the efficacy of MDMA.

Table 137: 3,4-Methylenedioxymethamphetamine (MDMA) after oral administration of 70 mg/70 kg body weight (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M) (8M)	21-30	75	128(2!)	0.530(2!)	1.58(2!)	9.04(2!)	0.400(2!)	69.8(2!)
de la Torre et al., 2000	Non-linear pharmacokinetics of MDMA (1)	21-31	50	134(1!)	0.598(2!)	6.80(2!)	5.73(2!)	0.286(2!)	86.1(2!)
«	(1)	21-31	100	176(1!)	0.734(2!)	9.12(2!)	6.09(2!)	0.441(2!)	96.9(2!)
Samyn et al., 2002	+(oral fluid and sweat wipe concentrations) (8M/4F)	21-30	75	193(1!)	0.480(2!)	49.5	8.13(2!)	0.656(2!)	93.4(2!)
Hernández-Lopez et al., 2002	MDMA and alcohol interaction (9)	19-36	100	-	-	-	-	-	-
Farré et al., 2004	repeated dose administration (9M)	21-33	100	170(2!)	0.612(2!)	0.898(2!)	5.64(2!)	0.721(2!)	82.0(2!)
Farré et al., 2007	interaction of MDMA and paroxetine (12M)	19-34	100	-	-	-	7.88(2!)	-	-
Kolbrich et al., 2008	controlled oral administration (10M/7F)	21.5±2.5	1 mg/kg	200(2!)	0.561(2!)	1.40(2!)	6.59(2!)	0.398(2!)	96.1(2!)
Kolbrich et al., 2008a	physiological and subjective responses (6M/2F)	21.1±0.8	1 mg/kg	209(2!)	0.644(2!)	5.92(2!)	5.73(2!)	0.430(2!)	99.6(2!)
Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	18-24	1 mg/kg	144(2!)	0.703(2!)	2.52(2!)	9.00(2!)	0.426(2!)	86.8(2!)
	Mean ± SD			**176 ± 29**	**0.559 ± 0.056**	**3.79 ± 3.0**	**7.35 ± 1.25**	**0.497 ± 0.132**	**89.4 ± 9.2**
	Number of trials			7	7	7	7	7	7
	Number of observations			52	52	52	52	52	52

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng∗h/mL)	G (kg)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M)	130(2)	2.2(2)	1648(2!)	74.4

de la Torre et al., 2000	Non-linear pharmacokinetics of MDMA (1)	112(1)	3.0 (2)	1183(1)	-
«	(1)	132(1)	2.0 (2)	1424(1!)	66-93
Samyn et al., 2002	+(oral fluid and sweat wipe concentrations) (8M/4F)	166(1)	3.0 (2)	2908(1!)	66-83
Hernández-Lopez et al., 2002	MDMA and alcohol interaction (9)	156(1)	1.5(2)	-	67.4
Farré et al., 2004	repeated dose administration.(9M)	132(2)	2.0(2)	1249(2!)	73.3
Farré et al., 2007	interaction of MDMA and paroxetine (12M)	151(2)	1.5(2)	1502(2!)	71.0
Kolbrich et al., 2008	controlled oral administration (10M/7F)	167(2)	2.4(2)	1745(2!)	76.7±17.8
Kolbrich et al., 2008a	physiological and subjective responses (6M/2F)	142(2)	2.25(2)	1532(2!)	72.2±7.7
Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	147(2)	2.25(2)	1813(2!)	-
	Mean ± SD	**150 ± 14**	**2.2 ± 0.5**	**1706 ± 409**	
	Number of trials	8	8	7	
	Number of observations	62	62	52	



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	179	±	29	ng/mL
Ka:	1.24	±	0.11	h^{-1}
α:	0.183	±	0.081	h^{-1}
β:	0.0943	±	0.0137	h^{-1}
t_0:	0.497	±	0.132	h
V%:	89.4	±	9.2	%

				derived from time-course of plasma concentrations	
C_{max}:	150	±	14	144 (137-153)	ng/mL
t_{max}:	2.2	±	0.5	2.6 (2.6-2.6)	h
AUC_{o-oo}:	1706	±	409	1819 (1538-2241)	ng_*h/mL

Figure 145: Plasma concentration-time curve of MDMA after oral administration of 70 mg/70 kg body weight.

Table 138: 3,4-Methylenedioxymethamphetamine (MDMA)after oral administration of 112 mg/70 kg body weight (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M)	21-30	125	229(2!)	0.595(2!)	1.45(2!)	9.48(2!)	0.437(2!)	65.4(2!)
Ortuño et al., 1999	identification of MDMA and its metabolites by GC with N-P-detection (1)	-	125	265(1!)	0.428(2!)	6.13(2!)	7.96(2!)	0.712(2!)	99.6(2!)
de la Torre et al., 2000	Non-linear pharmacokinetics of MDMA (1)	21-31	150	308(1!)	0.168(2!)	3.30(2!)	11.3(2!)	0.469(2!)	93.0(2!)
Kolbrich et al., 2008	controlled oral administration (10M/7F)	21.5±2.5	1.6 mg/kg	327(2!)	0.662(2!)	1.05(2!)	7.84(2!)	0.363(2!)	69.2(2!)
Kolbrich et al., 2008a	(physiological and subjective responses (6M/2F)6M/2F)	21.1±0.8	1.6 mg/kg	341(2!)	0.522(2!)	3.19(2!)	8.20(2!)	0.381(2!)	96.5(2!)
Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	18-24	1.6 mg/kg	294(2!)	0.703(2!)	4.85(2!)	8.20(2!)	0.150(2!)	93.0(2!)
	Mean ± SD			**304 ± 40**	**0.616 ± 0.098**	**2.46 ± 1.60**	**8.36 ± 0.74**	**0.347 ± 0.115**	**79.6 ± 13.5**
	Number of trials			6	6	6	6	6	6
	Number of observations			43	43	43	43	43	43

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M)	225(2)	2.4(2)	3086(2!)	74.4
Ortuño et al., 1999	identification of MDMA and its metabolites by GC with N-P-detection (1)	205(1)	2.0 (2)	2488(1!)	-
de la Torre et al., 2000	Non-linear pharmacokinetics of MDMA(1)	330(1)	1.5 (2)	3462(2!)	66-83
Kolbrich et al., 2008	controlled oral administration (10M/7F)	301(2)	2.4(2)	5015(1!)	76.7±17.8
Kolbrich et al., 2008a	physiological and subjective responses (6M/2F)	283(2)	2.5(2)	3811(2!)	72.2±7.7

Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	255(2)	2.4(2)	3307(2!)	66±10
	Mean **± SD**	**273** **± 30**	**2.4** **± 0.2**	**3431** **± 305**	
	Number of trials	6	6	6	
	Number of observations	43	43	43	

