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Summary statistics for drugs and alcohol concentration recovered in post-mortem femoral blood in Western Switzerland

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ABSTRACT

In post-mortem investigations of fatal intoxication, it is challenging to determine which drug(s) were responsible for the death, and which drugs did not. This study aims to provide post-mortem femoral blood drug levels in lethal intoxication and in post-mortem control cases, where the cause of death was other than intoxication. The reference values could assist in the interpretation of toxicological results in the routine casework.

To this end, all post-mortem toxicological results in femoral blood from 2011 to 2017 in Western Switzerland were considered. A full autopsy with systematic toxicological analysis (STA) was conducted in all cases. Results take into account the cause of death classified into one of four categories (as published by Druid and colleagues): I) certified intoxication by one substance alone, IIa) certified intoxication by more than one substance, IIb) certified other causes of death with incapacitation due to drugs, and III) certified other causes of death without incapacitation due to drugs.

This study includes 1 990 post-mortem cases where femoral blood was analysed. The material comprised 619 women (31%) and 1 371 men (69%) with a median age of 50 years. The concentrations of the 32 most frequently recorded substances as well as alcohol are discussed. These include 6 opioids and opiates, 3 antidepressants, 6 neuroleptics and hypnotics, 1 barbiturate, 11 benzodiazepines (and related drugs), 2 amphetamine-type stimulants, cocaine, paracetamol, and tetrahydrocannabinol (THC).

The most common substances that caused intoxication alone were morphine, methadone, ethanol, tramadol, and cocaine. The post-mortem concentration ranges for all substance are categorized as I, IIa, IIb, or III. Statistical post-mortem reference concentrations for drugs are discussed and compared with previously published concentrations. This study shows that recording and classifying cases is time-consuming, but it is rewarding in a long-term perspective to achieve a more reliable information about fatal and non-fatal blood concentrations.

1. Introduction

Post-mortem toxicology involves detecting and quantifying certified toxic, or potentially toxic, substances in whole blood obtained from a full autopsy. The measured concentration plays a major role in the interpretation process that contributes towards the determination of the cause of death. Although this alone is not sufficient, factors including clinical history and other autopsy findings, and results of supplementary analyses, circumstances surrounding the death, diseases, alcohol and substance abuse history etc… should be taken into account. Reference databases on therapeutic and toxic concentration in human are often used as an aid to interpretation [1–4]. However, these concentrations must be used carefully if they are to be considered for post-mortem cases, principally because of possible post-mortem drug redistribution [5–8]. Due to this phenomenon, these data need to be supplemented by post-mortem concentrations rates [9,10].

While case reports and small case series could be used to a certain extent, these data are often heterogeneous in terms of the origin of the blood samples analyzed (e.g. femoral or cardiac) and based only on one or a short series of exceptional cases with high concentrations of drugs. In addition, one single case report cannot be generalized to the whole population since the individual's response

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to the drug (e.g. tolerance) and substance interaction needs to be taken into account. The alternative approach presented here consists of taking into account all the cases in which drugs and/or alcohol were detected.

This approach has been developed for several years in Sweden [9]. Druid and colleagues show that blood, sampling, processing, analysis and review of post-mortem drug concentrations using a standardized protocol is one of the most powerful tools to enhance toxicological interpretation [9,10]. In these published papers, cases are subdivided into three post-mortem groups: poisoning by one substance only (group A), multi-substance poisoning (group B) and deaths not involving incapacitation (group C). Druid and colleagues also compared the results of these three groups with the concentrations obtained from cases of driving under the influence and concentrations observed in therapeutic drug monitoring cases. Another study conducted by Launiainen, Ketola & Ojanperä, followed an all-causes-of-death approach, which means that they did not split the data into post-mortem groups based on the causes of death. Such an approach offers an idea of the concentration ranges to expected for different drugs, which are valuable for laboratories planning to set up verification methods, and does not require a manual review of the cases, but the drawback is that a certain cut-off of e.g. 95% for toxic concentrations may be reasonable for some drugs, but higher or lower cut-offs may apply for other drugs [11–13].

In this present paper, the approach developed is one using the groupings presented by Druid and colleagues [9]. In Western Switzerland, when the legal authorities require a full-autopsy, toxicological investigations are performed at the University Centre of Legal Medicine (CURML) - located at the University Hospitals of Lausanne and Geneva.

From 2011–2017, all cases where drugs and/or alcohol concentrations were measured in post-mortem femoral whole blood were collected and divided into several groups according to the certified causes of deaths. The aim of this study is to provide blood reference concentrations observed in lethal intoxications and in post-mortem control cases for 32 substances and alcohol.

2. Materials and methods

2.1. Inclusion criteria

All of the following post-mortem cases involve toxicological investigations of whole blood obtained from full autopsies performed in Western Switzerland (Geneva, Lausanne, Jura, Neuchatel, Fribourg and Valais) during a period ranging from 2011 to 2017.

2.2. Sample collection

Prior to analysis, femoral blood was sampled in tubes containing preservatives, such as Ethylene Diamine Tetra Acetic acid (EDTA) or sodium fluoride, and stored at 4 °C.

2.3. Toxicological analysis

A systematic toxicological analysis (STA) of therapeutic drugs, drugs of abuse, volatiles, cyanide, and pesticides are performed using validated analytical procedures. The STA used is based on screening procedures and quantification analyses as described in previous publications [15–18] and relies on toxicological literature [14,19,20]. Screening procedures include immunoassays (Siemens; Specialty Diagnostics; Randox) using the manufacturer's recommended cut-off, colour tests (Fujiwara; Cyantesmo), and chromatographic analyses which consist of: gas chromatography coupled to mass spectrometry (GC-MS, Agilent), liquid chromatography coupled to diode array detectors (HPLC-DAD, Agilent), and head-space gas chromatography coupled to flame ionisation detectors (HS-GC-FID, Agilent). Basic, acidic and neutral semi-volatile and non-volatile drugs were identified using commercial libraries [47-50]. When drugs were detected, quantitative analyses were performed using GC-MS, HPLC-DAD, HS-GC-FID or liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Some substances, such as carboxyhemoglobin (CO-Hb) and gamma-hydroxybutyric acid (GHB), were not included in the STA, and their analyses were performed only in the case of suspicion of exposure to these substances [21–23].

2.4. Selection and classification of cases

During the six-year study period (1 January 2011 – 31 December 2017), drug findings in post-mortem femoral blood from 1 990 autopsy cases were recorded. A total of 146 drugs were detected at least once. For 10 substances, only qualitative data were recorded (theobromine, nicotine, cotinine, caffeine, phenacetin, ephedrine, etifoxine, etomidate, fluconazole, metoclopramide). As highlighted in Söderberg et al.'s work [24], the sample size has an impact on the data, therefore the following set limit was chosen. Drugs were selected according to two criteria: (1) the drug had been detected and quantified at least 50 times and/or (2) the drug had been involved in certified intoxication by one substance (group I, detailed hereafter). A total of 32 substances and alcohol correspond to one of the criteria, among them, twenty were selected and plotted as boxplots to have a better visualization of the data.

