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

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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.



## 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

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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 |
| E-958 B | Suicide by fire |
| E-958 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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**Table 2**
Lower limit of quantification for the included substances in the postmortem analyses.

| Substance | Postmortem analyses (μg/g) |
|---|---|
| Alprazolam | 0.02 |
| Buspirone | 0.05[a] |
| Clomethiazole | 0.2 |
| Clonazepam | 0.05 |
| 7-Amino clonazepam | 0.05 |
| Diazepam | 0.05 |
| Nordazepam | 0.05 |
| Flunitrazepam | 0.02[b] |
| 7-Amino flunitrazepam | 0.02[b] |
| Hydroxyzine | 0.05 |
| Lorazepam | 0.02 |
| Midazolam | 0.02 |
| Nitrazepam | 0.05 |
| 7-Amino nitrazepam | 0.05 |
| Oxazepam | 0.1 |
| Propiomazine | 0.03 |
| Dihydropropiomazine | 0.03 |
| Triazolam | 0.002 |
| Zaleplon | 0.05 |
| Zolpidem | 0.05 |
| Zopiclone | 0.02 |

Abbreviations: DUI, Driving under the influence.
[a] Until 2005. From 2006 the LoQ was 0.001 μg/g.
[b] The LoQ was 0.01 μg/g until 1998 and 0.02 μg/g thereafter.

DUI data were given as μg/g whole blood. In order to facilitate comparisons, the TDM data were recalculated into the same unit, *i.e.* μg/g. An assumption was made that 1 mL serum weighed 1 g. A transformation factor was calculated by the equation $10^{-6}$/Mw (molecular weight) to convert the concentration in nmol/L into μg/g. Furthermore, the same drug limits of quantification as for the postmortem cases were applied on the TDM-data to enable group comparisons (Table 2). Hence, by introducing arbitrary cut-off detection levels for the TDM population a "true" TDM cohort is not displayed in this paper but rather a restricted population for comparison purposes. Henceforth the TDM data are referred to as Group T.

### 2.2. Analytical methods used in medico-legal cases (Groups A–C)

Femoral blood from autopsy cases and whole blood from DUI cases were analyzed at the same laboratory using the same method for most of the substances [9]. In brief, this method implies an alkaline and a neutral liquid–liquid extraction and gas chromatographic (GC) analysis utilizing HP 5890 GCs equipped with HP 7673 auto injectors and NP detectors. Alprazolam, clonazepam, diazepam, flunitrazepam, midazolam, nitrazepam, zaleplon, zolpidem, zopiclone, propiomazine, hydroxyzin and buspirone (until 2005) were analyzed in all medico-legal cases. The LoQs used in postmortem analyses are shown in Table 2. For clonazepam, diazepam, flunitrazepam, nitrazepam and propiomazine the metabolites were analyzed using the same methods as their parent drug.

Lorazepam, triazolam, clomethiazole, buspirone (from 2005) and oxazepam were analyzed upon request by the forensic pathologist. Clomethiazole was extracted by butyl-acetate at pH 7.0. The internal standard was allobarbital and prazepam. Clomethiazole was separated using a DB-5 column and was detected using NPD [13]. Oxazepam was extracted by liquid–liquid extraction at pH 8.9 and was detected using GC–UV with diode array detection. The organic phase was evaporated and dissolved in the mobile phase and injected on Agilent 1100 series HPLC systems after separation on C8 columns. Buspirone was extracted (from 2005) by butyl-acetate at pH 11.0 and analyzed by LC–MS–MS on a PE Sciex API 2000 triple quadruple instrument equipped with turbo ion-spray interface after separation on a Zorbax Stable Blond Cyano column [14].

External accuracy was checked routinely with external control samples and precision was calculated from quality control samples. As an example the precision over 12 months was between 4.8 and 14.0% for the benzodiazepines and the Z-drugs ($N = 220–450$), 10.0–14.4% for hydroxyzine, propiomazine and its metabolite, and 12.2% for buspirone. External controls generally had *z*-scores less than 1 and almost always *z*-scores less than 2.