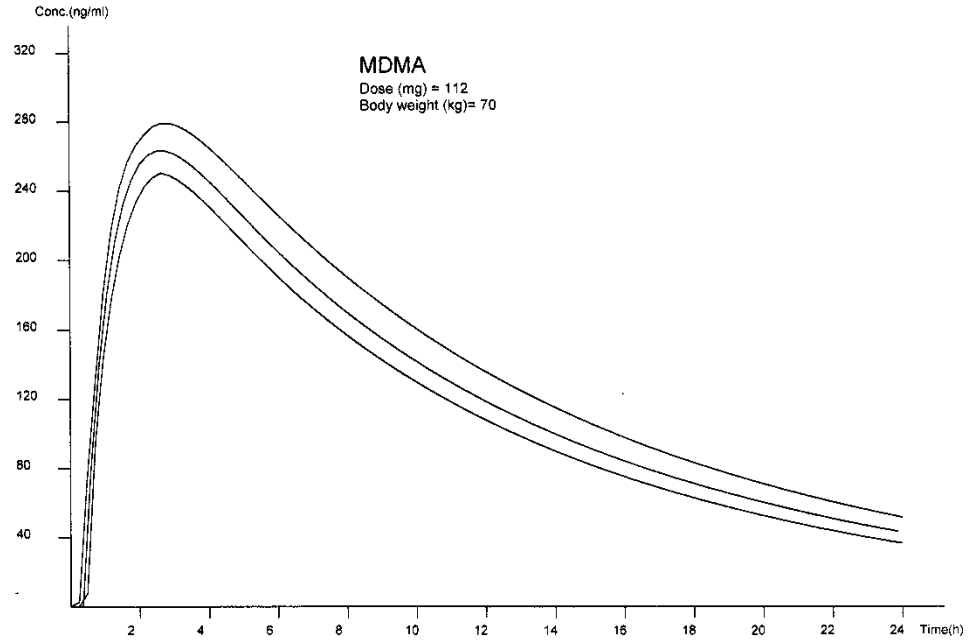


Figure 146: Plasma concentration-time curve of MDMA after oral administration of 112 mg MDMA/kg body weight.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	304	±	40	ng/mL
Ka:	1.13	±	0.16	h^{-1}
α:	0.282	±	0.111	h^{-1}
β:	0.0829	±	0.0067	h^{-1}
t_0:	0.347	±	0.115	h
V%:	79.6	±	13.5	%

				derived from time-course of plasma concentrations
C_{max}:	273	±	30	263 (251-279) ng/mL
t_{max}:	2.4	±	0.2	2.7 (2.6-2.9) h
AUC_{o-oo}:	3431	±	305	3602 (3225-4127) ng_*h/mL

Table 139: 3,4-Methylenedioxyamphetqmine (MDA)after oral administration of 112 mg/70 kg body weight MDMA (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M)	21-30	75	18.7(2!)	2.06(2!)	2.78(2!)	9.97(2!)	0.377(2!)	49.2(2!)
«	(8M)	21-30	125	15.8(2!)	1.73(2!)	10.8(2!)	16.7(2!)	0.377(2!)	93.0(2!)
Ortuño et al., 1999	identification of MDMA and its metabolites by GC with N-P-detection (1)	-	125	16.3(1!)	1.50(2!)	4.42(2!)	13.6(2!)	0.700(2!)	92.3(2!)
Farré et al., 2004	repeated dose administration (9M)	21-33	100	16.3(2!)	1.16(2!)	1.34(2!)	11.8(2!)	0.439(2!)	65.6(2!)
Kolbrich et al., 2008	controlled oral administration (10M/7F)	21.5±2.5	1.0 mg/kg	45.8(2!)	3.43(2!)	5.06(2!)	7.59(2!)	0.016(2!)	96.1(2!)
“	(10M/7F)	21.5±2.5	1.6 mg/kg	24.5(2!)	2.57(2!)	3.15(2!)	12.1(2!)	0.289(2!)	69.2(2!)
Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	18-24	1.6 mg/kg	13.1(2!)	0.667(2!)	6.93(2!)	27.1(2!)	0.101(2!)	96.1(2!)
	Mean ± SD			**25.5 ± 12.3**	**2.18 ± 0.95**	**4.74 ± 2.75**	**13.2 ± 6.0**	**0.243 ± 0.168**	**79.6 ± 16.9**
	Number of trials			7	7	7	7	7	7
	Number of observations			69	69	69	69	69	69

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Mas et al., 1999	+(cardiovascular and neuroendocrine effects) (8M)	12.4(2)	5.1(2)	234(2!)	74.4
«	(8M)	13.1(2)	7.1 (2)	356(2!)	74.4
Ortuño et al., 1999	identification of MDMA and its metabolites by GC with N-P-detection (1)	11.6(1)	6.0 (2)	288(1!)	-
Farré et al., 2004	repeated dose administration (9M)	10.7(2)	5.0(2)	250(2!)	73.3
Kolbrich et al., 2008	controlled oral administration (10M/7F)	13.4(2)	7.5(2)	279(2!)	76.7±17.8
“	(10M/7F)	13.8(2)	7.6(2)	316(2!)	76.7±17.8

Mueller et al., 2009	Direct comparison of MDMA disposition and metabolism in squirrel monkeys and humans (7M/2F)	13.3(2)	4.0(2)	503(2!)	**-**
	Mean **± SD**	**13.0** **± 1.0**	**6.4** **±1.4**	**318** **± 81**	
	Number of trials	7	7	7	
	Number of observations	69	69	69	

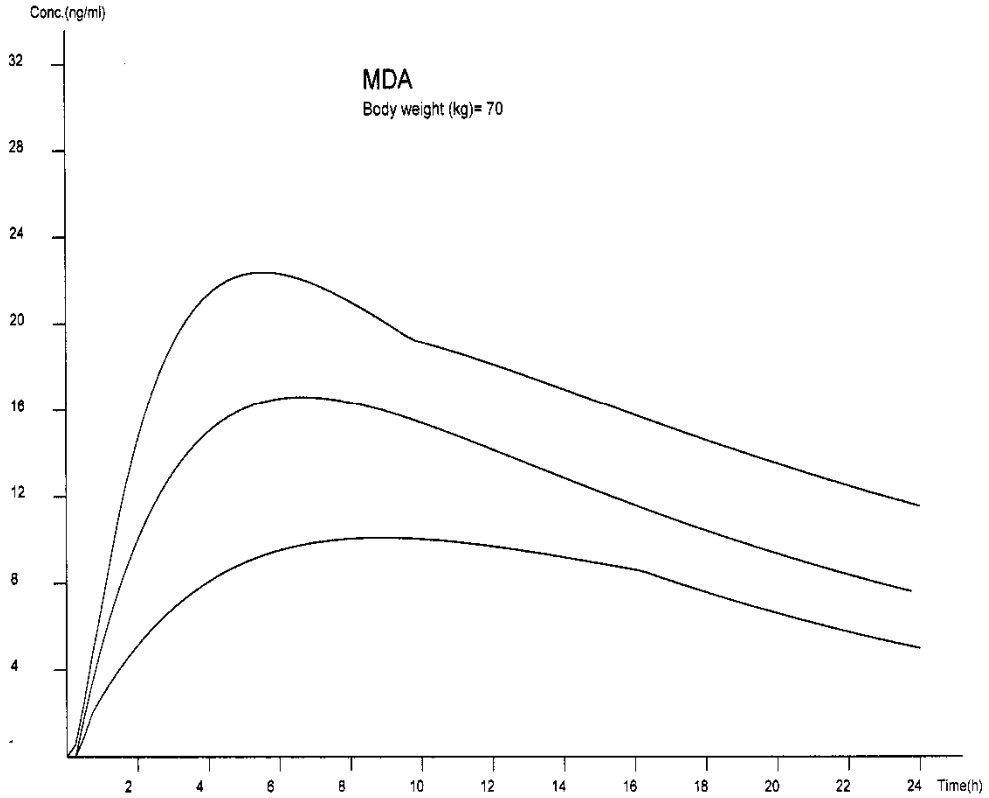


Figure 147: Plasma concentration-time curve of MDA after oral administration of 112 mg/70 kg body weight MDMA.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	25.5	±	12.3	ng/mL
Ka:	0.318	±	0.097	h^{-1}
α:	0.146	±	0.054	h^{-1}
β:	0.0525	±	0.0164	h^{-1}
t_0:	0.243	±	0.0168	h
V%:	79.6	±	16.9	%