If available, date of birth, date of death, sex, cause of death and drugs concentration in post-mortem blood were manually entered in a database once anonymized. All causes and manners of death have been coded using the International Classification of Diseases (ICD-10). Commonly reported codes being Y10-Y19 (poisoning, undetermined intent), X60-X84 (intentional self-harm), I21-I49 (diseases of the circulatory system, pulmonary and heart diseases), R99 (defined and unknown causes of mortality), V40-V49 (Transport accidents). Other external causes and manners, such as W00-W19 (Falls), X85-Y09 (Assault), W65-W74 (Accidental drowning and submersion), X00-X08 (Exposure to smoke, fire, and flames), J10-J18 (Influenza and pneumonia), Y21-Y29 (Hanging, drowning, undetermined intent) and I60-I86 (Cerebrovascular diseases), were reported but to a lesser extent.

The first author coded causes of deaths based on the immediate cause of death, and categorized all of the cases into four groups based on Druid and colleagues' work [9,10]: (I) certified intoxication by one substance; (IIa) certified intoxication by more than one substance; (IIb) certified other causes of death with incapacitation due to drugs; and (III) certified other causes of death without incapacitation due to drugs. Group III provides an idea of drug concentrations that may be observed without causing incapacitation. A second author (MA) reviewed the group assignments and database inclusions. Any discrepancies were checked against the original data to arrive at a consensus.

For each group, median, minimum, maximum and percentile (10th, 25th, 75th and 90th) concentrations (µg/L) were calculated. For each drug already published [10,13], concentrations were compared with previous studies. If several drugs were detected, but according to the toxicological report only one substance led to the death, the case was included in group I (i.e. single drug intoxication), and the value of the other drug was deleted. For certified fatal intoxications caused by more than one substance (IIa), concentrations were counted in all relevant substance groups (for example an intoxication involving both zopiclone and oxazepam counted for both). To distinguish group IIb and III, the final cause-of-death was extracted from the autopsy report and if the incapacitation was mentioned, cases were recorded in the IIb group: such a group has not been formed in Druid's studies. The purpose of group IIb is to provide ranges of concentrations observed in deaths by causes other than intoxication, but where drugs may have had an impact on the

sequences of events that led to the death. Statistical analyses were performed using Tableau Desktop 10.4.12 software and R.

3. Results

3.1. Socio-demographic characteristics

From 2011–2017, 1 990 post-mortem cases with femoral blood analysed were reported in the study. Sedative, hypnotic or psychoactive drugs (excluding caffeine) were detected in 1 338 cases (67%).

After assignment in predefined groups, 1 857 cases were included to one of the four groups. The 133 (6%) cases that could not be assigned were excluded. 115 (6%) cases were attributed to intoxication by one drug and/or alcohol (I), 303 (15%) cases related to certified intoxication by more than one substance (IIa), 324 (16%) cases were related to an external cause of death but drugs and/or alcohol may have caused incapacitation (IIb). In addition, 1 115 (56%) cases were related to another cause of death without incapacitation by drugs (III).

For all groups, the majority of cases reported were male (I: 55%; IIa: 69%; IIb: 76%; III: 69%). In total, the material comprised 619 females (31%) and 1 371 males (69%) with a median age of 50 years. Among the fatal intoxications, the age group 40–49 years was the largest group (group I: 29%, 33 cases; group IIa: 27%, 82 cases). The distribution of ages in the four groups of deaths are presented in Fig. 1. This age range is much lower compared to the death rates reported by decennial ages in Canton of Vaud (Western Switzerland; DR), where most deaths happen at 80 years or older [25].

3.2. Drug concentrations rates in the four groups discrimination

Table 1 shows the femoral blood concentrations of the 32 psychoactive substances selected in alphabetical order. They include, 6 opioids and opiates (fentanyl, methadone, morphine (free and total), oxycodone and tramadol), 3 antidepressants (amitriptyline, trazodone and venlafaxine), 6 neuroleptics and hypnotics (amisulpride, clomethiazole, clotiapine, clozapine, olanzapine and quetiapine), pentobarbital, 11 benzodiazepines and related drugs (alprazolam, bromazepam, citalopram, clonazepam, diazepam, lorazepam, midazolam, nordiazepam, oxazepam, zolpidem and zopiclone), 2 amphetamines type stimulants (amphetamine and MDMA), cocaine, paracetamol and, finally, tetrahydrocannabinol (THC). Among these 32 substances, 20 are plotted in Fig. 2 to highlight the difference between concentrations of the four groups.

Among the 1 857 cases considered for this study, benzodiazepines were detected in 38% (711 cases), antidepressants in 15% (281 cases), neuroleptics in 11% (212 cases), opiates in 11% (206 cases, including morphine (9.6%)), opioids in 13% (255 cases, including methadone (8.1%) and buprenorphine (0.2%)), cocaine in 4.5% (84 cases), sympathomimetics in 2.4% (46 cases, including amphetamines (2.2%)), carboxyhemoglobin (CO-Hb ≥ 20%) in 2.1% (40 cases), GHB in 0.2%

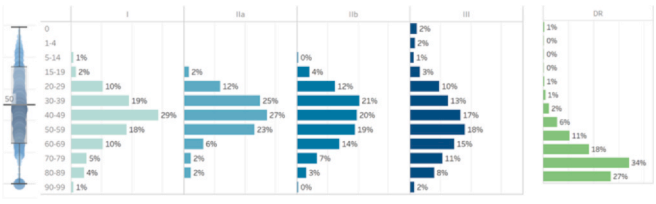

Fig. 1. The distribution of ages in single substance intoxication (I), multiple substance intoxication (IIa), other cause of death with incapacitation (IIb), and other cause of death without incapacitation due to drugs (III); number of deaths by decennial age groups, Western Switzerland, Canton de Vaud, sum of the cases between 2011 and 2017 (death rate, DR [25]).

(3 cases), paracetamol in 12% (240 cases), caffeine/theobromine in 83% (1 543 cases), and nicotine/cotinine in 25% (465 cases).

In Fig. 2, a graphical representation of the concentrations of 20 of the substances are shown. For 3 opioids and opiates (fentanyl, methadone and free morphine), the concentration between the 25th percentile and the 75th percentile in group I overlap with the values reported in the control groups (IIa, IIb and III). This is particularly the case for fentanyl, where 1.5 of the interquartile ranges from 1.0 to 21.0 for group I overlaps with the 25–75 percentile for group III (1.0–31.0). Trazodone, an antidepressant, is also interesting because the median (1 360 ug/L) for group I is higher than for the three other groups, but the range for group I is broad (from 720 ug/L to 2 000 ug/L) and overlapped with group IIa (180 ug/L to 1 300 ug/L). For neuroleptics, hypnotics and benzodiazepines, values do not overlap between the group I and the three other groups.