### 2.3. Analytical methods used in the TDM cases

Alprazolam, diazepam, flunitrazepam, clonazepam, nitrazepam, oxazepam, meprobamate, zopiclone and zolpidem were extracted from serum with liquid–liquid extraction using a mixture of dichloromethane/isopropanol (90:10) as extraction solvent. Promethazine was extracted from serum with liquid–liquid extraction using a mixture of hexane/acetonitrile (98:2) as extraction solvent.

All analytes were quantified by liquid chromatography–mass spectrometry (LC–MS) on Agilent MSD 1100LC–MS systems after separation on C18 columns and subsequent detection as pseudo-molecular ions (M + 1). Internal standards were always used. Mobile phases consisted of methanol, acetonitrile, formic acid (25 mmol/L) or ammoniumacetate (50 mmol/L) in different ratios. Together with the unknown samples, each analytical series contained seven calibrators covering therapeutic, sub-therapeutic and toxic concentrations. In addition, three quality control (QC) samples with representative target levels were always included.

Analytical accuracy was checked routinely with external control samples when available, and between series precision was calculated from quality control samples. As an example the precision over 12 months was between 5.5 and 12.0% for the benzodiazepines and the Z-drugs. External controls generally had *z*-scores ~~between −1 and 1~~ and almost always *z*-scores ~~between −2 and 2~~.

### 2.4. Fatal toxicity index

Fatal toxicity index [11,15–17] was estimated by relating the number of cases classified as Groups A and B to the sales of that substance in Sweden during 1992 through 2006. Sale statistics for the included substances, defined as the number of DDD (defined daily doses) sold in Sweden, was retrieved from Apotekens Service AB. The analyses of the fatal toxicity index were restricted to the years 2000–2006 for hydroxyzine, propiomazine, clomethiazole, clonazepam, zopiclone, zolpidem, buspirone and zaleplon since sales statistics from the earlier years were not available for these substances. We also compared the number of A and B cases for each substance with the total number of detections in postmortem cases as an additional means of estimating the relative toxicity.

### 2.5. Statistical analyses

The Mann–Whitney *U*-test (unevenly distributed data) was used for group comparisons. The *p*-values were adjusted for multiple comparisons using the Holm procedure [18]. Statistical significance was defined as $p < 0.05$. The R software v2.15.0 was used for statistical analysis [19].

## 3. Results

### 3.1. Reference concentrations

During the study period, toxicological analyses were performed in 73,321 autopsies, and sedatives and hypnotics were identified in 12,608 (17%) of these. After the assessment procedure 3560 (29%) individuals were included in the study; 498 individuals in Group A,

1555 in Group B and 1507 in Group C. In Group D 7455 individuals were included. Sedative and hypnotics were identified in 3593 TDM analyses, of which 1477 were included in Group T.

The median age was 66 years in Group A; 50 years in Group B; 53 years in Group C; 32 years in Group D and; 42 years in Group T. The proportion of women was 54% ($N = 271$) in Group A, 49% ($N = 766$) in Group B, 27% ($N = 403$) in Group C, 15% ($N = 1099$) in Group D, and 57% ($N = 841$) in Group T. Among the postmortem cases, the two main causes of death in Group C were hanging (70%, $N = 1062$) and CNS trauma such as gunshot wound to the head (19%, $N = 286$). The cause of death in Groups A and B was by definition intoxication, and the manner of death was most often suicide; 76% in Group A ($N = 376$) and 66% in Group B ($N = 1124$).

Table 3 shows the femoral blood concentrations of sedatives and hypnotics in intoxications and in controls. For nitrazepam, flunitrazepam, clonazepam and propiomazine, the concentrations presented in Table 3 are the sum of the parent drug and metabolite concentrations.

The median concentrations in Group A were significantly higher than in Group B for oxazepam, propiomazine, zopiclone and zolpidem, and the median concentrations in Groups A and B were significantly higher than in Group C for all substances except alprazolam and triazolam. Although significant differences in the median concentrations among groups were observed, the concentrations in some groups overlapped. The median concentrations in Group T were similar to the concentrations observed in Group D for most substances (alprazolam, clonazepam, flunitrazepam, nitrazepam, oxazepam, and zopiclone). However, for diazepam the median concentration in Group T was higher than in Group D. For midazolam no cases met the inclusion criteria for Group C. Midazolam was however detected in 46 postmortem cases that were excluded since they died in hospital. In those cases the median concentration was 0.1 μg/g femoral blood with 0.03 μg/g and 0.5 μg/g as the 10th and the 90th percentile, respectively. Regarding triazolam, one subject died in hospital and was not included in Group C. In this case triazolam was detected at a concentration of 0.01 μg/g femoral blood.

