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Differences in combinations and concentrations of drugs of abuse in fatal intoxication and driving under the influence cases

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ABSTRACT

Background: In toxicology, international classification systems focus on single intoxicants as the cause of death. It is, however, well known that very few drug related deaths are caused by a single substance and that information concerning the drug concentrations as well as the combinations of drugs are essential in order to ascertain the cause of death. The aim of the study was to assess whether those prone to fatal intoxications differ significantly from chronic drug users – in terms of demographics and drug exposure patterns.

Material and methods: Fatal psychoactive drug intoxications in Norway during 2012, where a forensic autopsy including toxicological analysis were performed, were included. Analytical findings in blood were compared with concentrations in blood from apprehended drivers under the influence of drugs and ethanol (DUID) during the same time period. The opioid and benzodiazepine concentrations were assessed as morphine and diazepam equivalents, respectively, in order to compare concentrations across the different groups.

Results: A total of 194 autopsy cases and 4811 DUID cases were included. Opioids were detected in around 90% of the drug intoxication cases, but in only 16% of the DUID cases. The number of substances detected in fatal intoxications was 4.9 compared to 2.6 in the DUID cases. The total opioid concentrations were significantly higher in the fatal intoxication cases compared to DUID cases (229 ng/mL versus 56.9 ng/mL morphine equivalents, respectively). Benzodiazepines were detected in 90% of the fatal cases. Only one fatal opioid mono-intoxication was found; a case with a very high methadone concentration (1238 ng/mL).

Discussion: Mono-intoxication with heroin was not seen in any of the fatal intoxications in Norway, and single drug intoxications were rare (1.5%). Fatal intoxications were caused by a combination of drugs with significantly more substances as well as higher total drug concentrations among the fatal cases compared to the DUID cases. The combination of opioids and benzodiazepines seemed to represent an increased risk of death.

Conclusion: The total load of drugs influence the degree of intoxication and the total concentration level must be considered, including the total number of substances. Our findings imply that international statistics regarding an opioid being the main intoxicant should have a shift in focus towards combinations of drugs (especially opioids and benzodiazepines) as a major risk factor for fatal drug overdoses.

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1. Introduction

Both national and international statistics indicate opioids to be the leading cause of fatal intoxications in Norway [1–3]. Heroin is the most commonly used opioid in Norway, and it is estimated that approximately 85% of the heavy opioid users inject heroin [1]. Injection of heroin is a drug administration route prone to cause fatal overdoses, and could partly explain the high overdose rate seen in Norway compared with many other European countries where injecting heroin is less common [2,4].

In the Global Burden of Health calculations, misuse of illicit drugs is ranked as the 10th leading risk factor for a reduction of disability-adjusted life years (DALYs) in Norway in 2015 [5]. More than 41 000 years of life lost (YLLs) are attributed to the use of alcohol and illicit drugs, and ranks as the 5th leading risk factor for early death in Norway in 2015; for the ages 15–49 years it is regarded as the leading contributor to early death. Fatal opioid-related intoxications among men are stated to be a strong driving force for the YLLs [5,6].

Drug induced deaths are classified according to the presence of drugs in toxicological samples, and most countries use international classification systems, like the ICD (International Classification of Diseases) [7], for diagnostic purposes. A single substance is typically chosen as the main intoxicant, and positive findings of e.g. morphine/heroin or methadone, lead to the classification of a heroin or methadone related death, respectively, by hierarchal traditions. However, in the majority of the fatal intoxications, several drugs may contribute to death [8–11]. There is consistent knowledge about the dose-response relationship for specific psychoactive substances and the risk of intoxication is highly related to the drug concentrations, still with individual variations [12]. A considerable overlap between concentrations of drugs of abuse seen in living persons and in fatal overdose cases has been reported [12]. Possible explanations include the administration route, drug combinations, variable tolerance and metabolism within and between individuals, and post mortem redistribution of drugs.

In order to prevent fatal drug intoxications and to develop appropriate preventive strategies, it is important to be aware of and further understand the interrelationships between risk factors for intoxication, and especially whether such increased risk might be related to drug combinations and concentrations.