3.3. Alcohol concentration in the four groups

Among the 1 857 cases considered, 25% of cases (464) contained ethanol above the threshold of 0.10 [g/kg] (threshold provided by the federal roads office in its road safety ordinance [26]). For group I, where deaths are induced by alcohol consumption only, the concentrations measured are higher than in the other groups. However, an overlap in the data is observed for the three other groups (IIa, IIb, III) with the same concentration range from the 25th to the 75th percentile.(Table 2).

4. Discussion

This study aimed to provide post-mortem femoral blood reference data to support the interpretation of drug concentration in post-mortem toxicology investigations. Following the method suggested by Druid and colleagues [9,27–29], the objective was to illustrate the differences between non-toxic and lethal concentration detected in femoral blood in post-mortem cases. In order to do so, a comparison was made between blood from one-substance poisoning (I), multi-substance poisoning (IIa), and from causes of death with (IIb) and without (III) incapacitation due to drugs. All the results are detailed and discussed below according to the groups defined in the result section. (Fig. 3).

4.1. Concentration of opioids and opiates

A large variation in post-mortem blood concentrations of opioids and opiates have consistently been reported in the literature, which can be explained by a large variation in tolerance between subjects. This pattern was also observed in the present study. Observations of lung edema and froth in the airways are rather a more important key to fatal opioid intoxication with the strong mu-opioid receptor agonists than their concentrations in post-mortem femoral blood.

Nevertheless, in this section, the results regarding concentration of morphine (free and total), buprenorphine, fentanyl, methadone, oxycodone, and tramadol are discussed. Ten cases recorded as certified intoxication by one substance alone (group I) were related to morphine detection (free and total). The detection of morphine in blood could be the result of heroin or morphine or codeine consumption. Among these ten cases, seven were related to heroin intake (confirmed by the presence of 6-monoacetylmorphine). Both free morphine and total morphine concentrations were measured, total morphine is calculated based on the concentration of free morphine, morphine-3-glucuronide and morphine-6- glucuronide [30]. For total morphine, the 25th percentile in the group I (1 028 µg/L) is higher than the 75th percentile of group IIa (670 µg/L). This is not the case for free morphine (94 µg/L for the 25th percentile of group I, 240 µg/L for the 75th percentile of group IIa). Since the data does not overlap, total morphine appears to be more adequate for interpreting

Table 1
Femoral blood concentrations of 32 substances in post-mortem cases, classified into four groups: I) Certified intoxication by one single substance (N = 115); II a) Certified intoxication by a combination of at least two substances (N = 303); II b) Certified other causes of death with incapacitation due to at least one substance (N = 324), III) Certified other causes of death without incapacitation (N = 1 115). The Lower Limit of Quantitation LLOQ for each substance is reported.

Drug	group	N	min	10th	25th	median	75th	90th	max
Alprazolam [µg/L] LLOQ 1.5 µg/L	I	0							
	IIa	42	2	5	14	38	100	170	300
	IIb	22	4	6	13	36	65	81	150
	III	18	< LLOQ	5	7	14	31	49	69
	Total	82	< LLOQ	5	10	29	67	134	300
Amisulpride [µg/L] LLOQ 20 µg/L	I	1	11 300	11 300	11 300	11 300	11 300	11 300	11 300
	IIa	8	160	180	425	1 550	3 500	11 500	19 000
	IIb	3	680	692	710	740	840	900	940
	III	4	130	193	288	470	1 075	1 930	2 500
	Total	16	130	172	405	840	2 375	9 110	19 000
Amitriptyline [µg/L] LLOQ 20 µg/L	I	1	2 900	2 900	2 900	2 900	2 900	2 900	2 900
	IIa	7	22	24	31	330	795	1 520	2 000
	IIb	3	20	22	25	30	290	446	550
	III	6	20	26	35	44	76	210	300
	Total	17	20	21	29	60	430	1 600	2 900
Amphetamine [µg/L] LLOQ 10 µg/L	I	2	450	487	543	635	728	783	820
	IIa	4	10	10	11	26	45	53	58
	IIb	4	12	23	40	67	68	68	68
	III	1	34	34	34	34	34	34	34
	Total	11	10	11	18	50	68	487	820
Bromazepam [µg/L] LLOQ 5.0 µg/L	I	1	11 950	11 950	11 950	11 950	11 950	11 950	11 950
	IIa	30	11	30	69	240	695	1 017	2 500
	IIb	11	5	25	76	160	310	430	480
	III	11	12	33	42	70	119	193	200
	Total	53	5	24	57	175	358	890	11 950
Citalopram [µg/L] LLOQ 1.0 µg/L	I	0							
	IIa	56	11	53	93	305	513	1 150	2 800
	IIb	27	34	66	90	250	340	622	2 200
	III	59	17	77	119	235	350	525	940
	Total	143	11	64	110	260	420	882	2 800
Clomethiazole [µg/L] LLOQ 1.0 µg/L	I	0							
	IIa	5	16	611	1 504	4 400	9 350	13 940	17 000
	IIb	4	3 500	3 660	3 900	4 300	4 700	4 940	5 100
	III	5							
	Total	14	16	1 008	2 375	4 300	6 375	11 900	17 000
Clonazepam [µg/L] LLOQ 1.0 µg/L	I	0							
	IIa	39	1.0	1.0	3.0	5.0	6.0	20	48
	IIb	16	2.0	2.0	6.0	11	33	62	72
	III	8	3.0	4.0	6.0	7.0	9.0	28	45
	Total	63	1.0	2.0	3.0	6.0	11	35	72
Clotiapine [µg/L] LLOQ 1.0 µg/L	I	0							
	IIa	8	25	32	41	59	103	475	1 000
	IIb	2	74	74	74	74	74	74	74
	III	5	20	28	40	60	114	146	167
	Total	15	20	25	41	60	103	167	1 000
Clozapine [µg/L] LLOQ 1.0 µg/L	I	1	1 130	1 130	1 130	1 130	1 130	1 130	1 130
	IIa	4	633	863	1 208	2 050	4 350	7 320	9 300
	IIb	4	960	1 032	1 140	1 800	2 625	3 030	3 300
	III	1	457	457	457	457	457	457	457
	Total	10	457	615	1 003	1 300	2 625	3 900	9 300
Cocaine [µg/L] LLOQ 10 µg/L	I	6	300	560	1 065	2 525	3 588	7 850	12 000
	IIa	52	10	10	17	28	95	594	2 300
	IIb	19	10	10	19	130	170	680	1 900
	III	7	10	10	20	44	106	170	200
	Total	84	10	10	19	35	200	1 480	12 000
Diazepam [µg/L] LLOQ 5.0 µg/L	I	0							
	IIa	28	17	27	41	152	335	426	2 000
	IIb	11	8.0	22	31	79	372	640	1 555
	III	17	10	15	24	70	186	438	660
	Total	56	8.0	20	33	116	308	499	2 000
Fentanyl [µg/L] LLOQ 0.5 µg/L	I	2	1.0	3.0	6.0	12	17	20	22
	IIa	2	3.0	3.0	3.0	4.0	4.0	4.0	4.0
	IIb	4	1.0	2.0	4.0	7.0	14	25	32
	III	8	2.0	2.0	3.0	6.0	21	41	55
	Total	16	1.0	1.0	3.0	5.0	12	31	55
Lorazepam [µg/L] LLOQ 3.5 µg/L	I	1	1 100	1 100	1 100	1 100	1 100	1 100	1 100
	IIa	45	< LLOQ	6.0	17	30	65	169	3 900
	IIb	35	< LLOQ	7.0	11	23	47	113	280
	III	52	5.0	5.0	8.0	16	39	63	160
	Total	133	< LLOQ	5.0	10	23	47	130	3 900