### 3.2. Fatal toxicity index

Table 4 shows the number of intoxications for each substance related to the respective drug sales in Sweden, as well as to the total number of cases where that substance was detected in medico-legal autopsies in Sweden. Hydroxyzine was the substance with the highest number of fatal intoxications related to the number of DDD sold (2.02 intoxications per ~~106~~ DDD sold). There were however not one single intoxication during this time period where hydroxyzine alone was determined to be the primary cause of death. Propiomazine had the highest number fatal intoxications (Group A and Group B combined) related to the total number of detections in medico-legal autopsies (24%), whereas flunitrazepam had the highest number of fatal intoxications (Group A alone) related to sales (0.43 cases per ~~106~~ DDD sold) as well as related to the total number of detections (8%). When combined, the hypnotic drugs had a higher number of fatal intoxications (Groups A and B combined) related to sales compared with the anxiolytic drugs (1.13 and 0.37 cases per ~~106~~ DDD sold, respectively) as well as when related to the number of detections in femoral blood among autopsy cases (22% and 5%, respectively).

## 4. Discussion

### 4.1. General

In this study we present reference values in postmortem femoral blood for 16 sedative-hypnotic drugs and clonazepam in fatal intoxications and in postmortem controls. These values were also compared with concentrations detected in DUI cases and in a TDM population. Reference information about postmortem blood drug concentrations can be found in published compilations (e.g. [3,20,21]) but almost all of these consist of literature reviews and the quality of the original publications referred to varies. In some studies, the type of blood sample analyzed is not specified. In this study, like in three previous publications [9–11] on the same issue, the results are based on a strategy that provides both concentrations in fatal intoxications and in postmortem controls. Group C is of particular importance, as it provides a better idea of drug concentrations that may be observed without causing incapacitation immediately prior to death.

### 4.2. Methodological aspects

It should be noted that the use of reference information of this kind is intended to assist in the investigation of suspected acute intoxications or obscure deaths that occur outside hospitals. The compilation excludes cases where the subjects died at hospital for two main reasons; firstly, the circumstances surrounding death in hospital are often clear and many medical data are already at hand; secondly, the treatment may include various pharmacological interventions, artificial ventilation and other life-saving medical support, distorting the interpretation of the drug effects. We do, however, present separately some data from hospitalized subjects for midazolam to provide an idea of the concentration spectrum in this setting. It should further be pointed out that reference levels do not replace a meticulous analysis of the individual case.

Regarding DUI cases, it is obvious that many of the subjects might have been inebriated, but still, all of them were alive and were able to drive a vehicle – although not necessarily safely. The concentrations comprise all results obtained, without evaluation of the individual cases. Hence a concentration of a substance in one case might represent an incidental finding while the concentration in another case might be the reason for poor driving.

The TDM levels were based on a large collection of analyses of serum samples from patients treated at various medical facilities. To make the concentrations identified in the TDM cohort comparable with the concentrations identified in the DUI and the postmortem cases, the volume unit (nmol/L) was converted to a mass unit (μg/g). Further, the forensic limits of quantification were applied on the TDM results. This implies that subjects with low drug concentrations (probably therapeutic or subtherapeutic) were excluded. The TDM concentrations presented in this paper is therefore not representative of the whole clinical TDM population. The differences observed between Groups C, D and Group T might partly be explained by differences in matrix used, since it is possible that some of the drugs included show an uneven distribution between serum and the erythrocyte fraction [22–24]. This area is however not well explored. According to Clarke's Analysis of Drugs and Poisons [24], there are known uneven distribution between of the plasma: whole blood ratio for alprazolam (1.35), clomethiazole (1.2), clonazepam (1.54), diazepam (1.8) and oxazepam (0.9). In addition, there are demographic differences between the populations included in the groups.

