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A Compilation of Fatal and Control Concentrations of Drugs in Postmortem Femoral Blood

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ABSTRACT: A compilation of postmortem femoral blood concentrations of drugs is presented. The samples are collected from cases in which the cause of death was: A) certified intoxication by one substance alone, B) certified intoxication by more than one substance and/or alcohol, and C) certified other cause of death without incapacitation due to drugs. The concentrations were compared with blood concentrations detected in suspected drugged drivers (D), and with previously published fatal and therapeutic concentrations. The special features of this compilation are: 1) exclusively femoral blood concentrations are quoted, 2) all analyses are based on samples handled according to a standardized, quality-controlled procedure, 3) two control groups are included, and 4) one-substance-only intoxications are separated from other intoxications. The material is based on a selection of 15,800 samples sent to the Department of Forensic Chemistry in Linköping, Sweden, during 1992 to 1995 from the six forensic pathology units in Sweden, and the list includes 83 drugs. The compilation includes drugs, where previously published data are scarce. Furthermore, the data gathered from cases with other cause of death than intoxication (group C) constitute a new kind of reference information, which probably offers a better estimate of obviously non fatal levels in postmortem blood than any compilation of therapeutic concentrations in living subjects. The possible factors influencing postmortem drug concentrations are discussed.

KEYWORDS: forensic science, forensic toxicology, postmortem, femoral blood, drug concentrations, fatality

The interpretation of postmortem toxicology data is often a crucial factor in the determination of cause of death. The diagnosis of a fatal intoxication must be based on reasonable toxicology results, postmortem findings and circumstances, all taken into account. The toxicological analysis results should never be considered alone, neither should the circumstances or postmortem findings.

Literature on postmortem blood concentrations in fatal intoxications is mainly available in the form of case reports. Some review articles summarize data on therapeutic, toxic, and fatal concentrations of various drugs (1–6), but so far, no compiled information is published about the normal postmortem concentrations of various drugs. Instead, data on therapeutic levels are provided as reference values for the range of normal serum or plasma concentrations. Because, however, neither serum nor plasma, but whole blood is used for postmortem toxicological analyses, clinical information about therapeutic concentrations is not always applicable, because of variations in erythrocyte binding between drugs.

Whereas the concentrations of some substances seem to remain essentially unchanged after death, others may increase or decrease postmortem (7–17). Furthermore, several studies have disclosed postmortem redistribution of various drugs (7,9,11–15,18–21) causing differences in concentrations between sampling sites. Unfortunately, the sampling site is not always stated in published material, making interpretation of the concentrations difficult. In addition, many reports lack information about method of collection, storage conditions, addition of preservatives, and presence of other drugs or alcohol. Therefore, present knowledge of therapeutic, toxic, and fatal levels probably contains several pitfalls.

Complaints about lack of correspondence between values presented in different compilations have recently led to debate (22,23). Discrepancies of this type may, of course, be explained by the fact that the authors tend to vary in their evaluation of published and own material. The major disadvantage with all compilations of published toxicology data is, however, the lack of standardized material. Values may be based on heart blood or peripheral blood, or both. In many reports, the sampling site is not even mentioned. For a number of drugs, the sampling site may considerably affect the blood concentration due to postmortem redistribution (7,9,11,12,15,18–21).

To overcome these problems, and because knowledge about the possible overlap between non fatal and fatal concentrations of various drugs must be generally available, consistent sampling and analyses of specimens from deceased control cases is necessary. Thus, we have compiled a list of postmortem drug concentrations, based on Swedish postmortem toxicology data obtained under standardized conditions regarding sample site, sampling technique, analytical methods, and sample storage and treatment.

Material and Methods

Material

During the 1992–1995 period, a total of 15,800 blood samples were collected at medicolegal autopsies performed in Sweden. All toxicology results were recorded in the forensic toxicology database, enabling rapid retrieval of all positive findings (24). In accordance with instructions from the National Board of Forensic Medicine (the authority responsible for all forensic pathology, toxicology, serology, and psychiatry activities in Sweden) all forensic pathology units in the country use the same standardized routines for sample collection and handling (25).

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Collection of Samples

At the autopsy, femoral blood (when available), is collected in a 20-mL plastic tube. The blood is collected by cutting off the iliac veins (avoiding the arteries) using a clean knife and pressing the blood in the popliteal and femoral veins into the tube. The blood from both sides is pooled. Potassium fluoride is added to a concentration of 1% using an automatic pipette. Care is taken to avoid blood from the lower vena cava; the blood in the upper portion of the iliac veins is pressed upwards before cutting.

Handling of Samples

All samples are labeled with case number, name, and civic registration number of the deceased, and with sample site. These data are verified by comparison with the label attached to the body, with the data in the police report, and with other documents. After addition of potassium fluoride, the samples are shaken carefully to achieve an even distribution of the additive and stored at 4°C until analyzed (except during transportation). The identity of each sample is checked on several occasions at the forensic pathology unit and at the forensic toxicology laboratory, in accordance with standardized routines.

Other Samples

Urine and vitreous humor are also routinely collected. For alcohol analysis, a separate portion of femoral blood and urine is collected in prefluoridized, 5-mL plastic tubes. Supplementary samples, such as heart blood, liver, skeletal muscle, liquor, and stomach content are collected if standard samples are lacking, or if this is considered necessary for obtaining additional information.

Selection and Classification

Information about the cases was obtained from the forensic toxicology and forensic pathology databases (24). The rough selection was based on the ICD-9 codes linked with the cause-of-death diagnoses made by the responsible pathologist.