(*continued on next page*)

Table 1 (*continued*)

Drug	group	N	min	10th	25th	median	75th	90th	max
MDMA [µg/L] LLOQ 10 µg/L	I	1	7 600	7 600	7 600	7 600	7 600	7 600	7 600
	IIa	4	20	35	57	84	399	940	1 300
	IIb	5	31	112	233	495	943	1 397	1 700
	III	1	580	580	580	580	580	580	580
	Total	11	20	30	77	440	1 148	2 290	7 600
Methadone [µg/L] LLOQ 10 µg/L	I	12	190	260	470	1 050	1 300	1 930	2 200
	IIa	101	26	128	238	455	903	1 200	3 400
	IIb	23	26	111	285	437	871	1 100	1 300
	III	13	50	95	155	485	1 125	1 290	1 500
	Total	149	26	122	275	480	950	1 300	3 400
Midazolam [µg/L] LLOQ 1.5 µg/L	I	0							
	IIa	45	5.0	10	20	46	120	280	3 500
	IIb	25	7.0	20	29	78	170	370	600
	III	84	< LLOQ	5.0	14	47	94	263	698
	Total	155	< LLOQ	8.0	20	49	115	298	3 500
Morphine (free) [µg/L] LLOQ 20 µg/L	I	10	20	66	94	275	455	2 170	11 800
	IIa	107	< LLOQ	< LLOQ	32	94	240	552	4 700
	IIb	26	< LLOQ	< LLOQ	< LLOQ	26	59	220	1 245
	III	36	< LLOQ	< LLOQ	< LLOQ	80	170	250	670
	Total	179	< LLOQ	< LLOQ	21	83	220	488	11 800
Morphine (total) [µg/L] LLOQ 20 µg/L	I	10	60	375	1 028	1 550	1 850	5 793	21 400
	IIa	111	< LLOQ	22	140	290	708	1 970	13 770
	IIb	28	< LLOQ	11	50	141	270	883	2 500
	III	37	< LLOQ	16	47	159	768	1 978	3 100
	Total	186	< LLOQ	20	85	260	770	2 000	21 400
Nordiazepam [µg/L] LLOQ 20 µg/L	I	0							
	IIa	96	< LLOQ	27	83	285	620	1 019	2 300
	IIb	42	< LLOQ	44	67	190	523	950	2 000
	III	39	< LLOQ	23	53	135	280	489	930
	Total	177	< LLOQ	27	67	210	535	958	2 300
Olanzapine [µg/L] LLOQ 20 µg/L	I	0							
	IIa	14	68	98	130	180	280	312	600
	IIb	6	20	34	55	74	147	263	340
	III	11	< LLOQ	39	46	60	107	250	300
	Total	31	< LLOQ	43	65	125	251	306	600
Oxazepam [µg/L] LLOQ 20 µg/L	I	1	4 440	4 440	4 440	4 440	4 440	4 440	4 440
	IIa	118	< LLOQ	< LLOQ	25	57	223	880	7 700
	IIb	66	< LLOQ	< LLOQ	30	70	263	760	2 000
	III	68	< LLOQ	< LLOQ	16	57	205	558	1 700
	Total	253	< LLOQ	< LLOQ	24	59	237	828	7 700
Oxycodone [µg/L] LLOQ 20 µg/L	I	2	480	485	493	505	518	525	530
	IIa	9	41	66	100	255	409	2 120	7 600
	IIb	2	29	34	42	56	69	77	82
	III	2	22	26	33	44	55	62	66
	Total	15	22	34	69	110	445	662	7 600
Paracetamol [mg/L]	I	6	30	45	61	109	180	195	200
	IIa	60							
	IIb	36							
	III	137							
	Total	239							
Pentobarbital [µg/L] LLOQ 0.2 µg/L	I	7	5 500	6 280	7 750	16 000	25 500	35 000	38 000
	IIa	0							
	IIb	0							
	III	0							
	Total	7	5 500	6 280	7 750	16 000	25 500	35 000	38 000
Quetiapine [µg/L] LLOQ 1.0 µg/L	I	0							
	IIa	51	1.0	31	67	250	910	2 120	10 850
	IIb	23	5.0	67	132	195	315	614	1 200
	III	26	5.0	11	27	79	160	270	600
	Total	100	1.0	20	62	160	495	1 380	10 850
Tetrahydro-cannabinol [µg/L] LLOQ 0.5 µg/L	I	0							
	IIa	19	1.0	1.0	1.0	3.0	8.0	16	100
	IIb	47	1.0	1.0	2.0	6.0	17	50	126
	III	34	1.0	1.0	4.0	8.0	19	33	290
	Total	100	1.0	1.0	2.0	6.0	15	42	290
Tramadol [µg/L] LLOQ 10 µg/L	I	7	1 400	1 760	2 050	2 700	4 700	5 320	5 800
	IIa	28	10	59	205	600	1 850	3 860	15 000
	IIb	13	10	107	493	830	1 150	1 390	2 000
	III	27	21	70	150	350	550	830	970
	Total	75	10	74	175	600	1 388	2 700	15 000
Trazodone [µg/L] LLOQ 10 µg/L	I	2	720	848	1 040	1 360	1 680	1 872	2 000
	IIa	20	28	94	183	298	1 200	1 720	10 000
	IIb	16	< LLOQ	75	145	300	645	832	1 800
	III	19	69	160	215	390	488	859	1 600
	Total	57	< LLOQ	90	190	360	690	1 560	10 000

(*continued on next page*)

Table 1 (*continued*)