In our present and previous compilations of postmortem blood concentrations of drugs [9–11], we have reviewed the cases without consideration of active metabolites and the results presented here are based on the levels of the parent compounds only (with the exceptions of clonazepam, diazepam, flunitrazepam, nitrazepam and propiomazine where the postmortem metabolite was added to the parent drug). For two of the drugs included – buspirone and hydroxyzine – both the parent drug and a main metabolite are active [25–27]. For the other drugs included,



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**Table 3**
Femoral blood concentrations of drugs in postmortem cases and blood concentrations in DUI cases and TDM cases (μg/g).

| Substance | Group | N | 10th percentile[a] | Median | 90th percentile[a] | p-Value |
|---|---|---|---|---|---|---|
| Alprazolam[b] | A | 4 | 0.13 | 0.30 | 0.40 | vs. B 0.23 |
| | B | 67 | 0.10 | 0.16 | 0.60 | vs. C 0.08 |
| | C | 51 | 0.02 | 0.05 | 0.12 | vs. A <0.01 |
| | D | 793 | 0.02 | 0.05 | 0.15 | |
| | T | 110 | 0.02 | 0.04 | 0.12 | |
| Buspirone[c] | A | 0 | | | | |
| | B | 11 | 0.05 | 0.20 | 1.10 | |
| | C | 0 | | | | |
| | D | 1 | 0.06 | 0.06 | 0.06 | |
| | T | – | | | | |
| Clomethiazole[c] | A | 5 | 4.50 | 7.00 | 28.0 | vs. B 0.4 |
| | B | 8 | 1.10 | 5.40 | 11.0 | vs. C 0.05 |
| | C | 5 | 0.30 | 0.40 | 3.00 | vs. A 0.04 |
| | D | 21 | 0.40 | 1.20 | 3.60 | |
| | T | – | | | | |
| Clonazepam[d,e] | A | 0 | | | | |
| | B | 51 | 0.14 | 0.30 | 0.75 | vs. C <0.01 |
| | C | 32 | 0.06 | 0.14 | 0.29 | |
| | D | 214 | 0.05 | 0.07 | 0.15 | |
| | T | 94 | 0.05 | 0.07 | 0.15 | |
| Diazepam[f] | A | 3 | 1.20 | 1.40 | 6.00 | vs. B 0.85 |
| | B | 20 | 1.09 | 1.45 | 2.60 | vs. C <0.01 |
| | C | 496 | 0.07 | 0.10 | 0.40 | vs. A <0.01 |
| | D | 4717 | 0.07 | 0.20 | 0.80 | |
| | T | 153 | 0.10 | 0.68 | 1.90 | |
| Flunitrazepam[d,e] | A | 175 | 0.11 | 0.30 | 0.74 | vs. B 0.23 |
| | B | 418 | 0.07 | 0.15 | 0.41 | vs. C <0.01 |
| | C | 192 | 0.01 | 0.03 | 0.14 | vs. A <0.01 |
| | D | 555 | 0.02 | 0.03 | 0.06 | |
| | T | 28 | 0.02 | 0.04 | 0.07 | |
| Hydroxyzine[c] | A | 2 | 0.70 | 1.60 | 2.50 | vs. B 0.34 |
| | B | 104 | 0.30 | 0.60 | 3.30 | vs. C <0.01 |
| | C | 73 | 0.06 | 0.10 | 0.40 | vs. A 0.04 |
| | D | 34 | 0.06 | 0.10 | 0.37 | |
| | T | – | | | | |
| Lorazepam[c] | A | 0 | | | | |
| | B | 2 | 0.29 | 0.55 | 0.80 | |
| | C | 0 | | | | |
| | D | 35 | 0.04 | 0.1 | 0.37 | |
| | T | – | | | | |
| Midazolam[h] | A | 0 | | | | |
| | B | 1 | 0.6 | 0.6 | 0.6 | |
| | C | 0 | | | | |
| | D | 30 | 0.02 | 0.06 | 0.12 | |
| | T | – | | | | |
| Nitrazepam[d,g] | A | 64 | 0.40 | 1.10 | 3.20 | vs. B <0.01 |
| | B | 258 | 0.30 | 0.60 | 1.70 | vs. C <0.01 |
| | C | 196 | 0.05 | 0.09 | 0.29 | vs. A <0.01 |
| | D | 446 | 0.05 | 0.08 | 0.28 | |
| | T | 92 | 0.05 | 0.11 | 0.44 | |
| Oxazepam[e] | A | 4 | ~~2.39~~ | 3.85 | ~~5.59~~ | vs. B 0.02 |
| | B | 79 | 1.08 | 1.80 | 3.44 | vs. C <0.01 |
| | C | 71 | 0.10 | 0.30 | ~~0.92~~ | vs. A <0.01 |
| | D | 476 | 0.20 | 0.40 | 1.70 | |
| | T | 726 | 0.07 | 0.23 | 1.50 | |
| Propiomazine[c,d] | A | 160 | 0.45 | 1.20 | 5.71 | vs. B <0.01 |
| | B | 660 | 0.23 | 0.60 | 2.70 | vs. C <0.01 |
| | C | 246 | 0.03 | 0.06 | 0.20 | vs. A <0.01 |
| | D | 26 | 0.03 | 0.04 | 0.10 | |
| | T | – | | | | |
| Triazolam[h] | A | 1 | 0.02 | 0.02 | 0.02 | vs. B 1.00 |
| | B | 4 | 0.01 | 0.02 | 0.04 | |
| | C | 0 | | | | |
| | D | 7 | 0.002 | ~~0.009~~ | 0.03 | |
| | T | – | | | | |



