Medicines and Driver Fitness - Findings from a Metaanalysis of Experimental Studies as Basic Information to Patients, Physicians and Experts

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ABSTRACT

Holding an enquiry into the topic 'medicines and driver fitness' sponsored by the Federal Highway Research Institute more than 1000 published experimental studies on performance following drug intake were gathered. By means of a metaanalytic approach important information of the studies were PC-extracted (among other things: number, age and sex of subjects, manner of treatment, time between drug intake and testing, tasks presented and the experimental findings) and analysed with the help of inferential statistics. Three examples will prove the benefit of this methodological approach: applied to diazepam detailed statements on kind, intensity and duration of impairment are given. A comparison between the alterations of some benzodiazepines assist the physicians in prescribing an optimum substance to drivers. The combination of blood concentration curves and time dependant curve of impairment can be a valuable tool to experts judging the danger of a medicine in terms of substance concentration.

INTRODUCTION

There exist a lot of experimental studies on medicines and performances related to driving containing a great variety of findings. Contrary to this extraordinary amount of information its exhaustion seems inadequate. On the one hand with respect to the scientific overall knowledge: comparative analyses of all studies of a specific drug or a group of drugs are conducted only by method of narrative reviews. To this end it is quite impossible to differentiate the interpretation of drug effects according to influencing factors such as dosage level, postingestion time of tests, gender and health status of subjects, quality criteria of the study design and further issues. On the other hand the exhaustion of information seems not adequate with respect to the transfer of results to customers: doctors and patients only receive very general information concerning warnings.

In order to overcome these shortcomings we collected experimental studies, encoded and anylysed the essential information and made quantitative evaluations conceiving the above mentioned gaps. The research project is financially supported by the Federal Highway Research Institute (Bundesanstalt für Straßenwesen).

We would like to set some examples to demonstrate the opportunities of evaluating the data.

MATERIALS AND METHODS

Our study is based on published empirical studies that include at least one performance test related to driving carried out after the intake of a medicine. Qualitatively adequate studies have been selected and their information systematically is extracted, such as the number, gender, and age of the subjects, applied agents, dosage, period of application, postingestion times of tests, classifications of the tests (classified according to Krüger et al., 1990), tasks, and the results of the observations in comparison with controls (in general placebo). The results (effects) are encoded as significant (at least 5%) improvement (+1), impairment (-1) or no changes (0). Most of the published studies have to be encoded into different data sets, such as studies including different dosages of the same drug or different times of testing performances. Every data set itself at most includes results of different performance tasks, for instance the results of tracking tests, of attention tests, of simulator tests. Further references about methods are to be taken from Berghaus (1993), Berghaus and Fleermann (1993).

By means of such a detailed technique a lot of information is gathered from every study.

RESULTS

Until now we have collected more than 1200 relevant publications, of which about 800 studies could be encoded. The distribution of extracted studies in dependency on drug groups is shown in Table 1. The total number of studies exceeds 800, because findings on more than one medicine are included in many studies. As expected, the psychopharmacologic drugs build up the greatest group, follwed by hypnotics and sedatives. Smaller are the groups of antihistamines, anti-hypertensive drugs, narcotics and local anaesthetics and finally the anti-epileptcs, stimulants, analgesics and ophthalmic drugs. More than 6000 data sets and more than 20000 effects, i.e. results of performance tasks are registered out of the about 800 encoded studies.

Table 1
Studies with Extracted Information
Dependency on Drug Groups (standing 2/95)

Psychopharmacologic drugs	475
Hypnotics / Sedatives	439
Antihistamins	102
Antihypertensive drugs incl. blockers, etc.	76
Narcotics / Local Anaesthetics	52
Antiepileptics	17
Stimulants	9
Analgesics	8
Opthalmic drugs	8
Total	1186

According to Lohse and Müller-Oerlinghausen (1994) there is establishing a trend in the past years to prefer the middle long acting benzodiazepines to the short acting ones within the substance group of hypnotics and sedatives. The medicines most frequently prescribed in Germany are lormetazepam and temazepam.

Information is extracted from 23 studies of lormetazepam including 121 experiments and 320 effects. The data bank of temazepam consists of 46 studies including 252 experiments and 902 effect findings.

As first results: the ability to perform tasks safely depends on 2 determinants, as it is shown in the Tables 2-3.

With regard to the discussion of the methodological aspect -testing healthy subjects or patients- these findings support the inclusion of patients: As shown by lormetazepam (Table 2) the experiments on patients reveal almost no significant impairments, testing healthy subjects the percentage of significant impairments was evidently higher.

Table 2
Lormetazepam - Impairments of Performances
Related to Driving: Dependency on the Health Status

Subjects	sign. impaired	no change	sign. improved	number of effects
healthy	17.1%	82.1%	.9%	234
ill	3.6%	96.4%	-	84
Total	13.8%	85.6%	.6%	318

Table 3
Temazepam - Impairments of Performances
Related to Driving: Dependency on the Duration of Treatment

Treatment	sign. impaired	no change	sign. improved	number of effects
single dose	25.2%	73.9%	0.9%	782
≤1 week	15.5%	82.7%	1.8%	110
≤1 month	-	100%	-	10
total	23.7%	75.3%	100%	902

Correlating to this result (Table 3), the decrements in performance depend on the duration of treatment as it is shown by temazepam: 25.2% of all effect findings after single dosage were impaired, but only 15.5% after treatment for several days, and 0% after treatment for several weeks. Although the total number of findings from treatments for several weeks is too small to be evaluated statistically, it is evident that the recovery of performances starts shortly after the initial phase of treatment. With respect to methodological questions is

clearly recognizable that more experiments should be carried out after treatments for days and weeks.