We decided to exclude illicit drugs from this compilation because the interpretation of these substances requires a different approach than that used for this study, particularly due to the extensive intravenous usage and significant interindividual differences in tolerance.

Furthermore, cases in which intravenous administration of other drugs could be suspected were excluded as far as possible. For most drugs, oral intake was either certain or highly probable, but for ketamin, lidocain, mepivacain, pethidine, and tiopental, intravenous administration was likely.

The remaining cases were primarily classified as follows:

Intoxications—Cases in which the pathologist had stated "intoxication by drug(s)" as the immediate cause of death. Manner of death was not taken into account. The continued computer-assisted selection comprised the following exclusion criteria: Lack of femoral blood, hypothermia, massive aspiration, drowning, concomitant gas poisoning, and severe diseases. Resuscitation was not an exclusion criteria, but cases subject to more intensive health care intervention were eliminated. The remaining cases constituted the A and B groups described below.

Controls—Cases in which the pathologist had diagnosed as hanging, shooting, self-stabbing, and suicide by other methods, but not drowning or intoxication. To this category we also added a number of cases with trauma diagnoses due to accidents.

The continued computer-assisted selection of these cases comprised the following exclusion criteria: Lack of femoral blood, injuries to thorax or abdomen, and health care intervention. In addition, all cases in which the circumstances left unanswered the question about possible impairment by drugs were excluded. The remaining cases constituted group C, described in detail below.

Further Selection and Considerations

All toxicology findings in the cases selected in the intoxication group were further subject to manual interpretation, independently by the authors and, finally discussed in detail. Each case was scrutinized regarding the importance of every substance present and special attention was paid to the concentration of alcohols (if present). Clean cases, i.e., cases with presence of one substance alone, constituted group A. In cases with high concentrations of two or more substances, both concentrations were classified as group B values. Thus, the same case may contribute to the B-group values of more than one substance.

Unexpectedly high or low concentrations were examined after the preliminary classification, autopsy protocols; police reports, and all other original documents from the A and B cases were perused. Accordingly, the original files of control cases with unexpectedly high concentrations were also checked.

Decomposition was not an exclusion criteria. Some degree of decomposition was present in 16% of the cases. Nine substances from different groups of drugs were studied with special reference to the influence of decomposition.

Special attention was paid to the concentration of alcohols (if present). For most drugs, a concentration of ethanol below 0.1% was accepted in A cases. We considered the possibility of classifying the C cases similarly, i.e., to separate cases with a given substance as the only finding from cases in which additional substances, including alcohol, were detected. Our conclusion was, however, that this was likely to cause confusion and complicate the interpretation of the list. This alternative was thus discarded, and a control case may therefore contribute to the C-group values of several substances.

In summary, the finally included cases were classified as follows: Group A: Certified deaths by intoxication including only clean cases, i.e., in which influence of alcohol or other substances and other contributory factors could be ruled out. Group B: Certified deaths by intoxication in which more than one substance and/or significant alcohol concentrations were found. Group C: Certified other cause of death, in which the circumstances excludes the possibility of incapacitation by drugs. In addition, a second control group was established: Group D: Suspected-drugged drivers (blood samples collected 1992–1994 from living subjects and analyzed at the Department of Forensic Chemistry in Linköping).

Following the selection procedure, statistical processing was performed using Statistica™ from StatSoft Inc, Tusla, Oklahoma, USA. Comparisons between means of the different decomposition groups were made by using Student's *t*-test. A *P*-value of <0.05 was considered significant. Percentiles were calculated if subgroups included at least 10 cases. Quartiles were calculated when subgroups contained four to nine cases. The median value was calculated for all subgroups.

Analytical Methods

In all cases, the following analytical methods were used. Ethanol and other alcohols were analyzed by head-space gas-chromatography. Analyses were always performed in two different specimens, normally femoral blood and urine or vitreous humor. Salicylate and oxazepam were analyzed using HPLC, and trichloro-ethanol was analyzed using a spectrophotometric method. All other drugs were analyzed by gas-chromatography utilizing HP 5880A gas chromatographs equipped with HP 7673A autoinjectors and NP detectors.

Two different extraction methods were used according to the following procedures. An alkaline extract was made by extracting 1.0 g of femoral blood with 0.4-mL butyl-acetate after the addition of 0.3-mL 1 M trisbuffer, pH 11, and 0.03-mL internal standard (0.05 mg cyclizine and 0.10 mg mesoridazine per mL). After extraction for 10 min and subsequent centrifugation, an aliquot was injected in split-mode into a DB-5 (15 m by 0.25 mm ID, 0.25 μm thickness). The injector temperature was 250°C, and the temperature was increased in increments from 200 to 300°C. The total run time was about 17 min.

A neutral extract was made using 1.0 g of femoral blood, 0.5 mL 0.5 M phosphate buffer pH 7.0, 0.05 mL internal standard (0.1 mg allobarbital and 0.01 mg prazepam per mL), and extraction with 0.5-mL butyl-acetate for 10 min. After centrifugation, an aliquot was injected in split-mode into the column. The injector temperature was 250°C and the column used was a SE-54 (25 m by 0.31 mm ID, 0.17 μm thickness). The temperature was increased in increments from 150°C to a final temperature of 300°C. The total run time was about 20 min.

Standard curves used for the quantitation of the drugs were made by adding known amounts of each drug to drug-free blood and plotting the area response ratio for drug and internal standard versus the concentration of the drug. For each drug investigated, a linear correlation was achieved. In each run, several internal controls were used to achieve high quality and similar results over time. The laboratory participates in international quality assurance programs.

