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Sedative and hypnotic drugs—Fatal and non-fatal reference blood concentrations

Anna Kristina Jönsson [a,b], Carl Söderberg [c], Ketil Arne Espnes [d], Johan Ahlner [e], Anders Eriksson [f], Margareta Reis [a], Henrik Druid [c,*]

[a] Department of Drug Research/Clinical Pharmacology, Faculty of Health Sciences, Linköping University, Linköping, Sweden
[b] Department of Clinical Pharmacology, County Council of Östergötland, Linköping, Sweden
[c] Forensic Medicine Laboratory, Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden
[d] Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway
[e] Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Linköping, Sweden
[f] Section of Forensic Medicine, Department of Community Medicine and Rehabilitation, Umeå University, Umeå, Sweden

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ABSTRACT

In postmortem investigations of fatal intoxications it is often challenging to determine which drug/s caused the death. To improve the interpretation of postmortem blood concentrations of sedative and hypnotic drugs and/or clonazepam, all medico-legal autopsies in Sweden – where these drugs had been detected in femoral vein blood during 1992–2006 – were identified in the databases of the National Board of Forensic Medicine. For each drug, concentrations in postmortem control cases – where the cause of death was not intoxication and where incapacitation by drugs could be excluded – were compiled as well as the levels found in living subjects; drugged driving cases and therapeutic drug monitoring cases. Subsequently, fatal intoxications were assessed with regards to the primary substances contributing to death, and blood levels were compiled for single and multiple drug intoxications. The postmortem femoral blood levels are reported for 16 sedative and hypnotic drugs, based on findings in 3560 autopsy cases. The cases were classified as single substance intoxications ($N = 498$), multiple substance intoxications ($N = 1555$) and postmortem controls ($N = 1507$). Each autopsy case could be represented more than once in the group of multiple intoxications and among the postmortem controls if more than one of the included substances were detected. The concentration ranges for all groups are provided. Overlap in concentrations between fatal intoxications and reference groups was seen for most substances. However, the concentrations found in single and multiple intoxications were significantly higher than concentrations found in postmortem controls for all substances except alprazolam and triazolam. Concentrations observed among drugged drivers were similar to the concentrations observed among the therapeutic drug monitoring cases. Flunitrazepam was the substance with the highest number of single intoxications, when related to sales. In summary, this study provides reference drug concentrations primarily to be used for improving interpretation of postmortem drug levels in obscure cases, but which also may assist in drug safety work and in pharmacovigilance efforts.

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1. Introduction

Statistics of fatal intoxications are highly dependent on reliable information from medico-legal death investigations. It is however a challenge to establish which drug/s is/are the main cause of death. Reference data based on postmortem analytical results are particularly valuable. Compilations of therapeutic and toxic concentrations [1–3] in living subjects are often used when interpreting the results of the toxicological analyses. However, such concentrations cannot directly be translated to a postmortem setting [4–7]. Another problem is that compilations based on postmortem data are a mix of literature reviews and case reports. This is problematic since drug levels that may be observed in cases of death attributed to causes other than intoxication are not commonly included. Furthermore, there are discrepancies in samples chosen for analysis, sampling procedures, analytical methods, selection of cases, and methodological procedures [8]. In Sweden, the blood sampling and handling procedures are

* Corresponding author at: Forensic Medicine Laboratory, Department of Oncology-Pathology, Karolinska Institute, Retzius v. 3, SE-171 77 Stockholm, Sweden. Tel.: +46 703447544; fax: +46 13364270.
E-mail address: henrik.druid@ki.se (H. Druid).

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standardized and all analyses are performed at one national, accredited laboratory. Fatal and non-fatal reference blood concentrations in Sweden have previously been assessed for 83 substances in 1997 [9], for flunitrazepam in 2001 [10] and for antidepressants in 2007 [11].

The aim of this study was to evaluate fatal and non-fatal reference blood concentrations in Sweden, with a focus on sedative and hypnotic drugs, to compare these concentrations with living controls and to relate the number of fatal intoxications to drug sales statistics.

2. Methods

2.1. Study populations

This compilation was based on drug concentrations in blood samples from medico-legal autopsies and individuals driving under the influence (DUI) in Sweden and from therapeutic drug monitoring (TDM) cases in Norway.

2.1.1. Postmortem cases

In Sweden, most suspected and certified unnatural deaths as well as unexplained deaths are reported to the police. The police request a medico-legal autopsy in a majority of these cases. Sweden has six forensic medicine departments and all of them follow a strictly standardized procedure for the sampling of femoral venous blood [9,12] to reduce the impact of postmortem redistribution [4,6,9]. All drug analyses are performed at one national, accredited laboratory [9], where the blood is screened for alcohols, pharmaceutical drugs and upon request also for illicit drugs. All toxicological results are recorded in a national database [12]. Femoral venous blood concentrations are consistently expressed in μg/g since they are based on weighed samples. This is also true for the DUI cases. The concentrations can be converted to μg/mL by multiplying with 1.06 (the average density of blood).