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**Table 3** (*Continued*)

| Substance | Group | *N* | 10th percentile[a] | Median | 90th percentile[a] | *p*-Value |
|---|---|---|---|---|---|---|
| Zaleplon[c] | A | 0 | | | | |
| | B | 0 | | | | |
| | C | 2 | 0.06 | 0.1 | 0.40 | |
| | D | 5 | 0.07 | 0.10 | 0.14 | |
| | T | – | | | | |
| Zolpidem | A | 25 | 0.6 | 1.50 | 3.32 | vs. B <0.01 |
| | B | 148 | 0.30 | 0.90 | 3.13 | vs. C <0.01 |
| | C | 52 | 0.06 | 0.16 | 0.59 | vs. A <0.01 |
| | D | 558 | 0.08 | 0.23 | 0.63 | |
| | T | – | | | | |
| Zopiclone[c] | A | 54 | 0.40 | 0.8 | 2.84 | vs. B 0.02 |
| | B | 344 | 0.30 | 0.70 | 1.90 | vs. C <0.01 |
| | C | 353 | 0.02 | 0.05 | 0.21 | vs. A <0.01 |
| | D | 502 | 0.03 | 0.08 | 0.27 | |
| | T | 274 | 0.02 | 0.05 | 0.56 | |

Abbreviations: DUI, driving under the influence; TDM, therapeutic drug monitoring. *Group A*: Certified death by intoxication with one single drug. The influence of alcohol (ethanol <0.1%) or other substances, as well as other contributory factors could clearly be ruled out. *Group B*: Certified death by intoxication with more than one drug and/or with drug/s in combination with a significant concentration of ethanol. *Group C*: Certified other cause of death, in which the circumstances excluded the possibility of incapacitation. *Group D*: Individuals driving under the influence. *Group T*: Therapeutic Drug Monitoring data.

[a] The 10th and 90th percentiles are shown if the number of cases exceeds 10, for lower *N* the minimum and maximum values are shown.
[b] TDM samples during 1999–2005.
[c] Lorazepam, propiomazine, zaleplon are not registered in Norway. Buspirone, clomethiazine and hydroxyzine are not included in the TDM analysis.
[d] The concentrations of parent substance and metabolite were added for Groups A–C.
[e] TDM samples during 1999–2006.
[f] TDM samples during 2005–2006.
[g] TDM samples during 1999–2001.
[h] There were no TDM analyses for midazolam and triazolam during the study period.

the metabolites are either not active, not detectable, or present at low concentrations only.