Results

Table 1 shows the femoral blood concentrations of the drugs studied, distributed according to the groups as described in "Selection and classification." The data are given in μg/g blood. The molecular weight of each substance is also shown. The parent substances are sorted alphabetically, with the metabolite (if presented) directly following the parent drug. Drugs with fewer than five cases in groups A, B, and C together are not listed.

Because of the significant postmortem transformation of the benzodiazepines clonazepam, flunitrazepam, and nitrazepam into their 7-amino metabolites, the concentrations of the parent drug and metabolite are added in the table.

Because nortriptyline is marketed as such in Sweden, it was considered to be the parent drug when found alone. However, when occurring together with amitriptyline, we counted it as the metabolite of amitriptyline, despite the (unlikely) possibility of ingestion of both nortriptyline and amitriptyline. Nortriptyline values are therefore presented twice in the table.

Desipramine as such is not marketed in Sweden. It occurs in the toxicology material as the result of the breakdown of either imipramine or lofepramine. Whereas imipramine is easily detected, lofepramine may escape detection. Thus, because the origin of desipramine often is unknown, it is presented separately.

TABLE 1—*Femoral blood concentrations of 83 substances. Group A = fatal intoxication with the substance exclusively. Group B = fatal intoxication with the substance in combination with other drugs and/or alcohol. Group C = other cause of death without incapacitation due to drugs. Group D = Concentrations in whole blood from suspected-drugged drivers. In groups A to C, concentrations refer to femoral blood. LOW = lower percentile (N > 9), lower quartile (N = 4–9), or minimum value (N < 4). HIGH = upper percentile (N > 9), upper quartile (N = 4–9), or maximum value (N < 4). FLU = flunitrazepam. CLO = clonazepam. NIT = nitrazepam. All values are given in μg/g. The numbers beneath the drug names refer to the molecular weights, enabling calculation of molarities. Substance names are given according to Clark's isolation and identification of drugs (3). For some drugs, common synonyms are displayed in brackets.*

Substance	Case Type	*N*	Low	Median	High
Acetaminophen	A	0			
(*Paracetamol*)	B	139	90	170	320
151.2	C	168	1.0	5.0	13
	D	67	0.9	4.0	22
Alimemazine	A	11	1.0	1.6	3.2
(*Trimeprazine*)	B	9	0.5	0.9	1.2
298.4	C	15	0.1	0.1	0.4
	D	3	0.06	0.1	0.1
Desmethylalimemazine	A	11	0.2	0.7	1.3
284.4	B	8	0.2	0.3	0.5
	C	9	0.1	0.2	0.2
	D	2	0.07	0.14	0.2
Alprazolam	A	0			
308.8	B	5	0.3	0.3	0.4
	C	6	0.02	0.05	0.05
	D	22	0.02	0.05	0.18
Amitriptyline	A	49	1.2	3.2	14
277.4	B	39	0.5	1.4	6.0
	C	29	0.1	0.2	0.6
	D	7	0.05	0.09	0.1
Nortriptyline, metabolite	A	46	0.2	0.8	3.1
263.4	B	33	0.1	0.3	1.2
	C	23	0.1	0.1	0.4
	D	4	0.08	0.09	0.3
Biperiden	A	0			
311.5	B	4	0.25	0.29	0.66
	C	2	0.02	0.04	0.06
	D	0			
Caffeine	A	0			
194.2	B	9	21	30	32
	C	7	12	17	30
	D	0			
Carbamazepine	A	7	35	45	70
236.3	B	9	10	14	19
	C	56	0.5	4.5	10
	D	30	0.9	4.0	8.3
Carisoprodol	A	14	9.3	25.5	40
260.3	B	16	5.4	11.5	37
	C	7	0.4	0.7	1.8
	D	31	0.4	2.8	8.4
Chlordiazepoxide	A	1		4.4	
299.8	B	4	2.7	2.9	3.0
	C	12	0.1	0.2	1.3
	D	12	0.3	1.1	6.0
Chlormezanone	A	1		18	
273.7	B	7	11	14	16
	C	6	0.3	1.3	6.3
	D	17	0.4	1.5	14
Chloroquine	A	6	1.3	23.5	35.5
319.9	B	3	0.4	1.2	16
	C	9	0.2	0.9	1.7
	D	0			
Chlorpromazine	A	1		6.7	
318.9	B	2	0.8	1.6	2.4
	C	4	0.1	0.1	0.2
	D	0			