The aim of the study was to assess whether those who died from intoxications differed significantly from a group considered as chronic drug users regarding demographical data, choice of drug (s), and blood concentrations.

2. Materials and methods

2.1. Material

All instances of fatal intoxications in Norway subject to forensic autopsy during 2012 were assessed according to inclusion criteria described by Simonsen et al. [13]. The cause of death was determined to be intoxication. Mono-intoxications with ethanol were excluded.

According to the Norwegian Criminal procedure Act, a forensic autopsy is only mandatory where death is suspected to have been caused by a punishable act, in cases where the deceased is unidentified or among deceased younger than 18 years. However, a forensic autopsy is also recommended in suicides, accidents and cases of sudden, unexpected death. Further, the doctor is obliged to report such cases to the police, also including cases of suspected drug related deaths [14]. A forensic autopsy is thus not performed in all suspected intoxication deaths, but it is estimated that approximately 90% of the cases are subject to such an autopsy [15].

Whole blood samples collected during autopsies were, for 95% of the cases, analysed at the Department of Forensic Sciences, Oslo University Hospital (OUH). The remaining 5% were analysed at the Department of Clinical Pharmacology, St. Olavs Hospital – Trondheim University Hospital.

In fatal overdoses, several drugs are often detected in blood [16]. We do not know whether the pattern of number of drugs and concentrations reflect regular drug use. Therefore, we wanted to compare findings among deceased with findings among a population of living drug users. The preferred comparable data would be findings from non-fatal intoxications, but such data are not available. The comparison with DUID cases was considered the second best option because drivers apprehended by the police often are chronic drug users, reflected in the fact that they frequently test positive for more than one psychoactive substance in high concentrations [17]. In a study of apprehended drivers in Norway one or more drugs were detected in concentrations above the limit for graded sanction corresponding to 0.12% blood alcohol concentration (BAC) in about 40% of the cases [18]. Other studies have shown that a significant number of drivers killed in traffic accidents had been apprehended by the police due to impaired driving at previous occasions [19]. The DUID cases in the present study thus consist mainly of persons with significant drug use, and represent, to a certain extent, individuals with characteristics similar to those of fatal drug deaths in terms of dangerous/problematic drug use.

Samples from drivers apprehended by the police nationwide due to suspected driving under the influence of drugs and ethanol (DUID) in 2012, were included for comparison of drugs involved, drug concentrations and demographic data. All DUID cases were analysed according to a standard protocol at OUH for ethanol and approximately 40 medicinal substances and illicit drugs.

2.2. Samples

From the autopsy cases, only cases with whole blood samples collected from the femoral vein were included in the study. The samples were collected into 20 mL Steriline® tubes (Bibby Sterilin, Staffordshire, UK), containing 0.3 mL 67% (w/v) potassium fluoride (KF) solution as a preservative. Blood obtained from a peripheral vein from DUID subjects were collected into 5 mL Vacutainer® tubes, containing 20 mg NaF (a preservative) and 143 IU of heparin (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK).

2.3. Analyses

The samples were analysed shortly after arrival at the laboratories. Fig. 1 illustrates the distribution and analytical principles of the sample handling.

The autopsy samples received at OUH were analysed for around 100 different psychoactive compounds in total. Ethanol screening was performed by an enzymatic method [20] and a positive finding was confirmed by gas chromatography [21]. Amphetamines, cannabinoids, cocaine metabolites, and opiates were screened for by an immunological method [22]. Screening for other drugs was performed using high-performance liquid chromatography with mass spectrometry detection (LC–MS) [23]. Confirmatory analyses were done by gas chromatography with mass spectrometry (GC–MS) or LC–MS [23–26].

In the autopsy samples received at St. Olavs Hospital, whole blood was subjected to specific analyses for alcohols (ethanol, methanol, isopropanol, acetone) using a headspace GC–MS method, and specific analyses for benzodiazepines (diazepam, nordiazepam, oxazepam, nitrazepam, 7-aminonitrazepam, flunitrazepam, 7-aminoflunitrazepam, clonazepam, 7-aminoclonazepam, alprazolam, midazolam), opioids (morphine, codeine,