Clinical Impairment of Benzodiazepines – Relation between Benzodiazepine Concentrations and Impairment in Apprehended Drivers.

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Benzodiazepines, psychomotor impairment

Abstract
Acute intake of benzodiazepines has shown to be followed by concentration dependent deterioration of psychomotor performance and cognition in controlled experimental studies with volunteers. Whether similar concentration-effect relationships exist in a more diverse population of benzodiazepine users is uncertain. We wanted to address this question by studying a population of apprehended impaired drivers.

Our data indicated highly different benzodiazepine intake patterns amongst the drivers during the period prior to apprehension. Impaired subjects had significantly higher blood levels of diazepam and oxazepam than those not impaired. The risk of being assessed as impaired did rise with increasing benzodiazepine blood level. This corresponded to a similar rise in such risk in a reference group where alcohol was detected.

Of the various characteristics studied for the studied subjects the blood concentration of benzodiazepines was the only, which was related to clinically assessed impairment. The results open for further studies and discussion on legal limits for benzodiazepines in relation to driving.

Introduction
Benzodiazepines are drugs widely used as anxiolytics and hypnotics that also have additional medical indications. They are commonly abused drugs. In drivers apprehended for suspected impaired driving, 10-15% will have benzodiazepines in their blood upon testing (1, 2).

Most research on the concentration effect relationship of benzodiazepines has been performed with healthy volunteers given acute moderate doses of the drugs. In such studies benzodiazepines have shown a deteriorating effect on psychomotor performance and cognitive function (3, 4). An almost linear relationship between drug blood concentration and effects has been found for almost all benzodiazepines (5).
Less research exists concerning the concentration effect relationship amongst experienced benzodiazepine users. Tolerance is known to develop more rapidly for hypnotic sedative effects than for anticonvulsant and anxiolytic effects (6). Also for motor effects there appears to be a development of tolerance in animal models (7). Some authors have studied psychomotor impairment after acute intake of benzodiazepines in chronic benzodiazepine users (1, 8-10).

The aim of the present study was to see whether blood benzodiazepine concentration levels detected in a population having taken the drug at diverging times and in varying doses were related to a physicians conclusion of “not impaired” or “impaired” as assessed by a clinical test for drunkenness (CTD). A group of drunken drivers with only alcohol in their blood was used as reference group.

Methods
Of approximately 90 000 blood samples from cases of suspected driving under the influence from the period 1987 to 1998 approximately 9 500 samples contained benzodiazepines. 1201 samples containing only one benzodiazepine were drawn for further study. In these cases no other drugs or alcohol was detected. The detection and quantification of benzodiazepines, as well as the exclusion of alcohol and other drugs in these samples, was based on a battery of analytical methods used according to forensic toxicological principles. 383 samples were excluded due to various non-analytical reasons. The remaining 818 cases constituted the material for this study.

10 759 blood samples containing only alcohol from suspected drivers in 1987 were used as reference group. In the reference group no background variables were available, only the physician’s conclusion and blood alcohol concentrations (BAC).

A physician performs the CTD shortly after apprehension of drivers suspected of driving under the influence of non-alcoholic drugs. The test consists of 27 observations and simple psychomotor tests designed to evaluate driving fitness (11). This reports main dependent variable was the physician’s conclusion to CTD. The main independent variables were the results of the drug analysis. For more advanced analysis the different benzodiazepines were grouped together in four groups with drug levels designated “therapeutic” or “mildly –“, “moderately –“ or “highly elevated”. The background variables were partly related to the suspected driver, partly to the incident resulting in an examination, and partly to the test situation itself.

Results
The study of the background characteristics of our material revealed few interrelations, except for an expected gender differences with respect to BMI, and an age difference between male and female drivers where the female drivers were older than the male drivers ($P < 0.01$).

Generally the type of benzodiazepine found in the blood samples did not relate to the background variables, nor did the blood concentration of the benzodiazepine found. The blood drug concentrations of benzodiazepines were high, with average concentrations highly above what would be considered a therapeutic level. The average BAC that was found in our reference sample was also relatively high. When combining all the different benzodiazepines and grouping them in four groups according to drug blood concentration the different levels did not relate to the background variables.
159 suspected drivers (19%) were determined to be “not impaired”, while 659 (81%) were determined to be “impaired”. The background variables were not found to predict the physician’s conclusion to CTD. In the reference group where only alcohol was detected, 1002 suspected drivers (9%) were determined to be “not impaired”, while 9757 (91%) were determined to be “impaired”.

The type of benzodiazepine detected did not differ significantly between the “not impaired” and “impaired” groups. The impaired drivers had significantly higher levels of diazepam \( (P < 0.01) \) and oxazepam \( (P < 0.05) \) compared to not impaired drivers, and a similar trend was present for flunitrazepam, nitrazepam and alprazolam.