TABLE 1—*Continued*

Substance	Case Type	*N*	Low	Median	High
Desmethylchlorpromazine	A	1		0.1	
304.9	B	0			
	C	0			
	D	0			
Chlorprothixene	A	2	1.6	1.6	1.7
315.9	B	2	0.6	3.8	7.0
	C	1		0.2	
	D	0			
Chlorzoxazone	A	0			
169.6	B	13	8.0	11	28
	C	8	0.6	1.1	4.6
	D	6	0.3	2.2	3.1
Citalopram	A	8	3.4	7.0	10.5
324.4	B	13	0.7	1.1	4.7
	C	71	0.1	0.6	1.1
	D	22	0.06	0.15	0.4
Desmethylcitalopram	A	8	0.1	0.3	0.7
310.4	B	13	0.1	0.1	0.6
	C	43	0.1	0.2	0.3
	D	9	0.05	0.08	0.1
Clomipramine	A	9	1.6	1.9	2.4
314.9	B	37	0.6	1.1	5.0
	C	61	0.1	0.2	0.4
	D	17	0.02	0.08	0.4
Desmethylclomipramine	A	9	0.8	1.4	2.0
300.9	B	37	0.2	0.7	4.9
	C	46	0.1	0.2	0.7
	D	12	0.06	0.3	0.5
7-amino-clonazepam	A	0			
285.7	+CLO B	4	0.3	0.6	1.0
	C	6	0.06	0.13	0.18
	D	15	0.02	0.04	0.28
Clozapine	A	2	1.2	3.2	5.2
326.8	B	0			
	C	6	0.1	0.6	1.1
	D	0			
Codeine	A	1		0.6	
299.4	B	25	0.5	1.1	2.6
	C	20	0.02	0.05	0.4
	D	44	0.005	0.04	0.4
Desipramine	A	0			
266.4	B	4	0.9	1.2	1.5
	C	11	0.1	0.2	0.8
	D	2	0.05	0.06	0.06
Diazepam	A	0			
284.7	B	0			
	C	90	0.1	0.1	0.3
	D	275	0.1	0.2	0.8
N-desmethyldiazepam	A	0			
(nordazepam)	B	0			
270.7	C	89	0.1	0.1	0.3
	D	251	0.1	0.2	0.7
Diltiazem	A	0			
414.5	B	0			
	C	13	0.1	0.2	0.4
	D	0			
Dixyrazine	A	2	5.5	7.5	9.4
427.6	B	12	0.8	2.0	9.0
	C	3	0.2	0.2	0.5
	D	1		0.4	
Ephedrine	A	0			
174.2	B	0			
	C	10	0.1	0.2	0.6
	D	16	0.05	0.3	2.0
Ethylmorphine	A	0			
313.4	B	5	0.2	0.4	0.9
	C	0			
	D	7	0.01	0.01	0.02
Flunitrazepam	A	0			
313.3	B	0			
	C	5	0.02	0.03	0.05
	D	130	0.01	0.01	0.05
7-amino-flunitrazepam	+ FLU A	44	0.16	0.31	0.64
283.3	+ FLU B	139	0.06	0.14	0.43
	C	73	0.01	0.02	0.12
	D	143	0.01	0.02	0.06
Fluvoxamine	A	4	3.4	5.0	10.7
318.4	B	10	1.2	3.5	8.1
	C	9	0.2	0.5	0.7
	D	1		0.3	
Hydroxyzine	A	1		2.5	
374.9	B	8	0.9	1.3	1.5
	C	6	0.1	0.2	0.4
	D	5	0.05	0.2	1.0
Imipramine	A	0			
280.4	B	4	1.2	1.4	2.8
	C	4	0.1	0.2	0.5
	D	1		0.1	
Ketamine	A	0			
237.7	B	0			
	C	43	0.3	1.0	3.4
	D	5	0.1	1.0	1.0
Ketobemidone	A	3	0.2	0.3	0.6
247.3	B	5	0.3	0.4	0.5
	C	5	0.03	0.05	0.12
	D	2	0.05	0.06	0.07
Lidocaine	A	0			
234.3	B	6	1.0	2.1	2.1
	C	113	0.1	0.2	1.2
	D	5	0.06	0.2	0.3
Maprotiline	A	8	2.7	3.5	5.8
277.4	B	6	1.0	2.7	3.6
	C	11	0.1	0.3	0.9
	D	0			
Melperone	A	5	1.0	3.7	3.8
263.4	B	7	3.0	5.9	11
	C	6	0.1	0.2	0.2
	D	0			
Dihydromelperone	A	5	0.6	1.1	1.2
265.3	B	7	1.3	2.6	3.0
	C	6	0.1	0.1	0.2
	D	0			
Mepivacaine	A	0			
246.4	B	0			
	C	21	0.1	0.3	1.3
	D	8	0.2	0.3	0.3
Meprobamate	A	3	130	245	260
218.3	B	16	22	31	73
	C	5	2.8	3.5	4.6
	D	34	3.7	12.5	37
Methadone	A	6	0.5	0.8	1.1
309.5	B	0			
	C	3	0.1	0.1	0.3
	D	24	0.05	0.1	0.2
Methotrimeprazine	A	5	0.8	2.3	3.2
(Levomepromazine)	B	26	0.5	0.9	3.5
328.5	C	15	0.1	0.1	1.7
	D	4	0.04	0.07	0.1
Desmethylmethotrimeprazine	A	5	0.4	2.3	4.5
314.5	B	21	0.2	0.5	1.7
	C	11	0.1	0.2	1.0
	D	3	0.08	0.1	0.2
Mianserin	A	3	1.6	2.8	13
264.4	B	8	0.7	0.9	1.3
	C	50	0.03	0.08	0.2
	D	3	0.01	0.02	0.04
Desmethylmianserin	A	3	1.4	1.5	5.1
250.4	B	5	0.1	0.3	0.4
	C	26	0.03	0.1	0.2
	D	0			