Drug	group	N	min	10th	25th	median	75th	90th	max
Venlafaxine [µg/L] LLOQ 10 µg/L	I	1	10 000	10 000	10 000	10 000	10 000	10 000	10 000
	IIa	11	67	270	535	940	1 650	2 000	2 100
	IIb	22	10	100	190	620	1 200	1 600	6 100
	III	15	50	83	120	230	420	565	950
	Total	49	10	92	183	455	1 125	1 790	10 000
Zolpidem [µg/L] LLOQ 5.0 µg/L	I	3	480	604	790	1 100	2 050	2 620	3 000
	IIa	40	5.0	13	33	88	298	947	2 000
	IIb	33	9.0	18	29	109	208	353	707
	III	36	5.0	5.0	9.0	19	47	92	270
	Total	112	5.0	9.0	18	52	200	580	3 000
Zopiclone [µg/L] LLOQ 5.0 µg/L	I	2	1 900	1 910	1 925	1 950	1 975	1 990	2 000
	IIa	21	8.0	11	22	32	135	324	1 200
	IIb	8	18	18	20	55	202	910	1 970
	III	7	10	15	21	23	34	45	59
	Total	38	8.0	14	21	34	185	975	2 000

the post-mortem concentration rates, especially considering that the morphine-6-glucuronide could be a more potent analgesic than morphine [31]. Even if the results of the total morphine are more designated for the post-mortem interpretation, both free and total median values for group I are higher than for group IIa (free morphine: 275 µg/L and 94 µg/L; total morphine: 1 550 µg/L and 285 µg/L, for group I and group IIa respectively).

Only three cases of buprenorphine were recorded in the database. Consequently, this substance is not reported in Table 1. This finding is consistent with the fact that in Switzerland, methadone is more often prescribed than buprenorphine as part of the opioid substitution treatment [32]. Methadone was detected in 129 cases during the studied period (1 January 2011 – 31 December 2017), with 12 cases where intoxication was related to methadone intake only. An overlap was found between the methadone concentrations which had caused an intoxication and those which were incidental findings (groups I and IIa vs IIb and III). This result could be explained by the variability in each individual's response to the drug (addiction and tolerance). Due to this overlap, particular precautions need to be taken for interpreting the result of opioids, such as buprenorphine and methadone, post-mortem concentration by itself has a limited role in assessing the cause of death and the clinical history of the deceased need to be taken into account. The same methadone dose in two different individuals could be potentially inadequate to mask the side-effect of heroin cessation (clinical effective dose required) or fatal [33,34]. The same observation can be made for tramadol, for which the overlap observed between groups is related to the individual's tolerance to opioids.

In addition, fentanyl is highly potent and a small dose variation can lead to serious consequences, thus explaining the overlap between concentrations in the four groups.

Finally, for oxycodone, the 10th percentile of concentration in group I (485 µg/L) is higher than the 75th percentile of group IIa (409 µg/L), and the concentration rate of group III is the lowest (with the 90th percentile at 62 µg/L). This finding seems to suggest the existence of differences between normal and fatal concentrations. Among the 1 990 cases considered, oxycodone was detected in only fifteen cases. This result seems to indicate that the oxycodone crisis experienced in North America [35] has had a limited impact in Western Switzerland during the investigated period.

4.2. Concentrations of benzodiazepine and benzodiazepine-like drugs

Concentrations for 11 benzodiazepines and related substances (e.g. Z-drugs) were compiled, namely, alprazolam, bromazepam, clonazepam, diazepam, lorazepam, midazolam, nordiazepam, oxazepam, zolpidem, and zopiclone. One of the main challenges in the interpretation of benzodiazepine toxicology is the metabolism pathways known for the benzodiazepine family [36]. For example, the consumption of one medicine could lead to the detection of diazepam, nordiazepam and oxazepam in different ranges of concentration. Due to this metabolism pathways, it cannot be ruled that the benzodiazepine detected in whole blood are the result of one medicine or several. Among the 56 cases where diazepam is detected, 52 contained nordiazepam and 41 oxazepam. While, in the 253 cases where oxazepam is detected, 143 contained nordiazepam. In post-mortem toxicology investigations, the metabolism profiling is studied using the second matrix (if available). In the present study, only femoral blood results were considered and recorded.

The benzodiazepine group shows the highest frequency of detection (38%), but the substances rarely cause an intoxication alone (only 6 cases in group I, i.e. single substance poisoning). Regarding oxazepam, the median concentration in the single drug intoxication cases was ten times higher than the medians of the other groups. The reason why the median concentration of the group IIa cases is not higher might be explained by the subjective assessment of the results, where decisions to include low concentrations of oxazepam results in a low median. Concerning the other benzodiazepines and benzodiazepine-like drugs, most of them follow the oxazepam trend. The same trend is observed in group I for bromazepam, zolpidem, and zopiclone (concentrations in group I are ten times higher), while for cases not related to one substance only (groups IIa, IIb and III), the concentrations are in the same range. No intoxication from alprazolam, clonazepam, lorazepam and midazolam alone were reported during the period studied. These results suggest that the risk of fatal intoxication remains relatively low in comparison with the other benzodiazepines mentioned in this study. However, the interaction between benzodiazepine and other substances cannot be neglected and a study conducted in 2020, on the prescription of benzodiazepines in elderly people, suggests that benzodiazepine is overused among this population [37].

4.3. Stimulants and other drugs

For MDMA and amphetamine, the concentration rate for the 10th percentile of group I is higher than the 90th percentile of group IIa. Therefore, the post-mortem concentration rate should be a reliable tool to interpret the cause of death. For cocaine, cases related to one-substance poisoning (group I) show high concentrations and almost no overlap with the other groups. For cases not related to one substance only (groups IIa, IIb and III), the concentrations are in the same range. For most of the cases, cocaine-related deaths occurred after prolonged periods of drug use. Due to this long period, cocaine could have already initiated a series of changes in molecular and metabolization process. This problem is known, and literature offers considerable toxicological data about cocaine-related deaths [38,39] which report that correlation between concentration and toxicity is not directly applicable. The overlap observed in our data concerning