The expected period of impairment administering temazepam or lormetazepam has been calculated for healthy subjects receiving single dose (Table 4): both drugs are firstly similar in that the impairment of performance essentially concentrates up to 6 hours after application. Compared to lormetazepam, temazepam shows more impairments in the first two hours, namely in the resorption phase and less decrements thereafter.

Table 4
Lormetazepam, Temazepam - Impairments of Performances Related to Driving: Dependency on Time Intervals (healthy subjects, single dose)

post-ingestion time of tests (h)	Lormetazepam		Temazepam		Total	
0 < 2	32%	38	50%	153	47%	191
< 4	38%	22	30%	193	35%	215
< 6	20%	21	16%	109	15%	130
< 8						
< 10	11%	122	6%	182	7%	404
≥ 10						
Total	19%	203	24%	737	23%	940

Table 5
Flunitrazepam, Lormetazepam+Temazepam - Impairments of Performances Related to Driving: Dependency on Time Intervals (healthy subjects, single dose)

post-ingestion time of tests (h)	Lormetazepam + Temazepam		Flunitrazepam		Total	
< 2	47%	191	57%	44	49%	235
< 4	35%	215	63%	57	41%	272
< 6	15%	130	42%	67	24%	197
< 8			21%	94		
< 10	7%	404	17%	102	11%	643
≥ 10			16%	43		
Total	23%	940	33%	407	26%	347

In contrast to lormetazepam and temazepam, flunitrazepam is a long acting benzodiazepine of the hypnotics, sedatives. We encoded 40 studies including 164 experiments and 713 effect findings. The percentage of significantly impaired performances by flunitrazepam is obviously higher than by lormetazepam and temazepam (Table 5). In all time periods, flunitrazepam reveals a higher percentage of impaired effect findings. The percentage of

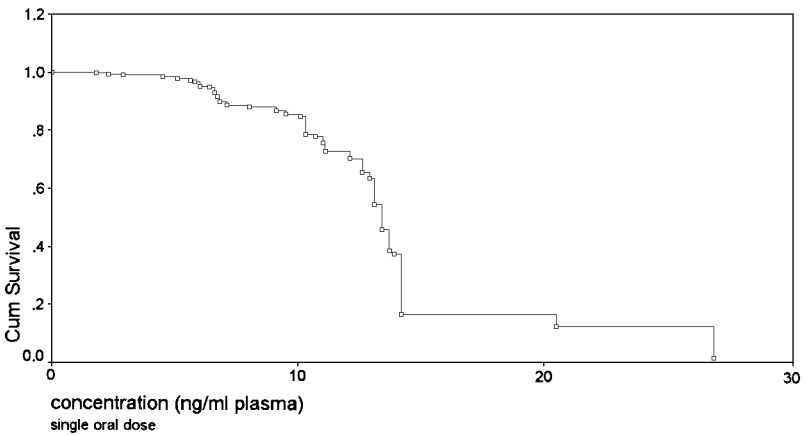
impaired effect findings is still considerable at even more than ten hours after the drug has been applied. Due to this it certainly makes sense and it is necessary to inform on such differences of intensity and period of impairments of performance in drug package inserts.

The correlation between plasma concentrations of the drugs and impairments of performance is of interest to experts in the field of traffic safety. The concentrations calculated for each dosage for the starting time of tests (according to Graß, 1989) were added to the data sets of the studies of single oral doses. Table 6 demonstrates the percentages of significant impairments of different groups of concentrations. As expected, with increasing plasma concentration, the percentage of significant impaired effect findings increases up to 55% in the group of concentrations over 10.3 ng / ml plasma.

Table 6
Flunitrazepam - Impairments of Performances Related to Driving: Dependency on the Concentration (single dose)

ng/ml plasma	sign. impaired	total no. of effects
≤ 5.80	9%	126
≤ 7.10	25%	88
≤ 10.30	39%	59
> 10.30	55%	152
Total	33%	425

Figure 1
Performance Effects - Flunitrazepam



Finally, we present the relationship between concentration and performance with the help of survival analysis (Figure 1). The curve indicates the percentage of cumulated effect findings, which have not yet been impaired at given concentrations. The course of the curve

evidently shows that with lower concentrations only little changes occur. From approximately 10 to 11 ng/ml plasma flunitrazepam however, there is an obvious decrement of performance. Such concentrations are expected after applications of at least 2 mg flunitrazepam at the highest levels of plasma concentration curve. This means that not therecommendednormal dose of 1 mg, but the higher doses predominantly affect driver fitness. If we compare the concentration and performance curves of flunitrazepam and alcohol (Krüger und Berghaus , 1995), the concentrations of approximately 13-14 ng/ml plasma flunitrazepam are equivalent to 0.7-0.8‰ alcohol.

PERSPECTIVE

In our opinion, the previous examples demonstrate the advantages of metaanalytical evaluations based on systematical extraction of information of experimental studies in offering very valuable information to patients, doctors and experts.

Further more, much more possibilities of evaluation emerge, among other things, the comparison of performance profiles between different drugs as well as drug groups. By combining data of homogeneous groups and increasing the number of cases, a detailed analysis in dependency on other moderator variables such as age or gender of the subjects will become possible. Multivariate statistical methods can be used among other things for questions of classification and of differentiation. The broad data basis finally can lead to an estimation of safety intervals and hence to reasonable recommendations on type, intensity and period of impairments. At last, the equivalence to alcohol concentrations can be established too.

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