TABLE 1—*Continued*

Substance	Case Type	*N*	Low	Median	High
Midazolam	A	0			
325.8	B	0			
	C	21	0.03	0.05	0.4
	D	0			
Moclobemide	A	0			
268.7	B	10	1.9	4.4	21
	C	17	0.2	0.6	2.1
	D	2	0.3	0.4	0.5
Oxomoclobemide	A	0			
282.7	B	10	0.3	0.9	2.4
	C	18	0.2	0.5	0.8
	D	1		0.5	
Nitrazepam	A	0			
281.3	B	0			
	C	12	0.01	0.02	0.03
	D	85	0.02	0.05	0.19
7-amino-nitrazepam	+ NIT A	16	0.5	1.2	2.8
251.3	+ NIT B	57	0.2	0.8	1.8
	C	90	0.04	0.08	0.2
	D	83	0.02	0.05	0.2
Nortriptyline	A	5	1.6	3.8	4.0
263.4	B	8	1.9	2.3	3.3
	C	0			
	D	0			
Orphenadrine	A	18	5.3	15	145
269.4	B	10	4.6	8.9	40
	C	17	0.1	0.3	1.6
	D	9	0.1	0.2	0.2
Oxazepam	A	2	4.4	5.3	6.1
286.7	B	5	2.3	3.6	3.7
	C	20	0.1	0.3	0.7
	D	76	0.2	0.5	1.4
Paroxetine	A	0			
329.4	B	6	0.7	4.5	4.6
	C	15	0.09	0.3	0.5
	D	1		0.09	
Pentobarbital	A	2	10	34	58
226.3	B	1		10	
	C	11	0.1	0.4	1.4
	D	10	0.1	1.2	4.9
Pethidine	A	0			
247.3	B	0			
	C	8	0.2	0.3	0.5
	D	9	0.1	0.2	0.3
Phenazone	A	0			
188.2	B	24	13	31.5	100
	C	10	2.1	6.3	28
	D	22	0.8	2.5	11
Phenobarbital	A	9	55	75	114
232.2	B	4	25.5	36.5	47
	C	4	2.5	7.0	13
	D	11	1.0	17	90
Phenylpropanolamine	A	0			
151.2	B	0			
	C	5	0.06	0.2	0.3
	D	4	0.09	0.1	0.2
Phenytoin	A	1		43	
252.3	B	1		80	
	C	14	1.0	5.0	14
	D	5	3.0	11	11.5
Promethazine	A	3	1.8	2.4	5.4
284.4	B	9	0.6	5.2	11.8
	C	11	0.1	0.1	0.3
	D	6	0.03	0.1	0.1
Desmethylpromethazine	A	3	0.3	1.4	1.8
270.4	B	9	0.1	0.3	1.6
	C	7	0.1	0.1	0.2
	D	1		0.07	
Propiomazine	A	24	0.1	0.9	5.4
340.5	B	85	0.08	0.3	1.9

TABLE 1—*Continued*

Substance	Case Type	*N*	Low	Median	High
	C	14	0.03	0.05	0.4
	D	4	0.03	0.04	0.08
Dihydropropiomazine	A	24	0.9	1.9	5.8
342.5	B	85	0.3	0.7	2.0
	C	44	0.03	0.08	0.2
	D	3	0.04	0.09	0.1
Propoxyphene	A	72	1.3	2.8	8.1
(dextropropoxyphene)	B	223	0.9	2.0	5.9
339.5	C	89	0.1	0.2	0.8
	D	31	0.04	0.1	0.4
Propranolol	A	7	4.6	11	13
259.3	B	5	3.9	5.8	5.9
	C	2	0.1	1.1	2.0
	D	3	0.1	0.1	1.9
Remoxipride	A	11	41	65	150
371.3	B	10	3.6	23.5	73
	C	15	0.7	1.6	4.1
	D	4	0.07	0.2	0.1
Salicylate	A	1		940	
138.1	B	3	150	158	230
	C	5	15	36	39
	D	0			
Theophylline	A	4	85	110	140
180.2	B	7	20	62	100
	C	27	1.0	4.0	10
	D	3	0.6	2.0	4.0
Thiopental	A	0			
242.3	B	0			
	C	36	0.1	0.5	2.1
	D	5	1.2	4.0	4.1
Thioridazine	A	5	2.4	3.3	3.5
370.6	B	14	1.0	1.8	3.8
	C	19	0.1	0.3	0.7
	D	9	0.1	0.2	0.4
Trichloroethanol	A	16	60	125	390
149.4	B	6	27	98	109
	C	0			
	D	0			
Trimethoprim	A	0			
290.3	B	0			
	C	6	0.4	2.2	5.9
	D	0			
Trimipramine	A	10	1.7	3.5	8.2
294.4	B	17	0.7	1.9	15
	C	8	0.4	0.5	0.8
	D	2	0.05	0.1	0.2
Desmethyltrimipramine	A	10	0.3	0.8	2.5
280.4	B	16	0.1	0.5	1.2
	C	7	0.1	0.2	0.5
	D	0			
Verapamil	A	1		3.9	
454.6	B	5	1.6	1.9	3.6
	C	20	0.1	0.2	1.0
	D	0			
Norverapamil	A	1		1.3	
440.6	B	5	0.1	0.8	0.8
	C	17	0.1	0.1	0.3
	D	0			
Vinbarbital	A	2	17	18	19
224.3	B	4	12.1	15.1	18.5
	C	0			
	D	0			
Zolpidem	A	0			
307.4	B	9	0.9	1.3	1.3
	C	3	0.08	0.1	0.12
	D	9	0.13	0.16	0.23
Zopiclone	A	4	0.6	0.7	1.8
388.5	B	16	0.4	1.2	2.3
	C	10	0.06	0.08	0.4
	D	26	0.03	0.11	0.4

Table 2 shows the influence of decomposition on concentrations of nine selected drugs. The degree of decomposition is based on the pathologist's note on the toxicology request, in which three alternatives are available: None, moderate, or severe. Cases with moderate or severe decomposition were treated as one group and compared with nondecomposed cases. Eight out of nine substances investigated were not affected by decomposition. Flunitrazepam (i.e., parent drug and 7-aminoflunitrazepam together), however, showed significantly higher levels in the decomposed than in the non decomposed group.