derived from time-course of plasma concentrations

C_{max}:	13.0	±	1.0	16.6 (10-22) ng/mL
t_{max}:	6.4	±	1.4	6.5 (5.5-8.9) h
AUC_{o-oo}:	318	±	81	430 (259-700) ng*h/mL

7.6.4 Methamphetamine

Application: The chiral structure of methamphetamine (MA) is of essential importance, because the two enantiomers differ markedly in their pharmacological activity. S-(+)-MA (dextrorotatory), also called d-MA, is abused in form of its hydrochloride as “ice” by smoking (Cook et al., 1993), by nasal or by oral intake and is a powerful CNS stimulating agent with a high potential for abuse (Huestis and Cone, 2007). Against that R-(-)-MA (levorotatory), also called l-MA, is available in prescription and non-prescription medications such as a nasal inhaler decongestant product. The effects of 0.25 mg/kg l-MA were similar to those of placebo. At high doses, l-MA intoxication approached to that of d-MA (Mendelson et al., 2006).

Detection of the d-enantiomer or a mixture of the d- and l-enatiomer clearly establishes the use of a controlled substance (Cody and Schwarzhoff, 1993), but it must be taken into account that methamphetamine may originate from drugs, which are precursors of MA such as Benzphetamine, Deprenyl, Dimethylamphetamine, Famprofazone, Fencamine, and Furfenorex (Musshoff, 2000) A method for estimating the intake of abused MA using an oral dose of deuterated l-MA as biomarker is described by Li et al. (2010). The bioavailability of MA is high, 79 % after intranasal administration and 67 % of the estimated delivered dose after smoking (Harris et al., 2003). In an experiment of Cook et al. (1993), the bioavailability of smoked MA was 90.3±10.4 %. The oral bioavailability from this study and a previous one was 67.2±3.1 %. The V_β value (volume of distribution in the elimination phase) was 3.24±0.36 for the smoked dose and 3.73±0.59 for the intravenous dose (Cook et al., 1993).

Biotransformation: Significant amounts of methamphetamine are excreted unchanged in urine. After a smoked dose of 21.8 mg S-(+)-MA the percentage was 37%, after injection of 15.5 mg the excreted MA amounted to 45 % (Cook et al., 1993). The demethylated product of MA, amphetamine (AMP), appeared in plasma with a rate of 14-17% calculated from the AUC values of MA and AMP. The excreted percentage in urine was only 7 %. of the dose (Cook et al., 1993). Investigations of Li et al. (2010) revealed that the N-demethylation is highly stereoselective. 7 % of the dose converted to S-(-)-AMP versus 2 % to the R-(+)-AMP. A major part than by N-demethylation is transformed to the p-hydroxy compound with minor stereoselectivity (8-11 %), in the case of AMP the amount of p-OH-AMP was 2-7 % (Li et al., 2010). Further metabolites are phenylacetone, norephedrine and p-hydroxynorephedrine (Schepers et al., 2003). Excretion of the metabolites containing aromatic hydroxyl groups occur predominantly as glucuronides.

Interaction: Interactions of amphetamine and related substances are reviewed by de la Torre et al. (2004a). Combination of MA and ethanol did not alter the pharmacokinetics of methamphetamine, but the subjective effects of ethanol were diminished and the cardiac work increased (Mendelson et al., 1995).

Evaluation of studies: In two studies, that of Schepers et al. (2003) and that of Huestis and Cone (2007), was used a substained release formulation for their pharmacokinetic trials. These were evaluated separately from the other studies, because some pharmacokinetic parameters (Ka, t_0, C_{max}, and t_{max}) are affected by the drug formulation. Thus the absorption half-life (1.62 h) after taking a sustained release tablet of methamphetamine is twice as long as after an intake of an immediate-release formulation (0.85 h) (Table 141, Table 142 and Figure 149, Figure 150). Still more rapidly proceeds the absorption of MA by smoking (Table 140 and Figure 148). The elimination half-lifes are in conformance (9.95 – 12.2 h). Due to relatively low concentrations, amphetamine contributes only marginally to the effects of methamphetamine (Table 143 and Figure 151).

Table 140: Methamphetamine after intravenous administration or by smoking 22 mg/70kg body weight methamphetamine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Perez-Reyes et al., 1991a	+ (clinical effects of methamphetamine vapor inhalation (6M)	26.7±1.7	22	68.3(2!)	0.272(2!)	6.13(2!)	11.9(2!)	0.002(2!)	99.6(2!)
Cook et al., 1993	Intravenous administration (6M)	26.7±1.7	15.45	-	-	-	13.1(2)	-	-
«	and smoking of S-(+)methamphetamine hydrochloride (6M)	26.7±1.7	21.8	-	-	-	11.8(2)	-	-
Mendelson et al., 1995	+ (intravenous methamphetamine and ethanol interactions. (7M/1F)	31.8±5.6	123	-	-	-	12.0(2)	-	-
	Mean ± SD			**68.3**	**0.272**	**6.13**	**12.2 ± 0.5**	**0.002**	**99.6**
	Number of trials			7	-	-	4	7	7
	Number of observations			52	-	-	26	52	52

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	V_β (L/kg)	B (%)	G (kg)
Perez-Reyes et al., 1991a	+ (clinical effects of methamphetamine vapor inhalation (6M)	56.6(2)±6.8	2.5(2)±0.5	1143(2!)		-	84.1±5.2
Cook et al., 1993	Intravenous administration (6M)	-	-	(1121)	3.73(2)		83.8±5.1
«	and smoking of S-(+)methamphetamine hydrochloride (6M)	-	-	1022(2)		91.2	83.8±5.1
Mendelson et al., 1995	+ (Methamphetamine and ethanol interactions. (7M/1F)	-	-	-	4.61(2)		76.9±10.8
	Mean ± SD	**56.6 ± 6.8**	**2.5 ± 0.5**	**1083 ± 62**	**4.23 ± 0.44**		
	Number of trials	-	-	2	2		
	Number of observations	-	-	12	14		

