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Impairment due to amphetamines and benzodiazepines, alone and in combination

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ABSTRACT

Introduction: The impairing effects of combined use of amphetamines and benzodiazepines among recreational drug users are not well described, but knowledge about this is important in the risk assessment of such combined drug use. The aim of this study was to compare the impairment, among apprehended drivers, as judged by a clinical test of impairment (CTI), in cases where a combination of amphetamines and benzodiazepines was detected, in blood, with cases where only one of the two drug groups was detected.
Methods: The results of CTI judgments were compared to toxicological drug tests of blood samples that were obtained at the time of CTI screening in cases containing amphetamines only, cases containing different benzodiazepines only, and cases containing a combination of amphetamines and benzodiazepines.
Results: There were significantly more drivers being judged as impaired in the combined group ($n = 777$), compared both with amphetamines alone ($n = 267$, $\chi^2 = 47.8$, $p < 0.001$) and benzodiazepines alone ($n = 153$, $\chi^2 = 7.0$, $p = 0.008$). This was also seen when only including the lowest concentrations of benzodiazepines ($\chi^2 = 4.3$, $p = 0.038$). The concentrations of the drugs were higher in the single drug groups, compared with the combined group.
Conclusion: This study indicates that during real-life driving, those influenced by both amphetamines and benzodiazepines are more impaired, as judged by the CTI, compared with those influenced by either drug alone, although the combined group showed lower drug concentrations.

1. Introduction

Amphetamines and benzodiazepines are popular among recreational drug users. These two drug classes are also frequently combined, and this is verified by the frequent detection of benzodiazepines and amphetamines together (seen in about 15% of some categories of forensic blood samples; Bogstrand and Gjerde, 2014; Gjerde et al., 2013; Ojaniemi et al., 2009; Verschraagen et al., 2007). Although the prevalence of amphetamines and benzodiazepine use among drivers vary by country, these drugs are frequently found in both impaired and fatally injured drivers (Gjerde et al., 2011a,b), and both benzodiazepines and amphetamines are documented to cause driving impairment (Bosanquet et al., 2013; Verster et al., 2006). The reason for the combined use is often to add stimulating or sedating effects to the drug experience, but the effects of this combination on drug related impairment are not well known. Debate exists as to whether a combination of the stimulant amphetamines and the depressant benzodiazepines will actually attenuate some of their individual impairing effects as indicated in some studies (Marks et al., 2014; Mintzer and Griffiths, 2003; Rush et al., 2004). Studies attempting to answer this question are, however, not necessarily transferable to real-life situations, where higher drug doses most often are ingested. Such studies are difficult to conduct with a controlled experimental design, due to ethical and safety restrictions in combing high doses of the respective drugs. Blood samples collected in real-life from suspected impaired drivers often contain drugs of abuse. In studies investigating blood samples collected from fatally injured drivers, alcohol and/or drugs have been found in 30–50% of the cases, with alcohol being the most prevalent drug, detected in 20–40% (Ahlm et al., 2009; Brady and Li, 2014; Carmen del Rio et al., 2002; Drummer et al., 2004; Gjerde et al., 2011a,b). These drivers are often experienced drug users and represent a population using benzodiazepines for non-therapeutic purposes (Bogstrand and Gjerde, 2014). In cases of

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suspected drugged driving, after apprehension a clinical observation of the suspect is performed by a doctor (when the blood sample is collected) to ascertain information on possible driver impairment.

Systematizing medical observations and relating these observations to the drug concentrations measured in toxicological blood samples may provide information about reciprocal attenuation or potentiation of the effects of the two drug classes (amphetamines and benzodiazepines) when used together in a naturalistic setting. The knowledge about impairment seen after this frequent drug combination is important for the risk assessment of this particular poly drug use and may also be of relevance when assessing the effects of other combinations of sedating/stimulating drugs. The aim of the present study was to compare the impairment observed in suspected drugged drivers, as judged by a clinical test of impairment (CTI), in relation to the detected blood concentrations of amphetamines and benzodiazepines, alone and in combination.

2. Materials and methods

2.1. Study group

The present study used data from the existing database at the Norwegian Institute of Public Health (NIPH), Division of Forensic Sciences. The database contains the analytical results from blood samples collected among suspected drugged and drunk drivers. The database was searched for apprehended driver cases in the time period between March 1st of 2012 and September 1st of 2013. Cases containing amphetamine and/or methamphetamine (hereafter referred to as amphetamines) and the benzodiazepines diazepam, N-desmethyldiazepam, flunitrazepam, clonazepam, nitrazepam, alprazolam, oxazepam, and fenazepam, with no other drugs being detected, were selected and divided into three groups: cases containing benzodiazepines only; cases containing amphetamines only; and cases containing a combination of amphetamines and benzodiazepines.

2.2. Toxicological analytical methods and CTI

In Norway, when drunk or drugged driving is suspected by the police, a clinical examination is usually performed by a physician at the same time as a blood sample is collected for toxicological analyses. The physicians are trained at medical school how to determine drug impairment by use of the CTI. Also, some physicians are employed at the police and especially experienced in performing the CTI.

2.2.1. Toxicological analytical methods. All of the analytical methods applied were fully validated for routine use at the NIPH. All blood samples were, according to the routine, initially screened for ethanol with a previously published enzymatic ADH method (Kristoffersen and Smith-Kielland, 2005). The analytical cut-off level (an administrative value just above the lower limit of quantification), used for ethanol in blood, was 0.02 g/kg, and only values detected above this level were reported as positive.

