

Coergisms between drugs and alcohol - a psychopharmacological review

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1. Alcohol, medical drugs and driving

Nowadays, we come across quite different, partly contradictory, statements on drug-ethanol interactions in handbooks /1, 3/ , official lists /10/ , reviews /6, 8/ and the media.

Until now, only a few reports dealing with medical drug usage in drinking drivers are based on empirical field studies (e.g., Garriott et al. /2/ , Möller /9/).

We may assume that traffic participants who are users of medical drugs continue to consume alcoholic beverages as if they were non users /4/. Consequently, about 30 percent of drivers who usually take medical drugs continue drinking alcohol. Among drivers involved in traffic accidents the number of misusers with "mixed consumption" approaches 50 percent.

The current discussion on which upper limit of blood alcohol concentration (BAC) should be provided with driving considers more and more possible coergisms (interactions) of medical drugs and alcohol even at low BAC values.

2. What does "coergism" mean?

"Coergism" means coaction of drugs from different chemical substances in a value-free manner. English terminology of pharmacologists prefers the term "interaction" which denotes the coaction of different drugs either with beneficial or adverse reactions. In clinical pharmacology, "interactions" indicate adverse/unwanted side effects more than beneficial responses. Interactions (coergisms) may be pharmacokinetic (alteration of the absorption, distribution, biotransformation or elimination/excretion of drug by another) as well as pharmacodynamic (e.g., interactions between agonists and antagonists at drug receptors). In general pharmacology, strongly, the term "coergism" designates synergistic or antagonistic changes of intensity due to drug-drug coaction, whereas "interactions" include changes of intensity and quality of drug effect profiles.

3. Problems to evaluate studies on drug-ethanol coergisms with psychotropic drugs

Krüger et al. (1990) have selected, analysed and evaluated a large quantity of data from various studies on drugs and alcohol relative to psychological variables. They included studies only fulfilling defined criteria concerning

dependent variables of different psychological classes, blood alcohol concentration of 0.08 percent and below, drugs and alcohol applied orally. The basic criterion of selection was a multivariate standard design used by the investigators: placebo vs placebo, ethanol vs placebo, placebo vs drug, ethanol vs drug.

From a psychopharmacological perspective we compared the evaluations of Krüger et al. (A) with those drawn from the drug register "Rote Liste" (B):

Table 1: Differences of reported drug-ethanol interactions with psychotropic drugs.

Class of drugs	Review A	Review B
antidepressants	+/0	(+)
neuroleptics	0	+
tranquilizers/anxiolytics	+/0	+
nootropics	0	0
+ synergistic effect by interaction generally		
(+) synergistic effect in single substances		
0 no evidence for interaction		
+/0 contradictory observations		

Difficulties to generalize data from different studies may be demonstrated with the drug amitriptyline, a frequently prescribed antidepressant. Krüger et al. found six studies regarding drug-ethanol coergisms with amitriptyline mostly applied as a standard drug within a single dose regimen: 50 mg (3), 25 mg (2), 75 mg (1). Only women were included: 3 studies, only men: 2 studies, both: 1 study. Pretreatment time with ethanol: 60 min (4), 180 min (1), 0 min (1). BAC values (%) at beginning the test programme: 0.076 (3), 0.067 (1), 0.063 (1), 0.084 (1). Two studies with a repeated dose regimen were identified. Amitriptyline dosage used: 75 mg or 30 mg daily. Time of ethanol intake was equal to the time of drug application for testing psychological variables.

Among antidepressants /7, 11/, amitriptyline belongs to those effecting sedation and psychomotor inhibition. Pharmacokinetically, it differs from other antidepressants, especially because of a long-acting active metabolite. Therefore, amitriptyline seems to be rather unsuitable for acute studies with a single dose regimen. Together with alcohol (single dose), effects are determined on a very instable level from a pharmacodynamic and pharmacokinetic viewpoint. Generally peak concentration levels of drugs should be maintained for long time measurements. Unfortunately, none of the reported studies using amitriptyline based on steady state conditions.

Table 2: Antidepressants according to Schönhöfer and Schwabe /11/.

Drug name	t1/2	daily dose (hours)	active metabolite (mg)
Amitriptyline	17 - 40	50 - 150	nortriptyline
Clomipramine	18 - 24	50 - 150	
Desipramine	13 - 23	50 - 150	
Imipramine	10 - 16	50 - 150	desipramine
Nortriptyline	18 - 44	30 - 125	
Doxepine	11 - 23	50 - 150	desmethyldoxepine (t1/2:33-80hs)
Fluoxetine	48 - 96	100 - 300	norfluoxetine (t1/2: 7 days)
Paroxetine	24	20 - 50	
Trazodone	7 - 8	75 - 300	
Sulpiride	7 - 9	150 - 300	

Similarly, neuroleptics, tranquilizers/anxiolytics are nonhomogeneous classes of drugs because of their quite different pharmacodynamics and pharmacokinetics /5/. It should be mentioned that alcohol may inhibit drug metabolizing systems after intake acutely in non-users. Alcohol abusers may develop a metabolic tolerance by increasing the drug biotransformation /5, 8/. With antidepressants we must distinguish between drugs stimulating or depressing psychomotor behavior. Furthermore with some neuroleptics, we can find that smaller doses may produce increasing and higher doses depressing activity in patients. Moreover, in the special case of sulpiride a lower dose may be classified as an activating antidepressant, a higher dose as a depressant neuroleptic.

4. Clinical studies

The majority of drugs investigated in drug-ethanol interaction studies are used by patients (prescribed or self-medicated). Therefore, clinical studies should be promoted to allow a better evaluation of the hazardous aspects with combined ethanol-drug intake (see /13/). Modelling the actual behavior of patients as traffic participants for drug-interaction studies is needed (see also /12/). In contrast to healthy probands, clinical studies on drug-ethanol coergisms in patients are rare and connected with ethical problems. Therefore, information on drug-ethanol interactions will remain preliminary.

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