Table 3 displays the number of cases with a positive finding of the 100 most commonly detected substances, arranged according to number of cases. Ethanol and carbon monoxide are omitted, though commonly encountered.

Figures 1a–c shows graphically the levels of citalopram, carisoprodol, and methotrimeprazine. The line plots illustrates the differences in overlap between the A, B, C and D groups of these substances.

Discussion

The data presented in Table 1 are based on consistent sampling of femoral vein blood (when available) from all autopsy cases, not only from suspected intoxications. The primary selection is based on the diagnoses (immediate cause of death) made by the responsible forensic pathologist; not by the present authors. The adjustments made by the authors are few and mainly limited to exclusion of cases according to the specifications described above.

Compared with previously published compilations (1–6), the ranges for fatal concentrations are similar for most drugs presented in Table 1. Naturally, there are some differences, which may be explained by e.g., the population studied (the distribution of age, sex, and race) sampling site, average postmortem interval, and analytical methods.

It is hardly meaningful to compare our control levels with therapeutic levels, because we do not know whether the concentrations in the C group represents therapeutic, subtherapeutic, or toxic levels. What we do know is that the deceased in this group had some degree of capacity to perform complex tasks, and yet displayed the blood levels presented.

The same applies to the cases in group D. These suspected drugged drivers were either caught in routine police controls or

TABLE 2—*Effect of decomposition on blood drug levels. Mean ± SD. No = no significant decomposition changes of the body. Yes = moderate or severe degree of decomposition of the body.*

Substance	No	Yes
Alimemazine (*Trimeprazine*)	1.00 ± 7.39 (183)	1.06 ± 3.40 (41)
Amitriptyline	1.96 ± 4.32 (244)	1.28 ± 2.82 (52)
7-amino-nitrazepam	0.32 ± 0.48 (535)	0.32 ± 0.39 (138)
Citalopram	0.87 ± 2.91 (349)	0.91 ± 1.40 (52)
Clomipramine	0.82 ± 1.63 (232)	0.91 ± 1.03 (39)
Dihydropropiomazine	0.73 ± 4.75 (457)	0.73 ± 1.64 (108)
Propoxyphene (*Dextropropoxyphene*)	1.80 ± 5.50 (1017)	1.72 ± 3.43 (175)
7-amino-flunitrazepam	0.12 ± 0.19 (715)	0.19 ± 0.29 (133)*
Methotrimeprazine (*Levomepromazine*)	0.57 ± 1.16 (181)	0.63 ± 1.22 (39)

*P = 0.000,356.

TABLE 3—*The 100 most commonly detected substances in the postmortem material, arranged according to the number of positive cases. Note that the table displays data for the years 1992–1994, whereas a number of cases from 1995 are included in Table 1.*

Substance	1992	1993	1994	Total
Acetaminophen (paracetamol)	478	493	543	1514
Propoxyphene (dextropropoxyphene)	300	345	374	1019
N-desmethyldiazepam (nordazepam)	253	253	297	803
Diazepam	234	246	285	765
7-amino-flunitrazepam	225	256	237	718
7-amino-nitrazepam	197	211	189	597
Carbamazepine	155	198	176	529
Dihydropropiomazine	159	168	181	508
Codeine	122	154	151	427
Morphine	128	137	161	426
Lidocaine	148	148	110	406
Propiomazine	117	113	122	352
Amitriptyline	95	95	83	273
Clomipramine	87	87	71	245
Nortriptyline	93	84	67	244
Amphetamine	88	64	82	234
Isopropanol	77	65	76	218
Norpropoxyphene	64	86	61	211
Alimemazine (trimeprazine)	78	56	71	205
Theophylline	70	75	57	202
Desmethylclomipramine	79	60	62	201
Methotrimeprazine (levomepromazine)	68	57	70	195
Citalopram	0	32	156	188
Oxazepam	58	55	56	169
Thioridazine	53	54	57	164
Tetrahydrocannabinol	52	53	58	163
Orphenadrine	55	55	45	155
Phenytion	40	48	52	140
Mianserin	53	44	36	133
Desmethylcitalopram	0	23	107	130
Desmethylmethotrimeprazine	49	40	37	126
6-acetylmorphine	38	47	40	125
Nitrazepam	64	33	25	122
Desmethylalimemazine	53	31	35	119
Quinine/Quinidine	38	33	36	107
Flunitrazepam	29	44	32	105
Verapamil	36	35	34	105
Ketamine	32	35	35	102
Carisoprodol	26	39	34	99
Phenazone	39	29	30	98
Thiopental	44	36	18	98
Phenobarbital	28	24	38	90
Promethazine	27	27	33	87
Norverapamil	32	26	24	82
Caffeine	5	28	47	80
Zopiclone	3	17	59	79
Trimipramine	26	26	20	72
Remoxipride	24	38	6	68
Meprobamate	22	28	17	67
Midazolam	17	25	25	67
Chlormezanone	24	27	15	66
Moclobemide	21	22	22	65
Chlordiazepoxide	26	17	21	64
Desmethylmianserin	31	22	11	64
Hydroxizine	20	26	16	62
Insulin	17	20	25	62
Oxomoclobemide	19	22	20	61
Mepivacaine	16	26	15	57
Paroxetine	12	24	20	56
Cyanide	22	22	10	54
Diltiazem	17	21	14	52
Desmethyltrimipramine	18	20	13	51
Maprotiline	14	19	17	50
Methanol	19	13	17	49
Alprazolam	13	21	14	48
Chlorzoxazone	19	11	17	47
Melperone	12	21	14	47
Desmethylpromethazine	22	11	12	45