All blood samples were also screened for a number of other drugs and medications relevant to impairment, using a previously published ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) method (Oiestad et al., 2011). The drugs included in this method were opiates (morphine, hydromorphone, codeine, ethylmorphine, buprenorphine, methadone, fentanyl, and oxycodone), stimulants (amphetamine, methamphetamine, methylphenidate, cocaine, and MDMA), benzodiazepines (diazepam, clonazepam, oxazepam, bromazepam, fenazepam, nitrazepam, alprazolam, lorazepam, midazolam, and flunitrazepam), z-hypnotics (zopiclone and zolpidem), LSD, ketamine and tetrahydrocannabinol. In addition, all cases were screened for gamma-hydroxybutyrate (GHB) and pregabaline, using another separate analytical method (Dahl et al., 2012). Also, a small number of new designer drugs were analyzed in each case using a UPLC–MS/MS method. These latter drugs changed throughout the study period, but for most of the period, paramethoxyamphetamine (PMA), paramethoxymethamphetamine (PMMA), meta-chlorophenylpiperazine (mCPP) and 3,4-methylenedioxypyrovalerone (MDPV) were included.

Positive toxicological results for amphetamines, or benzodiazepines were confirmed and quantified with a secondary toxicological testing method and then compared with CTI screening results. Amphetamine and methamphetamine were confirmed using an UPLC–MS/MS method, with the chromatographic conditions being similar to those of a previous publication (Berg and Strand, 2011), and the analytical cut-off values being 0.20 μmol/L for amphetamine and 0.20 μmol/L for methamphetamine. All benzodiazepines were analyzed using a previously published UPLC–MS/MS method (Sauve et al., 2012), with the cut-off values for benzodiazepines, in the confirmation method (which were somewhat higher than in the screening method), being 0.20 μmol/L for diazepam, 0.20 μmol/L for N-desmethyldiazepam, 0.005 μmol/L for flunitrazepam, 0.0040 μmol/L for clonazepam, 0.05 μmol/L for nitrazepam, 0.010 μmol/L for alprazolam, 0.6 μmol/L for oxazepam, and 0.0050 μmol/L for fenazepam. Only concentrations detected above the cut-off levels were reported as positive.

2.2.2. CTI. Drivers are usually apprehended by the police because of suspicious driving or due to involvement in traffic accidents. A police physician draws a blood sample shortly after apprehension and at the same time also performs a CTI. The CTI consists of 25 tests and observations related to common signs of drug impairment. Examples of observations are the suspected driver's motor coordination ability, cognitive performance, degree of alertness, and appearance. The CTI has been described in detail elsewhere (Bramness et al., 2003). In the end the police physician must conclude on whether the driver is not impaired, mildly impaired, moderately impaired, or considerably impaired. Also, a conclusion of "impairment impossible to determine" can be given. These cases were excluded from the study. For some of the analyses performed in the present study, those subjects that were judged as mildly, moderately, and considerable impaired are merged into a single "impaired" group.

2.3. Ethics

The study was approved by the Higher Prosecuting Authority, which stands as the owner of all forensic materials in Norway. The project was assessed by the Regional Committee for Medical Research Ethics, in accordance with the Norwegian Research Ethics Act of June, 2006 and the Act on Medical and Health Research (the Health Research Act) of June, 2008. Due to the anonymous handling of the data, the committee considered the research project to be outside the remit of the Act on Medical and Health Research, and therefore it could be implemented without the approval from the ethics committee.

2.4. Statistics

IBM SPSS® Software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Means and standard deviations (SD) are reported for the continuous variables and frequency distributions were used for the categorical variables. The number of impaired drivers in the different groups was compared using Pearson Chi Square test (in the case of no cells with expected counts of less than five). The concentrations of benzodiazepines and amphetamines, in the impaired and the not impaired drivers, and in the different drug groups, were compared using the Student's *t*-test. *p*-values below 0.05 were considered statistically significant.

2.5. Calculations of diazepam equivalent concentrations

To summarize the concentrations of the benzodiazepines, all benzodiazepine concentrations were calculated into diazepam equivalent concentrations, using the concentrations for each benzodiazepine achieved after ingestion of a previously defined "impairing drug dose", according to the Norwegian per se law on drugged driving (Vindenes et al., 2012). These limits include equivalent concentrations for all benzodiazepines in the present material, except for N-desmethyldiazepam. For N-desmethyldiazepam, the concentrations were divided by 2 to achieve the diazepam equivalent concentration. After all of the benzodiazepine concentrations were calculated into diazepam equivalent concentrations, the concentrations were summarized (in cases with more than one benzodiazepine detected in blood).

3. Results

During the study period, 13,225 cases, from suspected drunk or drugged drivers, were received for toxicological analysis. Of these cases, 196 contained benzodiazepines only, 322 contained amphetamine only, and 899 contained benzodiazepines and amphetamine in combination. Cases where the result from the CTI was inconclusive ($n = 220$) were excluded from the study. This left 153 cases containing benzodiazepines only, 267 cases containing amphetamines only, and 777 cases containing benzodiazepines and amphetamines in combination, included for analyses. These included cases contained no other drugs except for amphetamines and benzodiazepines.

Table 1 shows the number drivers testing positive for benzodiazepines alone, amphetamines alone and benzodiazepines and amphetamines in combination. The percentage of drivers judged as impaired (mildly, moderately, or considerably impaired) was 75% among the cases where only benzodiazepines were detected, 64% among the cases where only amphetamines were detected, and 84% among the cases where benzodiazepines and amphetamines were detected in combination. The number of impaired drivers was significantly higher in the combined group compared with both the benzodiazepines alone ($\chi^2 = 7.0$, $p = 0.008$) and the amphetamines alone ($\chi^2 = 47.8$, $p < 0.001$). The number of impaired drivers was also