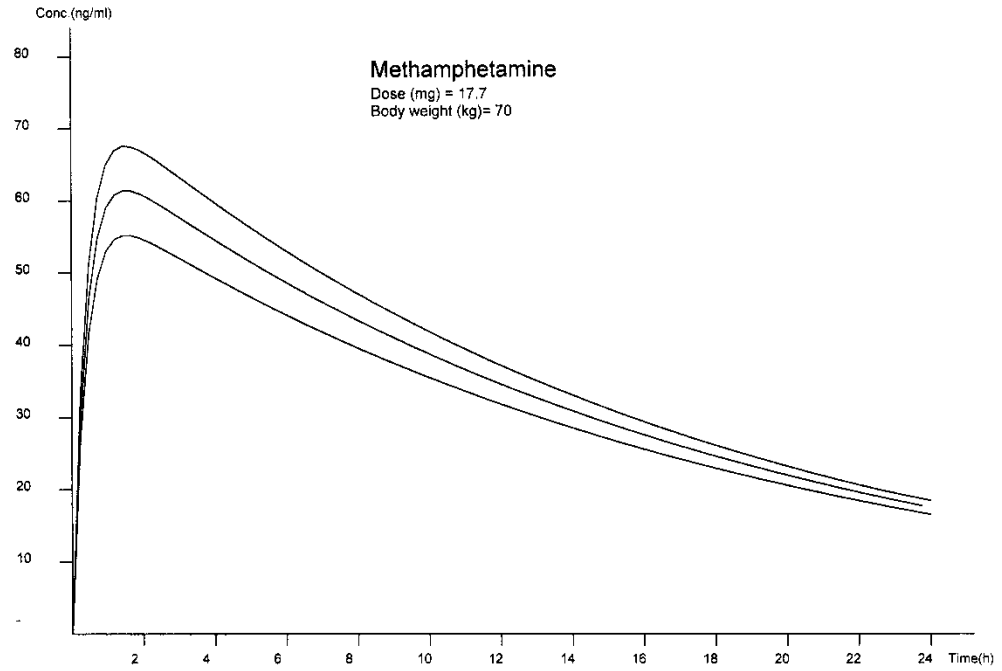


Figure 148: Plasma concentration-time curve of methamphetamine after smoking 22 mg/70 kg body weight methamphetamine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	68.3			ng/mL
Ka:	2.55			h^{-1}
α:	0.113			h^{-1}
β:	0.0568	±	0.0022	h^{-1}
t_0:	0.002			h
V%:	99.6			%

				derived from time-course of plasma concentrations
C_{max}:	56.6	±	6.8	61.4 (55.2-67.6) ng/mL
t_{max}:	2.5	±	0.5	1.5 (1.5-1.5) h
AUC_{o-oo}:	1083	±	62	1176 (1076-1277) ng*h/mL
V_β:				3.45 ± 0.40 L/kg
B:	91.2			91.3 %

Table 141: Methamphetamine after oral administration of 20 mg/70 kg body weight methamphetamine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Driscoll et al., 1971	+ (GC-determination of pentobarbital, solution (10)	-	12.5	30.3(1!)	(5.86)	4.62(2!)	21.3(1!)	(0.001)	92.3(2!)
Perez-Reyes et al., 1991	+ (clinical effects of daily (6M)	24.7±2	10	52.9(2!)	0.881(2!)	7.30(2!)	12.1(2!)	0.314(2!)	93.0(2!)
«	administration (6M)	24.7±2	10	53.9(2!)	0.828(2!)	5.55(2!)	12.1(2!)	0.337(2!)	93.0(2!)
“	(6M)	24.7±2	10	-	-	-	9.51(2!)	-	-
Cook et al., 1992	Effects of repeated daily dosing (6M)	17-32	9.1	64.8(2)	0.874(2)	-	8.46(2)	0.547(2)	/100)
	(6M)	17-32	18.2	54.1(2)	0.632(2)	-	11.5(2)	0.531(2)	(100)
Shapell et al., 1996	Chronopharmacokinetics (5M) Day session	23-29	30	68.0(2)	0.845(2)	-	9.11(2)	0.88(2)	(100)
“	chronopharmacodynamics (5M) night session	23-29	30	52.0(2)	1.10(2)	-	10.8(2)	0.93(2)	(100)
	Mean ± SD			**54.0 ± 10.8**	**0.853 ± 0.135**	**5.60 ± 1.1**	**11.7 ± 3.6**	**0.571 ± 0.236**	**92.7 ± 0.4**
	Number of trials			7	6	3	8	7	7
	Number of observations			44	34	22	50	44	44

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Driscoll et al., 1971	+ (GC-determination of pentobarbital, solution (10)	32.3(1)	(2.0)	940(1!)	-
Perez-Reyes et al., 1991	+ (clinical effects of daily (6M)	44.2(2)	3.0(2)	888(2!)	72.6±1.1
«	administration (6M)	45.8(2)	3.5(2)	907(2)	72.6±1.1
“	(6M)	-	-	-	72.6±1.1
Cook et al., 1992	Effects of repeated daily dosing (6M)	45.3(2)	3.6(2)	704(2)	73.5±2.9
“	(6M)	42.5(2)	3.23(2)	754(2)	73.5±2.9

Shapell et al., 1996	Chronopharmacokinetics (5M) Day session	62.7(2)	3.6(2)	809(2)
"	chronopharmacodynamics (5M) night session	40.2(2)	4.85(2)	713(2)
	Mean **± SD**	**44.7** **± 8.1**	**3.6** **± 0.6**	**816** **± 90**
	Number of trials	7	6	7
	Number of observations	44	34	44

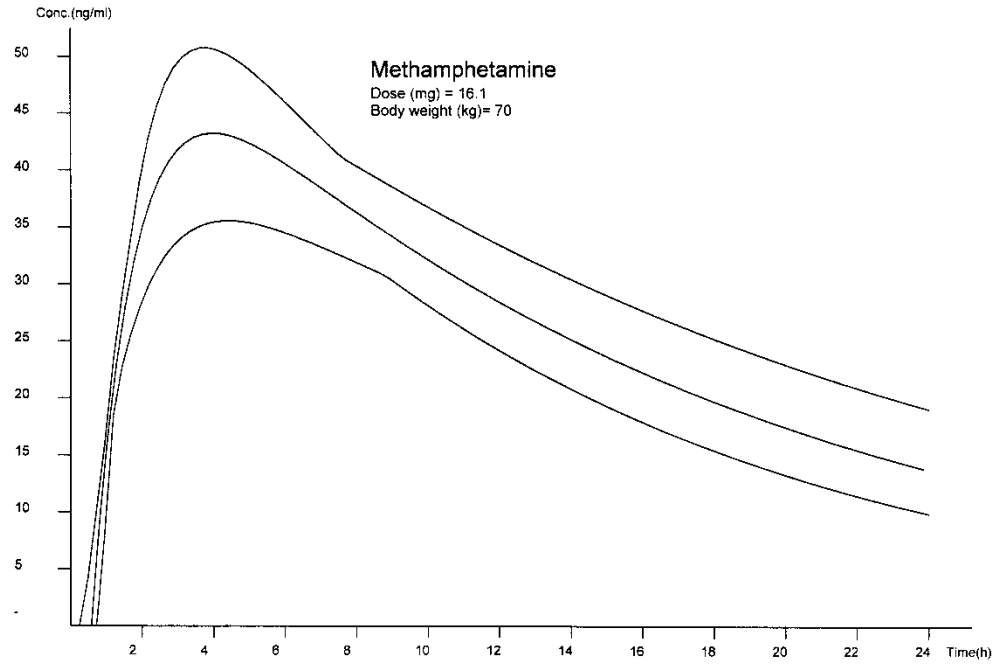


Figure 149: Plasma concentration-time curve of methamphetamine after oral administration of 20 mg/70 kg body weight methamphetamine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	54.0	±	10.8	ng/mL
Ka:	0.813	±	0.111	h^{-1}
α:	0.124	±	0.021	h^{-1}
β:	0.0592	±	0.0139	h^{-1}
t_0:	0.571	±	0.236	h
V%:	92.7	±	0.4	%

				derived from time-course of plasma concentrations
C_{max}:	44.7	±	8.1	43.2 (35.6-50.8) nmol/L
t_{max}:	3.6	±	0.6	3.9 (3.8-4.3) h
AUC_{o-oo}:	816	±	90	874 (665-1185) nmol*h/L