TABLE 3—*Continued*

Substance	1992	1993	1994	Total
Pentobarbital	13	18	12	43
Dixyrazine	13	15	14	42
Fluvoxamine	18	9	15	42
Salicylate	8	12	22	42
Desipramine	14	18	8	40
Propranolol	9	15	16	40
Chloroquine	14	12	12	38
Ketobemidone	15	12	10	37
Methadone	15	11	11	37
N,N,dimethyl-4,4-diphenyl-3-buthen-2-amine	13	15	6	34
Chlorpromazine	11	18	5	34
Dihydromelperone	8	18	8	34
Ephedrine	10	14	8	32
Trimethoprim	7	16	9	32
7-amino-clonazepam	5	6	19	30
Clozapine	9	7	12	28
Fluconazole	10	5	13	28
Pethidine	13	8	7	28
Trichloroethanol	7	10	11	28
Digoxin	8	7	11	26
Biperiden	9	8	7	24
Ethylmorphine	6	7	11	24
Chlorprothixene	8	8	4	20
Metoclopramide	0	2	18	20
Cyclizine	1	5	13	19
Imipramine	6	10	2	18
Haloperidol	10	3	3	16
Diphenhydramine	8	3	4	15
Phenmetrazine	0	5	10	15
Clomethiazole	3	5	6	14
Naproxen	1	5	7	13
Primidone	1	3	9	13

stopped because of deviant driving behavior. In common with group C, they all had the capacity to perform complex tasks, such as driving a car (although not always safely). As in group C, the concentrations in group D may represent therapeutic, subtherapeutic, or toxic levels. The other important similarity between groups C and D is that the analyses were made on whole blood, whereas therapeutic levels reported in the literature almost invariably refer to concentrations in plasma or serum. The advantage of including groups C and D as controls to groups A and B is illustrated in Fig(s). 1a–c, where the overlap between the groups is evident. This overlap implies that concentrations within this range in some cases may be due to intoxication and explain the death, whereas in other cases, the deceased may not have been significantly incapacitated.

Some work has been conducted regarding the influence of time after death on postmortem drug levels (7–9,11–17,20,21,26). It seems obvious that some drugs may accumulate in different organs, such as the lungs and the liver, and a subsequent diffusion from these sources to the blood presumably takes place for several substances postmortem, causing a rise in blood concentration with time (7–9,11–15). For some substances, postmortem degradation may be a more important phenomenon (10,16,17,27, unpublished observations). In conclusion, current knowledge concerning influence of time after death on drug concentration changes should be borne in mind when using the data presented in Table 1.

In 16% of the total material, some degree of decomposition was reported by the pathologist in charge. However, eight out of nine studied substances did not show significant changes due to decomposition. Therefore, we decided not to exclude cases because of decomposition. For natural reasons, severely decomposed cases are underrepresented, because femoral blood often is lacking under such circumstances. These cases comprise considerable diagnostic problems in many respects, and interpretation of toxicology data

