

An Intersubstance Approach to Drug-Concentration-Drug Effect Correlation via Metaanalytic Data of Experimental Studies

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Key words

drug effects – human performance – pharmacokinetic – stochastic correlation

Abstract

Based on a metaanalytical analysis of experimental studies combined with pharmacokinetic data we tried to correlate the time of worst human performance and the time of highest serum-concentration after oral application of several drugs. Critically discussed we can postulate – as a first result – that the dosage does not influence the time of highest concentration but the time of worst performance, and that for substances with short resorption times the maximum of performance decrements is situated after the maximum of concentration and vice versa.

Introduction

The comparison between the time-dependent development of performance decrements and drug-serum-concentration is of great importance to jurisdiction, to the best information of patients and to experts in court. Up to now research was done into this correlation at most regarding single substances like for example alcohol or using a single experimental design. In our opinion the approach based on an individual experimental design has the following shortcoming: The comparison holds true only for the specific performance test battery. If another research group with another experimental design and test battery tests the performance probably there will be other differences between the substances applied. Therefore a metaanalytic based comparison of as many as possible publications on experimental studies of the effects will avoid this shortcomings.

Using the metaanalyses of experimental studies on cannabis and medicines (BERGHAUS et al. 1998, BERGHAUS 1997), today an extension of time correlation of drug concentration and drug effect of different substances is possible.

Material and Method

1. Metaanalyses of experimental studies

The great amount of information in publications on experimentally based effects of alcohol, illicit drugs and medicinal drugs today only can be handled as a whole by a systematic extraction of the essential information and the storage in a PC. This approach enables a detailed evaluation of the results dependent on influencing factors.

Only those studies meeting the following criteria were included: supplied empirical data from experiments controlled by placebo; used observables with face validity for safe driving; supplied information about the quantity of substance consumed; gave the time interval between application and testing; calculated substance concentration during the test by combining the dose applied, the time difference between application and test and by theoretically based pharmacokinetic data. The effect of the active substance was characterised for each test (observation) in a study as +1 (better than placebo, at least 5%-level of significance), 0 (no difference) or -1 (worse than placebo).

2. Pharmacokinetic data

The basic pharmacokinetic data describing the resorption, distribution and elimination of any substance in serum after incorporation in human bodies are selected from published studies. Using a cumulative and rated evaluation of those data, a kinetic profile for example for several benzodiazepines was documented (GRAß 1989). The listed parameters in the tables are based on these data.

Additionally a mathematical calculation by a computer program developed by STICHT (unpublished) for a personal computer integrates the kinetic data from literature and allows plotting concentration curves in serum after incorporation of a drug taking into account the standard deviation of pharmacokinetic parameters. Using this calculation the time of highest drug concentration was decoded from the graphs.

Results

First details are given in table 1 and 2, where the kinetic parameter T_{max} (time of highest concentration) is correlated with the time of highest decrease in performance (hours after application).

With look at the pharmacokinetic data we must postulate, that the quantity and quality of the published data differed. Only few publications included all relevant parameters for a well-done description of the kinetic. Some parameters were documented in only one publication. At last we have to point out, that the kinetic parameters were based on studies with young and mostly male volunteers. A comparison between the two different ways (publication, mathematical calculation) of establishing the maximum of concentration (T_{max}) shows, that these numerical values are not equal, but mostly similar. The dissimilarity is based on the fact, that T_{max} is a descriptive parameter given from the kinetic progress. This progress itself is influenced by several kinetic parameters (constant of resorption and distribution, volume of distribution, fictitious value at the beginning) which are used in the mathematical calculation.

Similar shortcomings have to be taken into account for the quality and quantity of the given experimental data in the literature. Even if it was possible to analyse more than 600 studies, the main point is the variable quantity of test results. A critical check of the collected data pool gave as a result, that only for Diazepam 5 – 20 mg and Lorazepam 2,5 mg enough results for a significant interpretation were collected. Further more by far most of the experimental studies concern the single oral application to healthy subjects (at most young people). Summing up these remarks we must postulate, that the kinetic and behavioural parameters are approximated values and the interpretation must be cautiously done.

Table 1: pharmacokinetic and pharmacodynamic data for several dosages of Diazepam

substance	dose	classification of pharmacol. effect (acting)	time of highest concentration Tmax (h p.a.)		time of highest decrease of performance (h p.a.)
			literature $\square \pm SD$	kinetic model \square	
Diazepam *	5 mg	long	-	2,2	3.
	10 mg		$3,7 \pm 0,4$	2,2	2. – 3.
	15 mg		-	2,2	2.
	20 mg		-	2,2	1. -2.

Table 2 : Synopsis of pharmacodynamic and pharmacokinetic data for selected benzodiazepines and cannabis

substance	dose	classification of pharmacol. effect (acting)	time of highest concentration Tmax (h p.a.)		time of highest decrease of performance (h p.a.)
			literature $\square \pm SD$	kinetic model \square	
Midazolam	- 15 mg	short	$0,7 \pm 0,3$	0,4	2. – 3.
Flurazepam *	30 mg	long	$1,2 \pm 0,5$	1,0	4.
Flunitrazepam	2 mg	long	$1,4 \pm ?$	1,6	1.
Triazolam	0,5 mg	short	$1,5 \pm 0,5$	0,7	3.
Temazepam	20 mg	medium	$1,9 \pm 0,2$	1,8	1.
Lorazepam	2 mg	medium	$2,3 \pm 0,5$	1,7	6.
Nitrazepam	10 mg	long	$2,3 \pm 1,0$	1,5	3.
Cannabis (smoking)	20 mg		0,3		0,6

(* with active metabolite)

In spite of the mentioned shortcomings we think to be able to derive the following hypotheses from our data:

Overall, as it is expected, there is no one-fold dependency between the period of maximal pharmacological effects and the pharmacokinetic pattern.

- The dose does not influence the Tmax, but the peak of worst performance can be influenced by the dose: With increasing doses applied the maximum of decrements is brought forward. The influence of the dosage as documented for diazepam may be enlightened by the hypotheses that a higher dosage induces a higher concentration during the period of resorption at the place of main pharmacological effect; this may induce an earlier peak of worst performance.

- For some benzodiazepines (clobazam, diazepam, lorazepam, midazolam, oxazepam, triazolam) the time a.p. of decrements does not depend on the dosage, whereas for other benzodiazepines (Flunitrazepam, Flurazepam, Nitrazepam, Temazepam) the time p.a. of decrements is elongated when the dosage increases.

Except the long acting benzodiazepines there seems to be a stochastic correlation: For substances with short resorption times the maximum of decrement timely is situated after the maximum of concentration (for example cannabis and midazolam). For substances with longer resorption times a contrary effect must be postulated (for example diazepam). Hence, on the basis of existing pharmacokinetic data and the time dependent development of performance as gained by metaanalytic analysis of experimental studies we can categorise the substances (alcohol, cannabis and several benzodiazepines) in the two types of mechanism leading to different maxima of behaviour effects and drug concentration: the "time delay"-mechanism (the maximum of effects occurs after the maximum of concentration, i.e. cannabis) and the "rate of change"-mechanism (vice versa, i.e. diazepam).

- Probably there are further differences, depending on the fact whether the substance has active metabolites or not.

Concerning remarks

These hypotheses and other interactions between the pharmacological effect and pharmacokinetic pattern should be verified in the future as a basement for an optimal understanding and – possibly – a prediction of drug effects, specially with regard to the human performance.

We are hopeful that this analysis can be the basement for a theoretical grounded model, which will yield valid information about the period of highest decrease of human performances effected by drugs.