For some substances, the number of Group A cases (single drug fatal intoxication) is low or even lacking. The question then arises whether or not these drugs are potentially lethal. Although the authors do consider these drugs to be potentially lethal in certain settings, caution is advised when referring to the drug levels defined in this study. The reason for paucity or lack of single drug intoxications with these substances might be either that they typically are used in combination with other drugs with toxic properties (resulting in classification as a B case), or that they actually do have a low toxicity. For these drugs, a larger number of cases needs to be reviewed to appreciate their toxicological profiles.

### 4.3. Comparison with previous work

The reference values presented in this paper are difficult to compare with other reported concentrations due to major differences in study design. However, for substances where

**Table 4**
The number of Group A and Group B cases related to the total number of positive identification for each drug in the databases of the National Board of Forensic Medicine (femoral blood samples), and to Swedish sales statistics. The substances regrouped as sedatives or hypnotics and listed according to the number of Group A and Group B cases related to sales.

| Substance | Total number of detections among Swedish medico-legal autopsies (*N*) | Group A cases (*N*) | Group A and Group B cases (*N*) | Proportion of Group A cases among total detections (%) | Proportion of Group A and Group B cases among total detections (%) | Total sales in Sweden (DDD, $\times 10^{-6}$) | Number of Group A cases related to sales | Number of Group A and Group B cases related to sales |
|---|---|---|---|---|---|---|---|---|
| Hypnotics | | | | | | | | |
| Propiomazine[a] | 1507 | 68 | 366 | 4.50 | 24.30 | 245 | 0.28 | 1.49 |
| Flunitrazepam[b] | 2233 | 176 | 594 | 7.88 | 26.60 | 414 | 0.42 | 1.43 |
| Nitrazepam[b] | 1709 | 64 | 322 | 3.74 | 18.80 | 250 | 0.26 | 1.29 |
| Clomethiazole[a] | 31 | 2 | 6 | 6.50 | 19.40 | 7 | 0.30 | 0.89 |
| Zopiclone[a] | 1306 | 30 | 229 | 2.30 | 17.50 | 289 | 0.10 | 0.79 |
| Zolpidem[a] | 525 | 20 | 112 | 3.80 | 21.30 | 214 | 0.09 | 0.52 |
| Midazolam[b] | 227 | – | 1 | – | 0.44 | 5 | – | 0.22 |
| Triazolam[b] | 12 | 1 | 5 | 8.30 | 41.70 | 24 | 0.04 | 0.21 |
| Zaleplon[a] | 9 | – | – | – | – | 5 | – | – |
| Sedatives | | | | | | | | |
| Hydroxyzine[a] | 223 | – | 69 | – | 20.90 | 34 | – | 2.02 |
| Clonazepam[a] | 177 | – | 4 | – | 2.30 | 5 | – | 0.81 |
| Alprazolam[b] | 480 | 4 | 71 | 0.83 | 14.8 | 14 | 0.03 | 0.52 |
| Buspirone[a] | 25 | – | 5 | – | 20.0 | 10 | – | 0.49 |
| Oxazepam[b] | 596 | 4 | 83 | 0.67 | 13.9 | 192 | 0.02 | 0.43 |
| Diazepam[b] | 3873 | 3 | 23 | 0.08 | 0.59 | 280 | 0.01 | 0.08 |
| Lorazepam[b] | 10 | – | 2 | – | 20 | 33 | – | 0.06 |

Abbreviation: DDD, defined daily doses.
[a] During the years 2000–2006.
[b] During the years 1992–2006.



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previously published case reports and case compilations [3,20,21,28–41] are available, the concentrations in fatal intoxication cases generally compare well with the ranges presented in this study. Most of the case reports and case compilations [20,21,29–32,34,36–40] do not provide control cases, which impedes evaluation of their proposed toxic levels. The deviations from the results in this study are likely to be mainly attributed to the larger sample size and the standardized procedures; the latter reducing the incidence of extreme results. Minor differences might be related to the characteristics of the study populations. Apart from our previous paper [9], no published postmortem reference values regarding propiomazine could be found. Regarding diazepam, the levels in multidrug intoxications (Group B) show a good correlation with previously published material [31]. The extremely high number of detections and low number of single drug intoxications with diazepam strongly support the general appreciation of diazepam as a substance with very low toxicity. Actually, among the C cases, there were 14 cases where the concentration exceeded 1 μg/g. The nitrazepam levels in single drug intoxications were substantially lower than previously reported [20], which might be explained by our larger population size.