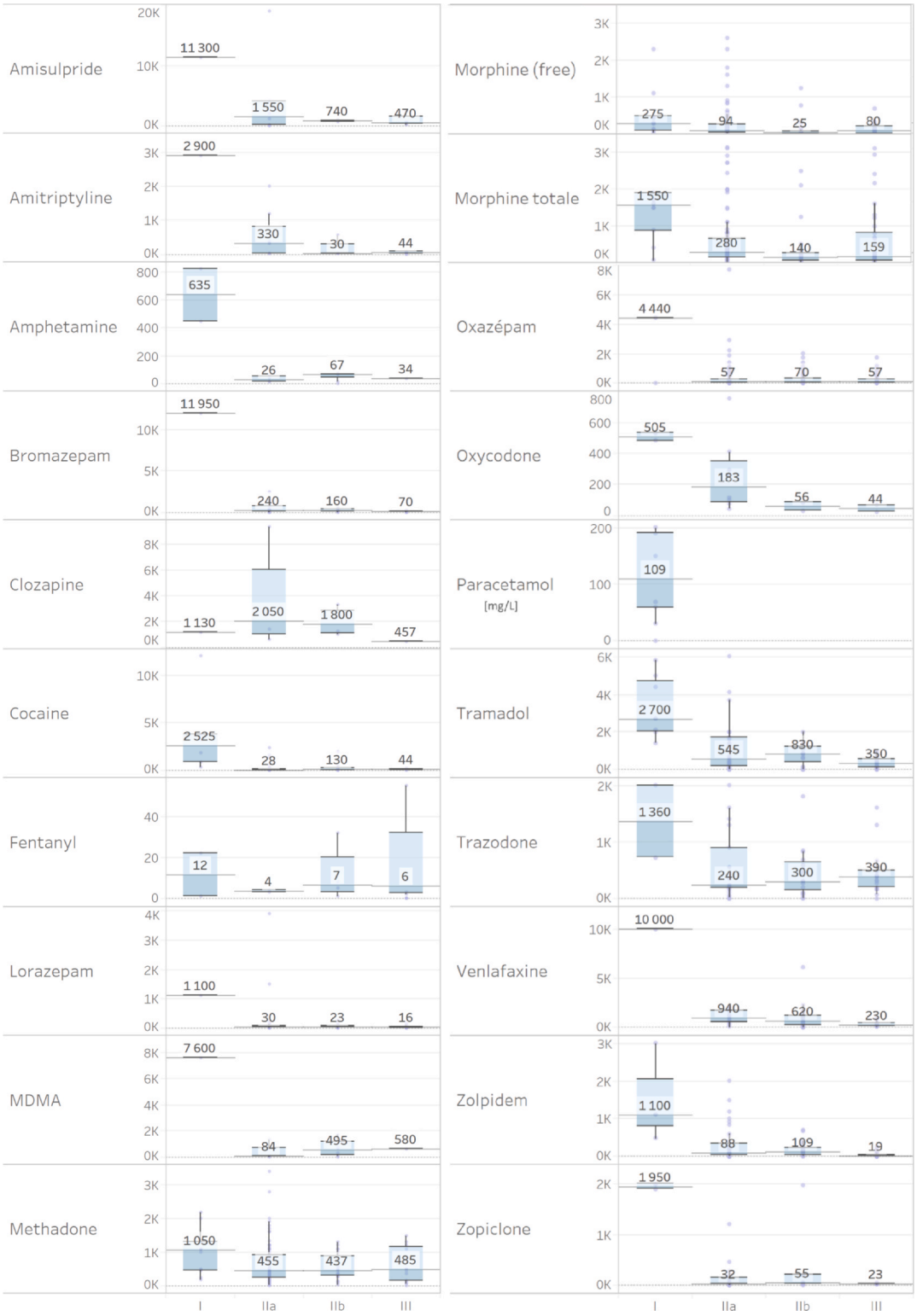

Fig. 2. Femoral blood concentrations of drugs in post-mortem cases, median concentration reported (µg/L). I) certified intoxication by one substance, IIa) certified intoxication by more than one substance, IIb) certified other causes of death with incapacitation due to drugs, and III) certified other causes of death without incapacitation due to drugs. In the boxplot, the whiskers are 1.5 times the interquartile range (IQR), and outliers are shown as circles.

groups other than one-substance poisoning confirms that for cocaine more information is needed to assess conclusions rather than the blood concentration only.

Regarding pentobarbital, all cases were assigned to a single substance intoxication (group I) (n = 7). In Switzerland, pentobarbital is mostly prescribed in protocols used to provide assistance to individuals wishing to end their own lives [40], as expected for these cases, concentration is the highest [6 280–35 000]. On the other hand, paracetamol is a very common medicine and sold over-the-counter in Switzerland. Consequently, even if paracetamol is frequently detected, it

Table 2
Femoral blood concentration detailed for the four groups (g/kg). LLOQ: 0.10 [g/kg].

[g/kg]	N=	min	10th percentile	25th percentile	Median	75th percentile	90th percentile	Max
I	12	2.21	2.91	3.16	3.63	4.23	4.56	5.11
IIa	95	0.10	0.19	0.71	1.28	2.07	2.44	3.92
IIb	188	0.17	0.57	1.08	1.62	2.17	2.61	3.35
III	169	0.10	0.16	0.35	0.71	1.17	1.62	2.1
Total	464	0.10	0.20	0.47	1.20	1.96	2.49	5.11

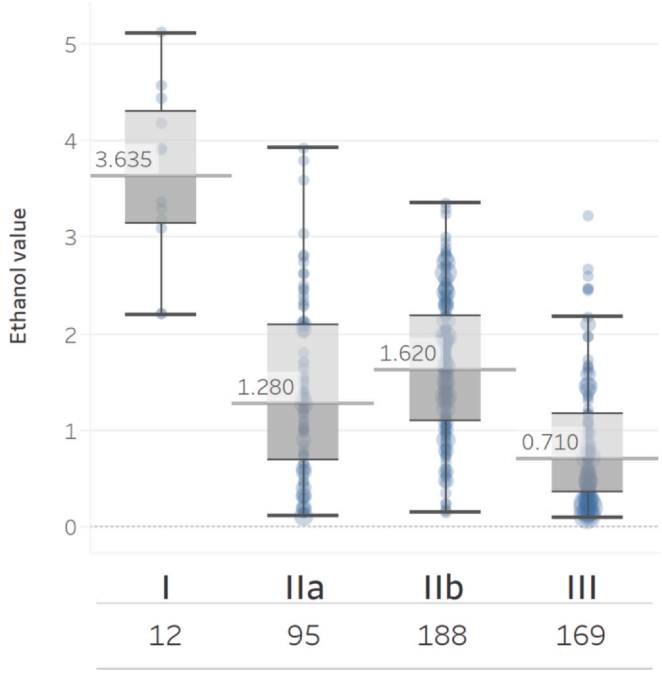

Fig. 3. Femoral blood alcohol concentration for the four groups (g/kg). I) certified intoxication by alcohol, IIa) certified intoxication by alcohol and one other substance, IIb) certified other causes of death with incapacitation due to alcohol, and III) certified other causes of death without incapacitation due to alcohol.

is rarely quantified (only when the forensic pathologists request one). Therefore, only a limit range of concentration is reported in this study and mainly for the high values in groups I.

For most drugs included in this study, the median concentration rate is higher in group I (single substance intoxication) than in the other three groups. In addition, 1.5 of the interquartile range between the group I and the other groups do not overlap. These concentrations could help to determine the range of concentration observed in post-mortem cases like reported from other studies [9,11].

4.4. Alcohol concentration

The results of this study confirm and extend previous work showing that ethanol is the psychoactive substance most frequently identified in autopsy blood samples, either alone or together with other drugs [41–44]. Indeed, blood alcohol concentration exceeded 0.10 [g/kg] for 25% of the cases. Herein, if we considered the cases attributed to alcohol intoxication only, the case distribution is extend is extend from concentration found in group III to highest concentration recorded (2.21–5.11 g/kg). However, this range relies on low number of cases (n = 12 for the group I) and thus, this result must be interpreted with caution. For the group IIa (intoxication attributed to alcohol in addition to other substances), the concentration observed (0.71–2.44 g/kg for 25th and 75th percentile) has a similar range as the two control groups (1.08–2.62 g/kg and 0.35–1.62 g/kg, for IIb and III, respectively). These results can be explained by a variable tolerance to alcohol, but also to a variation in the subjective assessment of the possible contribution of a given alcohol concentration to the death in the intoxication cases.