V_β: 4.23 ± 1.06 L/kg

B: 92 %

Table 142: Methamphetamine after oral administration of 20 mg 70/kg body weight substained released methamphetamine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Schepers et al., 2003	+ (pharmacokinetics in oral fluid (4M/3F)	26.7±1.7	10	67.0(2!)	1.35(2!)	0.92(2!)	8.69(2!)	0.223(2!)	73.8(2!)
«	(5)	26.7±1.7	20	54.1(2!)	1.76(2!)	1.35(2!)	10.0(2)	0.341(2!)	98.4(2!)
Huestis and Cone, 2007	+ (disposition in oral fluid (5)	26.7±1.7	10	51.3(2!)	1.92(2!)	4.75(2!)	11.6(2)	0.465(2!)	93.8(2!)
"	and urine (5)	31.8±5.6	20	52.5(2!)	1.56(2!)	7.70(2!)	10.0(2)	0.212(2!)	93.4(2!)
	Mean ± SD			**58.8 ± 7.1**	**1.62 ± 0.22**	**3.43 ± 2.78**	**9.95 ± 1.07**	**0.302 ± 0.102**	**88.4 ± 10.3**
	Number of trials			4	4	4	4	4	4
	Number of observations			22	22	22	22	22	22

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Schepers et al., 2003	+ (pharmacokinetics in oral fluid (4M/3F)	41.6(2)	5.4(2)	694(2!)	72.0±17.6
«	(5)	33.3(2)	7.5(2)	645(2!)	72.0±17.6
Huestis and Cone, 2007	+ (disposition in oral fluid (5)	32.4(1)	5.2(2)	760(1!)	-
"	and urine (5)	34.8(1)	7.5(2)	644(1!)	-
	Mean ± SD	**36.8 ± 4.1**	**6.3 ± 1.1**	**682 ± 40**	
	Number of trials	4	4	4	
	Number of observations	22	22	22	

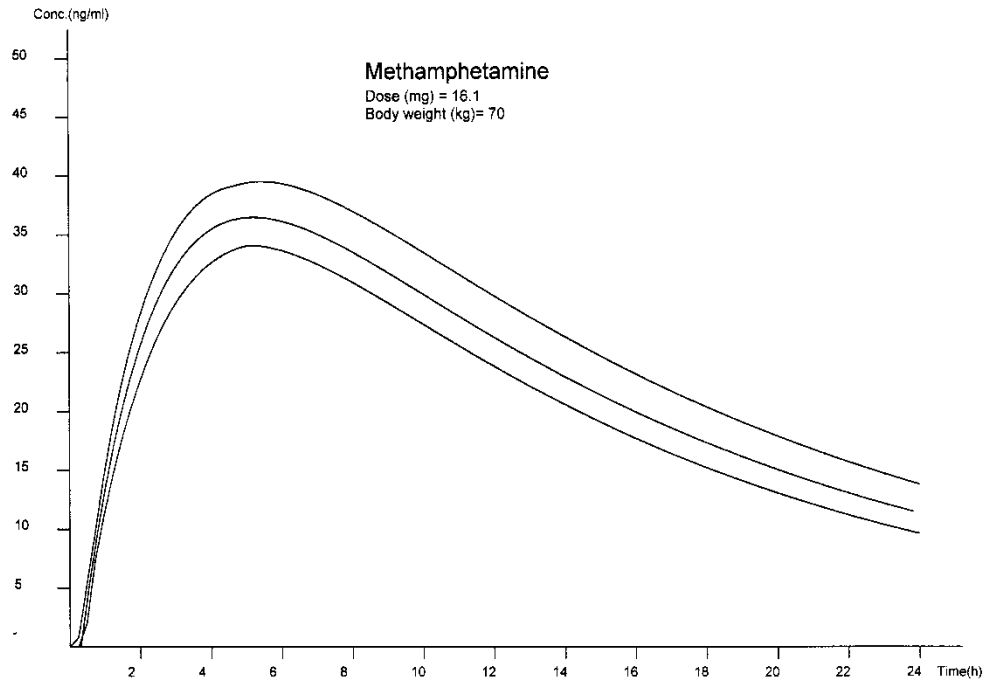


Figure 150: Plasma concentration-time curve after oral administration of 20 mg/70 kg body weight substained released methamphetamine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	58.8	±	7.1	ng/mL
Ka:	0.428	±	0.051	h^{-1}
α:	0.202	±	0.090	h^{-1}
β:	0.0697	±	0.0068	h^{-1}
t_0:	0.302	±	0.102	h
V%:	88.4	±	10.3%	

				derived from time-course of plasma concentrations	
C_{max}:	36.8	±	4.1	36.5 (34.1-39.5)	ng/mL
t_{max}:	6.3	±	1.1	5.1 (-5.5)	h
AUC_{o-oo}:	682	±	40	726 (635-852)	ng*h/mL

V_β: 4.23 ± 0.58 L/kg

B: 90.5 %

Table 143: Amphetamine from oral administration of 20 mg/70 kg body weight methamphetamine hydrochloride (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Cook et al., 1992	Effects of repeated daily dosing (6M)	19-32	9.1	5.08(2!)	3.19(2!)	13.9(2!)	31.1(2!)	0.472(2!)	96.9(2!)
«	(6M)	19-32	18.2	6.61(2!)	3.35(2!)	6.93(2!)	30.0(2!)	0.100(2!)	98.3(2!)
Schepers et al., 2003	+ (pharmacokinetics in oral fluid) (5)	35.3±4.2	10	10.8(2!)	1.51(2!)	3.17(2!)	13.4(2!)	0.028(2!)	93.8(2!)
"	substained release (5)	35.3±4.2	20	-	-	-	-	-	-
Huestis and Cone, 2007	+ (disposition in oral fluid (5)	-	10	10.6(1!)	4.78(2!)	17.8(2!)	12.5(2!)	1.57(2!)	74.9(2!)
«	and urine (5)	-	20	-	-	-	-	-	-
	Mean ± SD			**7.73 ± 2.49**	**3.21 ± 1.12**	**10.4 ± 5.6**	**22.5 ± 8.9**	**0.519 ± 0.602**	**91.6 ± 9.3**
	Number of trials			4	4	4	4	4	4
	Number of observations			22	22	22	22	22	22