2.1.2. Inclusion criteria and assessment procedure

All medico-legal autopsy cases in which sedative and hypnotic drugs (ATC codes N05B and N05C) and clonazepam (ATC code N03AE01) were detected in femoral blood during the study period from January 1992 through December 2006 were identified in the combined forensic medicine and toxicology national database [12]. This constitutes a real-time database and all data are continuously generated from the routine casework data management system for forensic medicine and toxicology. The ICD-9 system, with some supplemental diagnoses to improve specificity, is used to translate causes of death into codes. Based on the cause of death, the cases were divided into three mutually exclusive groups according to a previously described procedure [9,11]. The first two groups included cases with intoxication as the immediate cause of death; in Group A by one drug, and in Group B by two or more drugs and/or ethanol. Group C, the postmortem control case group, included violent suicides and select accidental trauma deaths (ICD 9 codes: 800–959, E953, E955, E956, or E958). If more than one sedative or hypnotic drug were detected, this case could be represented more than once in Group B or Group C. Cases with a cause of death that may imply incapacitation were excluded (Table 1) as well as cases where death occurred in a hospital. Each case was reviewed independently by two of the authors. For cases with unexpectedly high or low concentrations, and in cases where any other queries were raised during the evaluation, the original data files were examined in detail. Cases where the assessment between the authors differed were discussed until a consensus was reached.

In order to determine which concentration of a drug that could be regarded as insignificant with regards to toxicity, a concentration window was defined for each sedative/hypnotic substance, using additional information relating to concentrations found in the Group C cases, the DUI cases and the TDM data (see below). Further, an extensive literature search on maximum serum concentrations in clinical trials and in other TDM populations was performed to identify obvious non-toxic serum levels for each drug. These arbitrary concentration windows were used as guideline levels when reviewing the Group A and Group B cases. When evaluating and later compiling the drug levels identified in Groups A–C the concentrations of the parent compound were used. However, for clonazepam, nitrazepam, flunitrazepam and propiomazine, the 7-amino metabolites, and dihydropropiomazine, respectively, were added to the parent compounds, since all these metabolites are almost exclusively formed postmortem.

Table 1
Exclusion criteria for Group C based on ICD 9 codes (with supplementary suffices)[a] due to possible incapacitation or severe organ injury.

Cause of death (codes)	Definition
852	Subdural hemorrhage
861 K	Injury to heart and lung, gunshot wound
861 M	Injury to heart and lung, laceration
864	Liver laceration
869	Severe external and internal injuries
933	Foreign body in pharynx or larynx
934	Foreign body in trachea, bronchi or lungs
940–949	Burns
991 G	Hypothermia
994 B	Drowning or other submersion
Manner of death (codes)	
E850–E858	Accidental poisoning by drugs
E880–E888	Accidental fall
E910	Accidental drowning and other submersion
E954	Suicide by submersion
E958 A	Suicide by jumping/lying before a train
E958 B	Suicide by fire
E958 D	Suicide by hypothermia
E960–E969	Homicide/injury inflicted by other person
E980–E989	Injury undetermined

[a] Certain suffices are supplements to the ICD-9 codes defined by the Swedish Medico-legal Society and used by the Swedish forensic pathologists to provide more detailed diagnoses.

2.1.3. Individuals driving under the influence

The DUI material consisted of drivers apprehended while driving under the influence of substances other than alcohol, including pharmaceutical drugs and illicit drugs. All DUI cases in Sweden where sedative and hypnotic drugs were detected in blood, from January 1992 through December 2006, were identified and formed Group D. Cases where the substance of interest was detected in lower concentrations than the LoQ of postmortem analyses were excluded to enable group comparisons. Each individual could of course be suspected of drugged driving more than once during the study period. However, only the first analytical result for each substance detected in a single individual was used. If more than one sedative and hypnotic drug were detected in the analyses, one individual could be represented more than once in the dataset.

2.1.4. Therapeutic drug monitoring cases

At the Department of Clinical Pharmacology in Trondheim, Norway, serum samples from patients treated with sedative and hypnotic drugs were analyzed upon request by the responsible psychiatrist or general practitioner. The TDM samples collected during the years 1999 through 2007 were assessed. To ensure validity of the TDM data, only one sample per patient was used. Based on the free text in the database, usually including the requesting doctors' notes, intentional and unintentional overdose cases were excluded [11]. All TDM concentration data were originally given as nmol/L serum whereas the postmortem and the

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