4.5. Comparison with previous work

Jönsson, Druid and colleagues (2014) published post-mortem femoral blood concentrations of sedative and hypnotic drugs in a larger material in Sweden. Fig. 4 compares a few interesting substances (median) from their studies and the present one after applying a unit conversion of 1 000 µg/L to 1 µg/g.

In this case, median concentrations for drugs included in both studies are often very close to each other. It can be observed that there are similar patterns for some substances between different groups, especially for alprazolam (IIa and III), clomethiazole (IIa), diazepam (III), nitrazepam (III), oxazepam (I and III), zolpidem (I and III), and zopiclone (III). However, there are some exceptions, such as the diazepam median concentration for group IIa.

These differences can be explained partly by the limited number of cases in our study (e.g. one case with flunitrazepam for group IIa in our study versus 418 cases in the corresponding group in the study by Jönsson et al.). Another main reason for the observed differences is the lower LOQ for most drugs in our study, since this results in the inclusion of a number of cases with very low concentrations, which will make the median lower. The LOQ will not affect the medians of the intoxications, hence the medians of groups I and IIa versus the medians of groups IIa and III should be expected to differ more when many low concentrations are included in the control groups.

Finally, different practices in terms of drug consumption between Sweden and Switzerland could also explain this difference. For example, prescription of diazepam is more frequent in Switzerland, even in low dose, so the median reported for the control groups (IIa and III) is really lower than in Sweden. To have a better overview of these, the reported the number of defined daily doses sold, as in Jönsson's article [10], could allow to interpret in detail these differences. This result highlights the necessity to perform this approach in more than one country to see local specificities. If the usage and habits of consumers are different, some dissimilarities in the post-mortem concentrations could be expected. Jönsson and colleagues (2014) focused only on medicine, while herein, concentrations for illicit drugs, such as cocaine or MDMA, were provided as well. (Fig. 5).

Another comparison was made with the Launiainen and Ojanperä's study. As said in previous comparison, some differences could be explained by the low LOQ that affects the median drug concentrations. However, overall a good agreement is observed in both studies. Major gaps are observed for the amiodarone (C01BD01) and propofol (N01AX10) cases. These medications are involved in cardiac therapy and anaesthetic purposes. The gaps can be explained by the difference between sampling populations (by a factor 10). In this study, only a small number of cases contained these two substances (13 and 16 respectively). Moreover, the therapeutic range in plasma for amiodarone is 1–2 mg/L, while the median concentration range in post-mortem blood was found to be 3.4 mg/L. These differences could be explained by the post-mortem redistribution phenomenon [45], already published for some beta blockers [46]. These results show the added value of such an approach and this

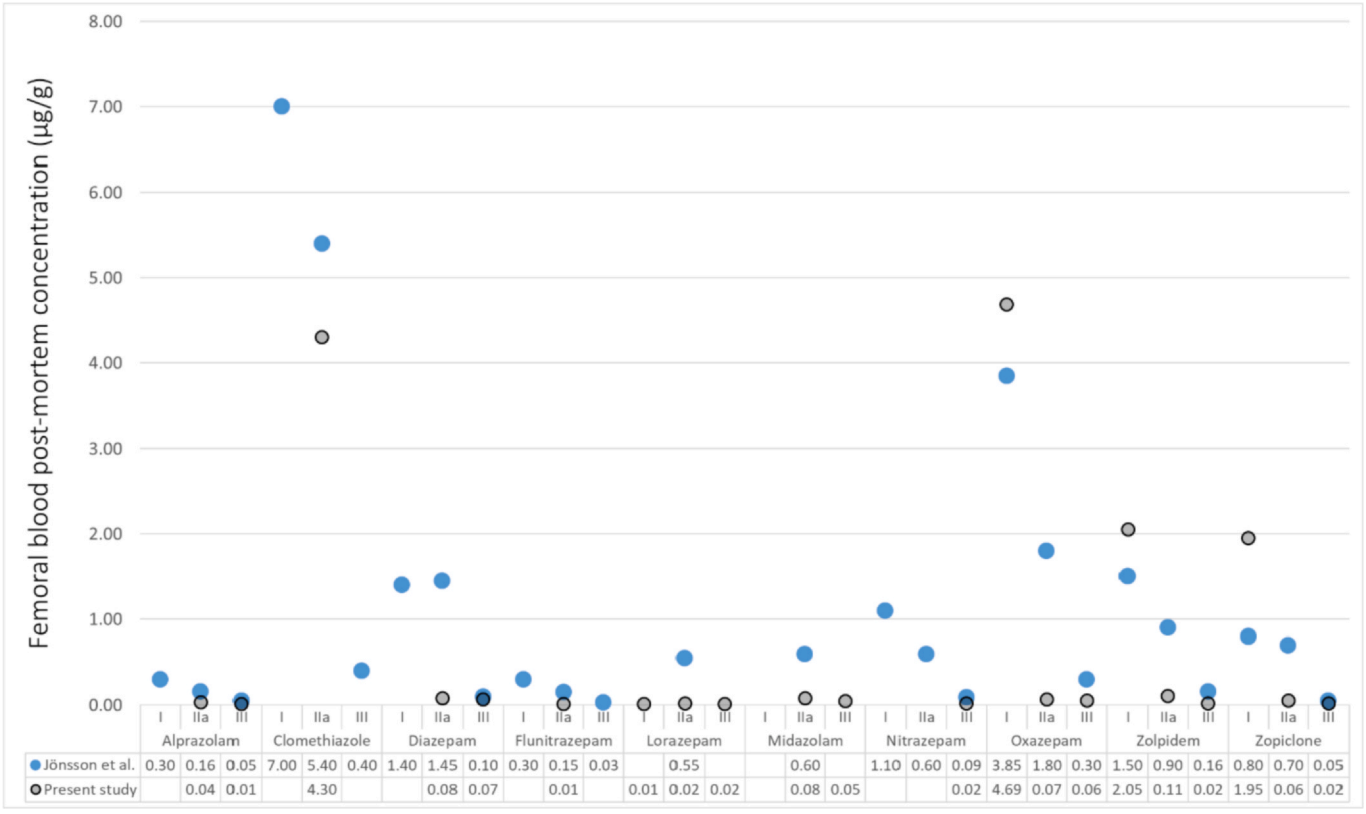

Fig. 4. Comparison of median post-mortem concentrations in our study and in the study by Jönsson & colleagues (2014) [10].