Evaluated studies	**Data from comparative single dose studies**	**C_{max} (ng/mL)**	**t_{max} (h)**	**B (%)**	**AUC_{o-oo} (ng*h/mL)**	**G (kg)**
Cook et al., 1992	Effects of repeated daily dosing (6M)	3.66(2)	11.7(2)		207(2!)	72.5±2.9
"	(6M)	4.57(2)	11.7(2)		254(2!)	73.5±2.9
Schepers et al., 2003	+ (pharmacokinetics in oral fluid) (5)	9.70(2)	11.9(2)		186(2!)	72.0±17.6
"	substained release (5)	5.76(2)	14.3(2)		-	72.0±17.6
Huestis and Cone, 2007	+ (disposition in oral fluid (5)	5.6(1)	13.9(2)		185(1!)	-
«	and urine (5)	8.2(1)	15.9(2)		-	-
Li et al., 2010a	Stereoselectivity in the human metabolism of methamphetamine (12M)			7		
	Mean ± SD	**5.70 ± 2.18**	**13.1 ± 1.6**	**7**	**213.1 ± 29**	
	Number of trials	8	8		4	
	Number of observations	32	32		22	

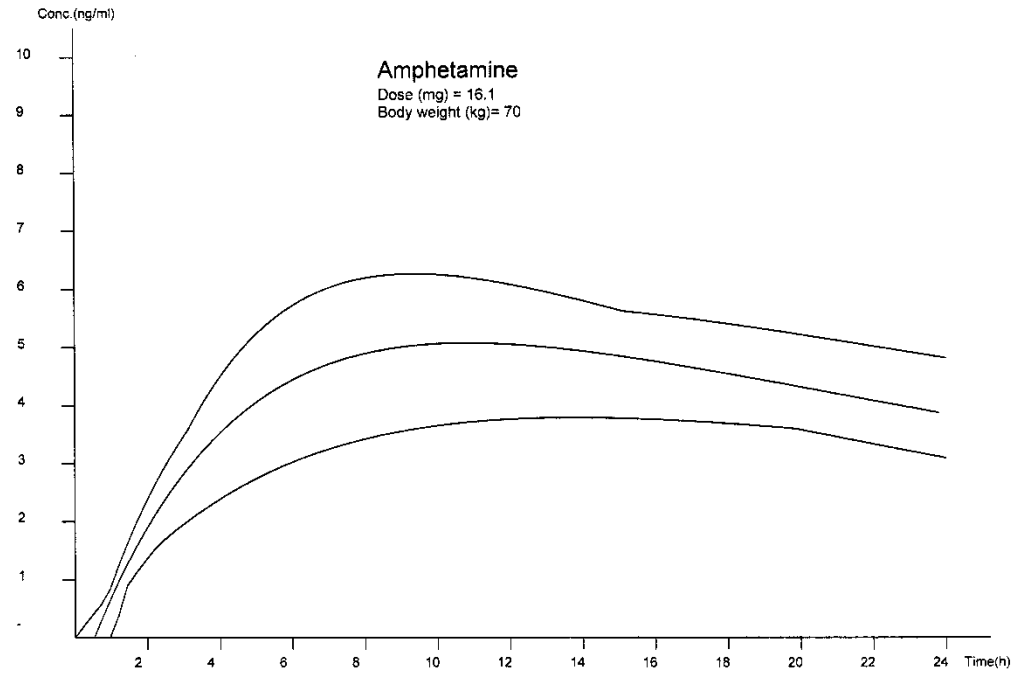


Figure 151: Plasma concentration-time curve of amphetamine from oral administration of 20 mg/70 kg body weight methamphetamine hydrochloride.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	7.73	±	2.49	ng/mL
Ka:	0.216	±	0.056	h^{-1}
α:	0.067	±	0.024	h^{-1}
β:	0.0308	±	0.0087	h^{-1}
t_0:	0.519	±	0.519	h
V%:	91.6	±	9.3%	

derived from time-course of plasma concentrations

C_{max}:	5.70	±	2.18	5.07 (3.8-6.3)	ng/mL
t_{max}:	13.1	±	1.6	10.7 (9.4-13.7)	h
AUC_{o-oo}:	213	±	29	222 (152-333)	ng*h/mL

V_β: 2.43 ± 1.15 L/kg

B: 7 %

7.6.5 Amphetamine

Application: Amphetamine is the prototype of a family of substances whose representatives are derived from phenethylamine. It is used mainly as sulphate. Medically it has an importance in the treatment of attention-deficit/hyperactivity disorder (ADHD). The abuse is based mainly on the psycho-stimulating effect, which manifests itself as euphoria and increased alertness. Energy and self-confidence are enhanced. Also appear peripheral stimulatory effects such as increase of blood pressure and pulse rate and pupil dilation. Amphetamine is used as racemate or as S-(+)-enantiomer, also called dextroamphetamine or d-amphetamine, with twice as strong effects as the racemate. S-(+)-amphetamine is considered to be a 3-4 times stronger stimulant than the R-(-)-enantiomer. Angrist et al. (1987) observed after oral administraton of 0.25 mg/kg d-amphetamine maximum cardiovascular effects at 1 hour and maximum behavioral and subjective effects 2 hours after intake of the drug. For treatment of ADHD there is used for once daily dosing MAS XR, an extended release formulation of a 3:1 ratio of d-amphetamine to l-amphetamine. The pharmacokinetic profiles of MAS XR 20, 40, and 60 mg were dose proportional for the two enatiomers and t_{max} ranged between 4.5 and 5.3 hours (Clausen et al., 2005).

Biotransformation: A high amount of the dose is excreted unchanged in urine. Without an artificial control of the pH, at doses of 5, 10, and 15 mg/70 kg body weight dextroamphetamine appeared in urine within 12 hours after administration (Evans et al., 1977). Because of the basicity and the renal excretion of amphetamine and related substances, the plasma half-life is dependent on the acidity of the urine. Wan et al. (1978) administered amphetamine as the racemic mixture and as (+)- and (-)-enantiomers under condition of urine acidification and alkalinization. (+)-Amphetamine was more rapidly eliminated than the (-)-enantiomer. The difference was maximal under basic urinary conditions. Excretion and pharmacokinetic parameters of amphetamine and related drugs are summarized in the review of de la Torre et al. (2004a). Metabolites are formed by hydroxylation in 3-position and at 4-position of the benzene ring yielding norephedrine, p-hydroxy-amphetamine and p-hydroxy-norephedrine. The majority of p-hydroxy derivatives are excreted conjugated with glucuronic acid (Shimosato et al., 1986). An extensive review on amphetamine metabolism has been published by Kraemer and Maurer (2002). It has to be taken into account that amphetamine may originate from methamphetamine, ethylamphetamine, Dimethylamphetamine or from drugs, which are precursors of amphetamine such as Amphetaminil, Clobenzorex, Fenethylline, Fenproporex, Mefenorex, Mesocarb, and others (Musshoff, 2000).

Interaction: Perez-Reyes et al. (1992) administered 0.09, 0.18 mg/kg dextroamphetamine in combination with 0.85 g/kg ethanol or placebo. The subjective ratings of ethanol intoxication were not decreased, but ethanol induced decrements in performance of the skills necessary to drive a car were compensated partially by dextroamphetamine.