When the different benzodiazepines were combined in groups according to blood drug concentration level, the odds ratio for being determined impaired rose significantly from one group to the next. There appeared to be no increase in OR moving from the moderately to the highly elevated drug level. The OR differences persisted when adjusting for the background variables (tab. 1). The relation was also checked for interactions between the background variables and drug level. No interactions were found.

In the reference group in which alcohol was detected the average BAC (SD) for drivers determined to be “not impaired” was 0.102% (0.055%) and drivers determined to be “impaired” 0.161% (0.071%) \( (P < 0.001) \).

Table 1 Odds ratios (95% CI) for being determined “impaired” on different elevated levels of drug concentration compared to the therapeutic drug level and odds ratios for being determined “impaired” on different BAC compared to the 0.025-0.050 % BAC.

<table>
<thead>
<tr>
<th>Blood benzodiazepine concentration</th>
<th>Binary regression analysis for drug concentration</th>
<th>Therapeutic*</th>
<th>Mildly elevated</th>
<th>Moderately elevated</th>
<th>Highly elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration alone</td>
<td>1</td>
<td>1.61 (1.05-2.46)*</td>
<td>3.65 (1.88-7.08)**</td>
<td>4.11 (2.22-7.60)***</td>
<td></td>
</tr>
<tr>
<td>Adjusted for all background variables</td>
<td>1</td>
<td>1.60 (0.84-3.05)</td>
<td>3.71 (1.34-10.27)*</td>
<td>3.75 (1.46-9.63)**</td>
<td></td>
</tr>
<tr>
<td>BAC (%)</td>
<td>Binary regression analysis for BAC</td>
<td>0.025-0.050*</td>
<td>0.051-0.100</td>
<td>0.101-0.150</td>
<td>&gt;0.150</td>
</tr>
<tr>
<td>BAC alone</td>
<td>1</td>
<td>1.49 (1.22-1.83)***</td>
<td>2.94 (2.38-3.63)***</td>
<td>10.49 (8.36-13.16)***</td>
<td></td>
</tr>
</tbody>
</table>

\*reference category, \* \( P < 0.05 \), \** \( P < 0.01 \), \*** \( P < 0.001 \)

**Discussion**

In this study we have used the physicians conclusion on the CTD as our dependant variable suggesting that this conclusion is a “gold standard” for the determination of impairment in the context of this paper. The CTD may have a low sensitivity for detecting roadside traffic relevant impairment (12-17). When subjects were given lower doses of benzodiazepines in controlled laboratory settings more sophisticated psychomotor were needed to demonstrate drug impairment. Some studies indicate that the CTD may be a reliable tool in revealing
impairment in a clinical setting when higher doses of benzodiazepines or combination of drugs are given (16, 18, 19).

Our use of the CTD as dependant variable implies some knowledge of the reliability of the test. In fact we only have a theoretically idea of this tests reliability and a reliability problem would obscure the concentration effect relationship in a study like the present.

There is a well-established concentration effect relationship between blood drug concentration of a certain benzodiazepine and the psychomotor effects (5). At the individual level, however, considerable intra- and inter-individual differences in the response to a certain dose have been demonstrated (3). Constitutional differences, acute or chronic tolerance to drug effects can partially explain these phenomena.

In the present study we obtained very limited background information about the subjects intake of drugs. In most instances, neither the dose nor the time of intake was known. A pharmacodynamic phenomenon like acute tolerance would greatly vary depending on time since last drug intake and dose ingested. The discussion of acute tolerance is beyond the scope of this article, but if it were to exist, it would obscure a concentration effect relationship in the present study.

A pharmacodynamic or functional mode of action can cause tolerance after repeated dosing. Pharmacodynamic tolerance for benzodiazepine effects is well-established (20) as for alcohol (21). There are probably also differences in degree of tolerance development when considering specific drug effects (22). In any case chronic tolerance would have had the capability to obscure a concentration effect relationship in the present study.

Some of the subjects in the present paper would have taken benzodiazepines as part of a therapeutic scheme for the treatment of epilepsy, anxiety or insomnia. Others might have ingested the drug for non-medicinal purposes and as part of drug abuse. Different indications could theoretically produce different response (23) and also obscure a concentration effect relationship.

Despite all these possible uncertainties and limitations we still found a clear concentration effect relationship measured as benzodiazepine drug concentrations and clinically assessed impairment. This relationship was maintained when adjustment is made for the background variables. The relationship is of a similar magnitude to that found in the reference group of drunken drivers, at least for mildly and moderately elevated BAC.

A lack of relationship between blood drug concentration and impairment has been one of the arguments against setting legal limits for benzodiazepine concentrations and driving (24). When comparing the present results on benzodiazepines and alcohol it seems that some arguments against the establishment of legal limits for benzodiazepines will have reduced value.

Future studies, e.g. in which more sensitive tests relevant to traffic safety can be applied in stead of CTD on a population of individuals with different patterns of benzodiazepine use, would further contribute to the knowledge background for setting such limits.
References