Several of the substances analyzed in this study were previously reviewed using the same strategy in 1997 [9]; alprazolam, clonazepam, diazepam, nordazepam, flunitrazepam, hydroxyzine, nitrazepam, oxazepam, propiomazin, zolpidem and zopiclone. In general, the extended study period for substances in this communication compared to the previous publication has provided a larger study sample in all groups (Groups A–C). For these drugs, evaluated twice by different reviewers and with different sample sizes, the median concentrations did not differ, lending support to the robustness of the evaluation strategy. Having said that, the ranges in all groups showed a tendency to be lower than in the previous study [9]; in particular, the concentrations in Group B for alprazolam, hydroxyzin and oxazepam (0.16 μg/g vs. 0.30 μg/g, 0.60 μg/g vs. 1.30 μg/g and 1.80 μg/g vs. 3.60 μg/g, respectively). Regarding oxazepam the Group A median concentration was lower than in previously published data (3.85 μg/g vs. 5.30 μg/g). This can most easily be explained by the large increase in the number of cases within these groups as compared with our previous study (more than 10-fold increase in Group B, and a doubling of oxazepam cases in Group A).

### 4.4. Fatal toxicity index

To assess differences in the risk of fatal intoxications between substances, fatal toxicity indexes are commonly used [15,16]. The fatal toxicity index has been shown to be related to the lethal toxicity in animals, to physiochemical factors known to be related to toxicity in humans and measures of cardiac effects (for antidepressants) [15,16]. In this study, flunitrazepam was the most frequent drug in Group A when related to sales. The fatal toxicity index should, however, be interpreted with caution due to the limited number of intoxications for some substances. Moreover, some of the substances included in this study are commonly used for "recreational purposes" and hence a proportion of the subjects might have taken these without a prescription. In a Swedish study [42] of DUI subjects, only 24% of the flunitrazepam positive cases, and 26% of the diazepam positive cases, had a prescription within the last 12 months. The corresponding proportion for zolpidem was 79% and for zopiclone 70%. When relating the number of fatal intoxications in this study to all detections, flunitrazepam was still in top.

In this study, hypnotics were associated with a higher number of intoxications in relation to sales compared with anxiolytics. This has also been observed in a British study [43] based on cause of death statistics and in two previous Swedish studies [44,45] based on medico-legal data. The number of fatal intoxications with anxiolytics in relation to sales has previously been shown to be small in comparison with the number of fatal intoxications attributed to barbiturates [17]. During 1961–1974, 118 deaths due to barbiturates and 6 deaths due to benzodiazepines per million prescriptions were identified in England and Wales [43].

We have previously performed similar analyses on intoxications related to antidepressants [11]. The overall number of intoxications was somewhat lower in this study compared with the antidepressants when related to sales and to the total number of detections. The top substance in that study was trimipramine with 1.91 Group A intoxications per million DDD sold, compared with 0.41 Group A intoxications for flunitrazepam per million DDD sold in the present study.

### 4.5. Strengths and limitations

The major strengths with this study are the strict inclusion criteria that all postmortem cases included were assessed by two independent reviewers, and that in cases with unexpected high or low concentrations, the original files were scrutinized. Moreover, only femoral venous blood concentrations were considered, and the samples were collected and handled according to a standardized procedure and analyzed at a single laboratory. Further, for most substances a large number of cases were evaluated and comparisons with previous evaluations using the same strategy showed that the results were robust.

However, for some substances the number of cases in one or more groups was low, and their medians and ranges should be used with caution. The low occurrence of these drugs in our postmortem data might be multifactorial. Since many more sedatives and hypnotics are marketed in other parts of the world, we encourage more studies using the same strategy.

### 4.6. Conclusions

In conclusion, this study provides blood reference concentrations that may assist forensic pathologists and toxicologists in the interpretation of postmortem drug levels.

## Conflict of interest

The authors declare no conflict of interest.

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