Evaluation of studies: Table 144 presents pharmacokinetik studies with immediate-release formulations and doses between 10 and 40 mg D- or DL-amphetamine. The normalized single values of Cp0, C_{max}, and AUC show a good accordance providing evidence of a dose depending linearity. The averaged V% is 93.5 % showing that the course of the plasma concentration-time curve (Figure 152) can also be described by a one compartment model and is not influenced by the α value. Table 145 containes pharmacokinetic parameters of studies using extended release formulations of amphetamine. Doses are between 7.5 and 45 mg D-amphetamine (in brackets the sum of D- and L-enantiomer with a ratio of 3 to 1). Cp0, C_{max}, and AUC values show only small deviations indicating a linear dependence on the doses. Comparing Figure 152 and Figure 153, the different courses of the two curves are obvious.

Table 144: Amphetamine from oral administration of 20 mg/70 kg body weight amphetamine (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Angrist et al., 1987	Clinical effects of D-amphetamine (4M/3F)	29-46	17.5	48.2(1!)	0.837(2!)	13.9(2!)	12.3(2!)	0.137(2!)	87.3(2!)
«	(4M/3F)	29-46	17.5	54.3(1!)	0.672(2!)	2.73(2!)	10.5(2!)	0.238(2!)	87.5(2!)
Brauer et al., 1996	+ (acute tolerance to subjective but not cardiovascular effects of D-amphetamine) (6M)	22-31	20	48.1(2!)	1.06(2!)	10.7(2!)	15.8(2!)	0.312(2!)	85.5(2!)
Wong et al., 1998	D-amphetamine and modafinil pharmacokinetics (24)	19-43	20	55.2(2!)	0.307(2!)	0.767(2!)	12.3(2!)	0.407(2!)	98.4(2!)
Mas et al., 1999	cardiovascular and neuroendocrine effects of DL-amphetamine and MDMA (8M)	21-30	10	38.5(2!)	0.495(2!)	18.2(2!)	15.0(2!)	0.256(2!)	96.5(2!)
Pizarro et al., 1999	Quantification of D,L-amphetamine (1M)	-	20	44.3(1!)	0.686(2!)	3.41(2!)	12.7(2!)	0.740(2!)	96.9(2!)
«	plasma concentrations by (1M)	-	20	30.5(1!)	0.172(2!)	7.15(2!)	17.7(2!)	0.321(2!)	84.8(2!)
«	GC-MS (1M)	-	30	-	-	-	-	-	-
«	(1M)	-	30	-	-	-	-	-	-
«	(1M)	-	35	-	-	-	-	-	-
«	(1M)	-	35	-	-	-	-	-	-
«	(11M)		40	36.2(1!)	0.515(2!)	3.89(2!)	14.7(2!)	0.256(2!)	93.0(2!)
	Mean ± SD			**48.9 ± 7.7**	**0.535 ± 0.244**	**6.12 ± 6.29**	**13.3 ± 1.7**	**0.311 ± 0.105**	**93.5 ± 5.0**
	Number of trials			6	6	6	6	6	6
	Number of observations			65	65	65	65	65	65

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	G (kg)
Angrist et al., 1987	Clinical effects of D-amphetamine (4M/3F)	40.3(1)	3.0(2)	928(1!)	-
"	(4M/3F)	45.3(1)	3.0(2)	795(1!)	-
Brauer et al., 1996	+ (acute tolerance to subjective but not cardiovascular effects of D-amphetamine) (6M)	42.3(2)	4.0(2)	1134(2!)	74.2
Wong et al., 1998	D-amphetamine and modafinil pharmacokinetics (24)	52.3(2)	2.6(2)	947(2!)	74.1
Mas et al., 1999	cardiovascular and neuroendocrine effects of DL-amphetamine and MDMA (8M)	34.7(2)	2.0(2)	842(1!)	74.4
Pizarro et al., 1999	Quantification of D,L-amphetamine (1M)	36.6(1)	3.0(2)	773(1!)	-
«	plasma concentrations by (1M)	38.8(1)	2.0(2)	825(1!)	
«	GC-MS (1M)	38.2(1)	3.0(2)	527(1)	
«	(1M)	38.5(1)	2.0(2)	502(1)	
«	(1M)	36.3(1)	2.0(2)	470(1)	
«	(1M)	32.9(1)	2.0(2)	433(1)	
«	(11M)	34.6(1)	2.2(2)	752(1!)	
	Mean ± SD	**44.6 ± 7.6**	**2.65 ± 0.54**	**901 ± 133**	
	Number of trials	6	6	6	
	Number of observations	69	69	69	

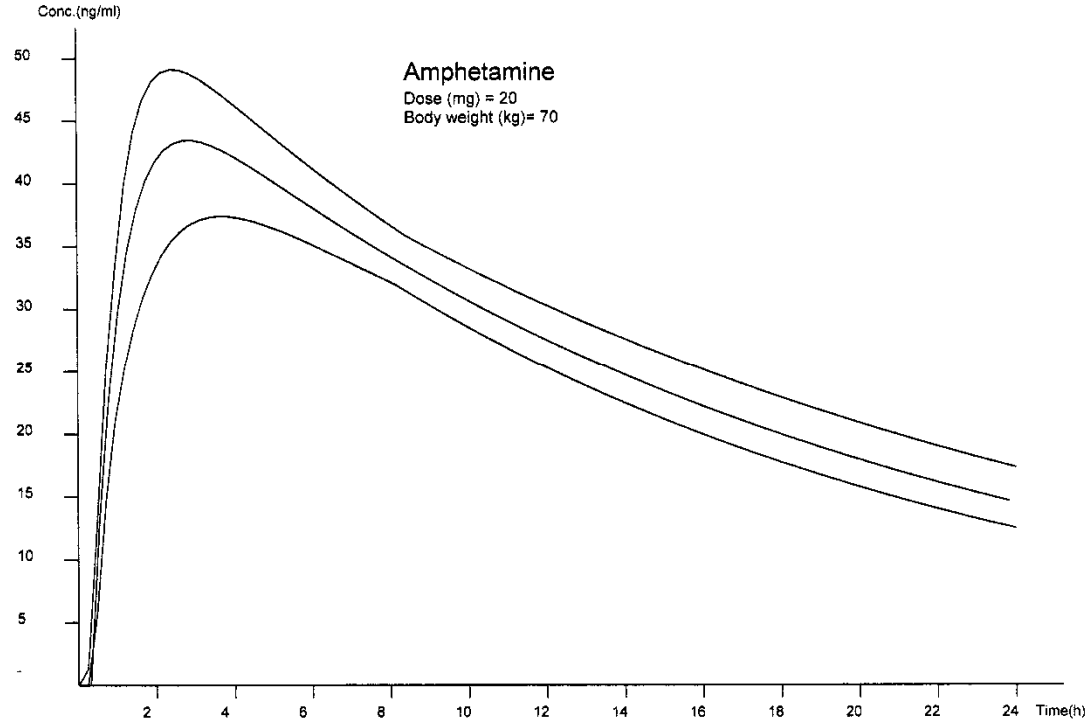


Figure 152: Plasma concentration-time curve of amphetamine from oral administration of 20 mg/70 kg body weight amphetamine.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	48.9	±	7.7	ng/mL
Ka:	1.30	±	0.41	h^{-1}
α:	0.113	±	0.057	h^{-1}
β:	0.0521	±	0.0059	h^{-1}
t_0:	0.311	±	0.105	h
V%:	93.5	±	5.0 %	

				derived from time-course of plasma concentration
C_{max}:	44.6	±	7.16	43.4 (37.4-49.1) ng/mL
t_{max}:	2.65	±	0.54	2.7 (2.4-3.6) h
AUC_{o-oo}:	901	±	133	928 (795-1101) ng*h/mL