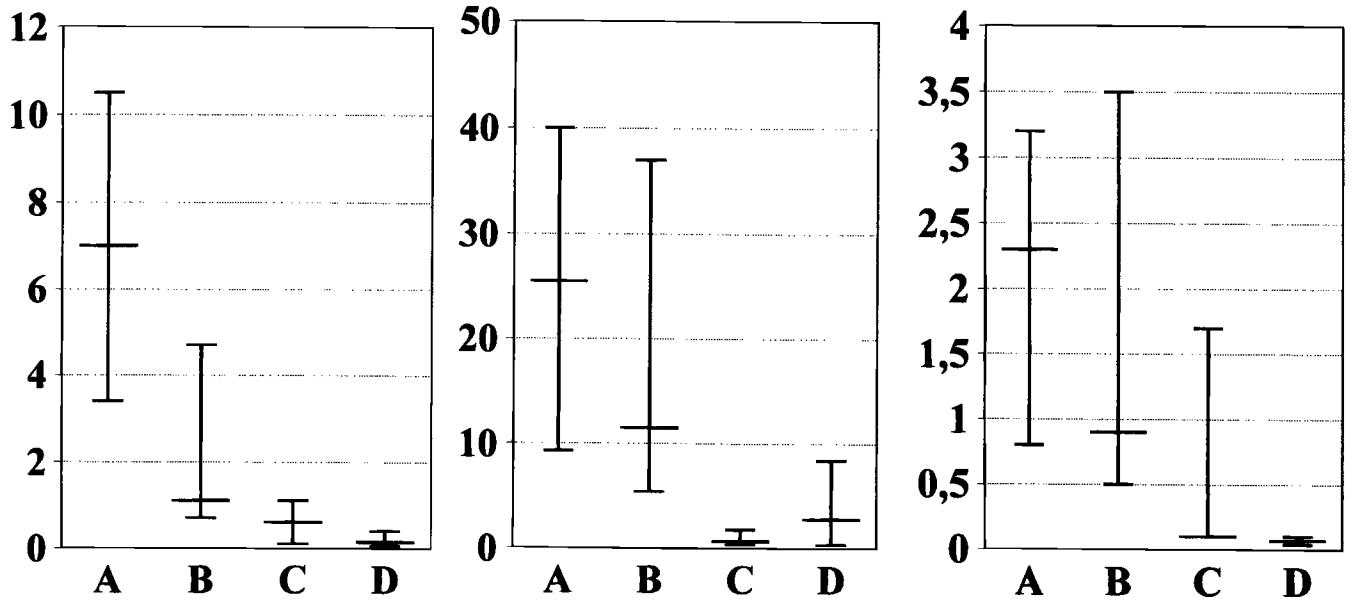

FIG. 1a–c—*Line plots showing the concentrations of citalopram (1a), carisoprodol (1b), and methotrimeprazine (1c), respectively. Group A = fatal intoxication with the substance exclusively. Group B = fatal intoxication with the substance in combination with other drugs and/or alcohol. Group C = other cause of death without incapacitation due to drugs. Group D = Concentrations in whole blood from suspected drugged drivers. In groups A–C concentrations refer to femoral blood. These line plots serve as examples of the variations of the overlap between intoxications and controls displayed by different drugs.*

as well as autopsy findings, must, of course, be made carefully in such cases.

The reason why we decided to present only femoral vein blood is the abundance of reports indicating that peripheral blood specimens are superior to central blood as to the stability and similarity to antemortem levels of alcohols and drugs (7,9,12,15,16,18, 19,28). We think it is high time to come to a general agreement upon a standard specimen to be used for comparisons, and we believe that femoral vein blood is the best candidate.

The ratio parent drug:metabolite (P:M) should probably be used for interpretation of the kind of ingestion (29–31). High ratios may indicate an acute overdose, low ratios a high chronic dosage. However, we must keep in mind that high concentrations of both parent drug and metabolite in combination with a low P:M ratio does not exclude an acute overdose, because of the possibility of a high chronic dosage preceding an acute overdose. Conversely, a high P:M ratio may, apart from an acute overdose, also be explained by reduced metabolic capacity. The presently most studied detoxifying enzyme is Cytochrome P450 2D6, which metabolizes a number of drugs of forensic importance (32,33). Slow metabolizers will exhibit much higher ratios than rapid metabolizers, and in addition, interaction between substances with different affinity to the enzyme may also affect the ratio. As yet, no data are available concerning the possible difference in fatal levels for slow and rapid metabolizers, and we have not considered this possibility in the present work. However, the possible influence of reduced metabolization rates on the P:M ratio may affect the interpretation of the manner of death.

The benzodiazepines clonazepam, nitrazepam, and flunitrazepam are subject to a significant postmortem conversion into their 7-amino metabolites (10). We feel confident that the sum of the parent drug and metabolite is the most relevant value to be used for the toxicological interpretation.

The hypnotic drug propiomazine is also significantly degraded to the main metabolite dihydropropiomazine postmortem (unpublished observations), and the sum of parent drug and metabolite would probably be the measure of choice also in this case.

Special caution should be used when considering the values of substances with a low number of included cases, because small samples will always carry a risk of yielding averages differing from what it would be if more cases were included. It is also difficult to identify outlayers if comparable reference data are lacking. For example, only one A case involving chlordiazepoxide could be included, and this value is probably not representative for most fatal cases.

There is always a risk that the lowest reported fatal value of a certain substance will be quoted. However, low extremes may be explained by anaphylaxis, idiosyncracy, or similar rare conditions, and would not be expected in the average routine case. Therefore, in Table 1, we have presented percentiles or quartiles instead of lowest and highest values (with some exceptions due to insufficient data), because such a presentation gives a more accurate view of the distribution of the values. Thus, data in the columns LOW and HIGH in the table do not represent the lowest or highest values found if the number of cases in the particular group is equal to or exceeds four.

Table 3 displays the panorama of postmortem toxicology in Sweden, which fairly well reflects the changes in therapy traditions over time, at least as far as neuroleptics, benzodiazepines, antidepressants, and analgesics are concerned.

It is tempting to compare the number of fatal cases for a certain substance in Table 1 with the number of positive detections in Table 3. However, the objective of this study was not to identify substances considered to be particularly dangerous or especially harmless, and the methods of selection make the accuracy of such a comparison doubtful. The numbers of excluded intoxications differ considerably among drugs, and in addition, some drugs may show a high number of B cases because of their occurrence in combination preparations. Thus, we dissuade the reader from making comparisons in this respect. The comparison should rather be focused on the low percentage of cases finally included in Table 1 depending on the strict selection criteria. The absence of A cases of paracetamol may additionally be explained by the delay between intoxication and death. Because we excluded cases with longer survival time at hospitals, intoxications with acetaminophen and accompanying fatal liver necrosis will not appear in our presentation.

Table 3 also shows some interesting trends, for instance, the steady increase of the new antidepressants, particularly the selective serotonine reuptake inhibitors (SSRI), and the decrease of some other drugs. With some exceptions, the barbiturates were withdrawn from the Swedish market many years ago. This is why no barbiturates (apart from phenobarbital and thiopental) are presented in Table 1.

Every approach to the compilation of fatal and toxic drug concentrations is susceptible to some degree of circular reasoning. If such compilations were strictly followed and consistently used for the diagnosis of intoxications, further compilations would be meaningless. Thus, in clear-cut cases, the forensic pathologist and toxicologist should not shrink from an intoxication diagnosis even if the levels differ from those given in this and other compilations. In uncertain cases, on the other hand, in which the diagnosis is an open question, a reliable toxicology reference is a great help. Thus, we hope that this contribution will assist forensic pathologists and toxicologists in such situations. In particular, the presentation of drug concentrations of controls will hopefully give a more comprehensive view of fatal levels.

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