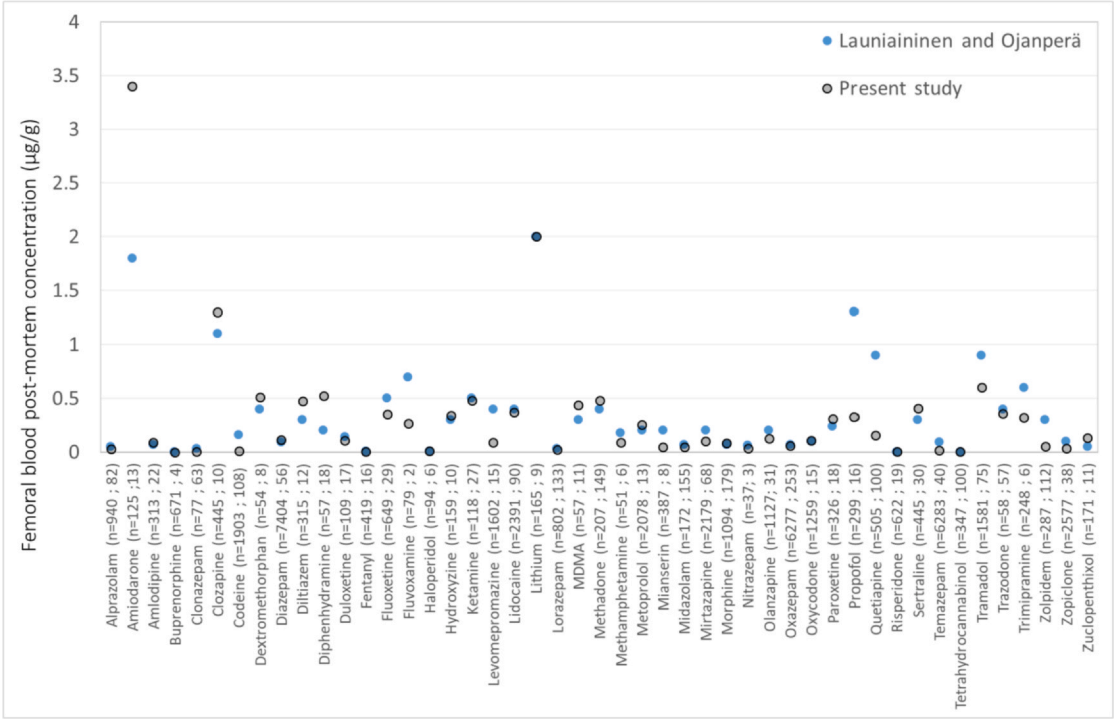

Fig. 5. Comparison of median post-mortem concentrations between the present study and Launiainen and Ojanperä study (2014) [13]; horizontal categories are composed from the name of the substances and the number of cases from Launiainen study and the present study on the bracket, respectively.

strategy may assist pathologists and toxicologist in the interpretation process.

4.6. Limitations

The major limitations of this study were the recording methods and the strict inclusion of each case in one of the four groups. In fact, causes of deaths are attributed through toxicological analysis, circumstances of death and ascertainment performed by forensic pathologists. In addition, considering that the cause of death (induced by one or several substances) was already based on the concentration value obtained during the toxicological analysis, a bias is induced. In this study, post-mortem cases were included by two independent reviewers, but some cases are tough to attribute to one of the four groups. In those cases, the original files were re-consulted, and a choice had to be made.

Another limitation is the number of cases, which is quite low for statistical interpretation. Here, 1 990 cases were analysed, whereas Launiainen and Ojanperä [13] did a similar study with almost 58 000 cases. A small number of cases indicate that the results (principally the concentration rate) should be interpreted with caution. This is especially true when the incriminated substance is present in only one case. For example, in the present study, there is only one case in group I for MDMA. Hence, interpretation needs to be carried out with caution.

Finally, the concentrations in intoxication cases will be affected by a variety of factors, including, but not limited to, variations in time between intake and death resulting in a variable degree of metabolism of the parent drug, post-mortem interval, allowing for variable degree of post-mortem redistribution, and certain medical care treatments, as has previously been pointed out [38,39]. For example, the findings of morphine, fentanyl, ketamine and midazolam may in some cases represent drug administration by health care staff. Another limitation of our study is the fact that for statistical consideration (like the percentile) to be representative, the number of cases needs to be equal to, or exceed 5, and in this study we could not reach this number for several of the substances.

Nevertheless, such an approach is already published and showed that the results were robust [9,10] and could be useful to help toxicologists and forensic pathologists in the interpretation process of post-mortem drug concentrations. The methodology should be extended to the whole country and even across Europe in order to increase the number of drugs for which post-mortem blood concentrations ranges are known, and in particular to increase the number of drugs for which fatal and non-fatal ranges are established. This work is not only important for an appropriate determination of fatal intoxications, but also for pharmacovigilance, since it is crucial that the correct responsible drugs are identified and to avoid that substances which are not responsible are blamed.

5. Conclusion

In order to improve the interpretation of drug concentration in post-mortem toxicology investigation, an epidemiologic study was conducted based on a compilation of all cases between 2011 and 2017 (1 990 cases) in Western Switzerland that involved toxicological investigations in femoral blood. Post-mortem femoral blood concentration were measured, and deaths were classified in four categories as previously published by Druid and Holmgren [27]: I – intoxication by one substance, IIa – intoxication by more than one substance, IIb – other causes of death with incapacitation due to drug consumption, III – other causes of death without incapacitation.

Results show that most cases involve the male population with a median age of 50 years. More than half of the cases were attributed to group III (other causes of death with no incapacitation). The most common substances causing single-drug intoxication were morphine, methadone, ethanol, tramadol, and cocaine.

Reference values for the most common 32 drugs detected in Switzerland between 2011 and 2017 are presented here. They have been used as cut-off values to differentiate normal vs fatal concentration of drugs detected in femoral blood in post-mortem cases. Even if no specific cut-off levels can be defined for fatal intoxication with any of the drugs, the medians and percentiles for each group offer a guidance to the forensic toxicologists and forensic pathologists as to which levels may be fatal and which ones most likely are not. The drug concentrations found in the different groups were similar to those reported for the same drugs in previous studies by Druid´s group, supporting the robustness to this strategy of selection, evaluation, and classification to obtain post-mortem femoral blood reference concentrations of drugs. There were certain differences in concentrations for a number of drugs, which may partly be due to the low number of cases, and by the use of different LOQ, two factors that are important to take into account in further studies. Further research should involve a higher number of cases, for example by extending the study to broader geographical regions, in order to be able to establish post-mortem reference concentrations of substances for which there are scarce post-mortem toxicological data.

CRediT authorship contribution statement

E. Lefrancois: Investigation, Writing - original draft, Writing - review & editing. **N. Raymond**: Writing - review & editing. **A. Thomas**: Writing - review & editing. **C. Lardi**: Investigation. **T. Francasso**: Investigation, Writing - review & editing. **M. Augsburger**: Supervision, Conceptualization, Investigation, Data curation, Writing - review & editing.

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Conflict of Interest

No conflict declared.

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