V_β: (6.09 ± 1.14 L/kg)

B: (100 %)

Table 145: Amphetamine from oral administration of 20 mg/70 kg body weight D-amphetamine extended release (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	Age (years)	Dose (mg)	Cp0 (ng/mL)	$t_{½}$Ka (h)	$t_{½}\alpha$ (h)	$t_{½}\beta$ (h)	t_0 (h)	V% (%)
Clausen et al., 2005	MAS XR, extended release formulation (5M/6F)	22-46	45(60)	68.1(2!)	1.82(2!)	3.24(2!)	10.5(2!)	0.165(2!)	69.8(2!)
«	in adults (6M/6F)	22-46	30(40)	62.0(2!)	1.75(2!)	5.78(2!)	11.7(2!)	0.075(2!)	86.1(2!)
Kramer et al., 2005	Mixed amphetamine salts (15)	13-17	7.5(10)	-	-	-	10.8(2!)	-	-
«	extended release (15)	"	15(20)	-	-	-	11.0(2!)	-	-
«	in adolescents withADHD (15)	"	30(40)	-	-	-	11.4(2!)	-	-
«	(6)	"	15(20)	-	-	-	12.4(2!)	-	-
«	(6)	"	30(40)	-	-	-	12.0(2!)	-	-
«	(6)	"	45(60)	-	-	-	13.2(2!)	-	-
Ermer et al., 2007	Mixed amphetamine salts extended release (8M/12F)	21-50	28.1(37.5)	63.9(2!)	3.09(2!)	6.36(2!)	10.7(2!)	0.229(2!)	70.0(2!)
	Mean ± SD			**64.4 ± 2.3**	**2.39 ± 0.66**	**5.40 ± 1.30**	**11.3 ± 0.7**	**0.170 ± 0.065**	**74.4 ± 7.3**
	Number of trials			3	3	3	9	3	3
	Number of observations			43	43	43	106	43	43

Continuation of Table 145: Amphetamine from oral administration of 20 mg/70 kg body weight D-amphetamine extended release (absorption, distribution and elimination).

Evaluated studies	Data from comparative single dose studies	C_{max} (ng/mL)	t_{max} (h)	AUC_{o-oo} (ng*h/mL)	V_β/F (L)	G (kg)
Clausen et al., 2005	MAS XR, extended release formulation (5M/6F)	50.2(2)	4.5(2)	911(2!)	-	74.2
"	in adults (6M/6F)	48.0(2)	5.0(2)	945(2!)		74.2

Kramer et al., 2005	Mixed amphetamine salts (15)	49.1(1)	3.93(2)	936(1!)	337	<75
«	extended release (15)	45.5(1)	4.99(2)	919(1)	352	<75
«	in adolescents withADHD (15)	52.2(1)	5.00(2)	1070(1)	351	<75
«	(6)	38.9 > 49.8(1)korr.	5.00(2)	785 > 1004(1)korr.	457	>75
«	(6)	40.5 >51.8(1)korr.	4.49(2)	785 > 1004(1)korr.	443	>75
«	(6)	36.3 > 46.4(1)korr.	7.48(2)	889 > 1138(1)korr.	431	>75
Ermer et al., 2007	Mixed amphetamine salts extended release (8M/12F)	37.7(2!)	8.0(2!)	828(2!)	-	73.8
	Mean ± SD	**46.0 ± 5.4**	**5.5 ± 1.4**	**930 ± 84**	**3.47(<75 kg) 4.44(>75 kg)**	
	Number of trials	9	9	9		**-**
	Number of observations	106	106	106		

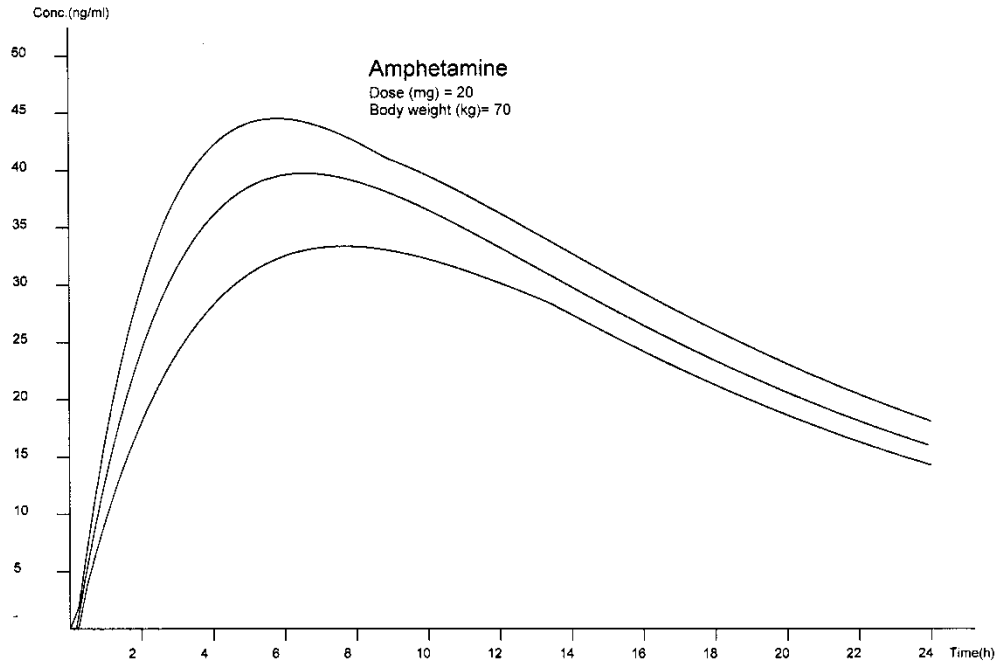


Figure 153: Plasma concentration-time curve of amphetamine from oral administration of 20 mg/70 kg body weight amphetamine extended release.

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	64.4	±	2.3	ng/mL
Ka:	0.290	±	0.063	h^{-1}
α:	0.128	±	0.025	h^{-1}
β:	0.0613	±	0.0035	h^{-1}
t_0:	0.170	±	0.065	h
V%:	74.4	±	7.3 %	

				derived from time-course of plasma concentrations
C_{max}:	46.0	±	5.4	39.7 (33.4-44.5) ng/mL
t_{max}:	5.5	±	1.4	6.5 (5.8-7.7) h
AUC_{o-oo}:	930	±	84	925 (797-1154) ng_*h/mL
V_β:				(5.63 ± 0.21) L/kg
B:				(100) %

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