

Summary statistics for drug concentrations in post-mortem femoral blood representing all causes of death

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Abstract

Concentration distributions for 183 drugs and metabolites frequently found in post-mortem (PM) femoral venous blood were statistically characterized based on an extensive database of 122 234 autopsy cases investigated during an 18-year period in a centralized laboratory. The cases represented all causes of death, with fatal drug poisonings accounting for 8%. The proportion of males was 74% with median age 58 years compared with 26% females with median age 64 years. In 36% of these cases, blood alcohol concentration was higher than or equal to 0.2‰, the median being 1.6‰. The mean, median, and upper percentile (90th, 95th, 97.5th) drug concentrations were established, as the median PM concentrations give an idea of the 'normal' PM concentration level, and the upper percentile concentrations indicate possible overdose levels. A correspondence was found between subsets of the present and the previously published PM drug concentrations from another laboratory that used grouping of cases according to the cause of death. Our results add to the knowledge for evidence-based interpretation of drug-related deaths.

Keywords: post-mortem toxicology; post-mortem drug redistribution; cause of death; drug concentration; post-mortem blood

Introduction

Organized post-mortem (PM) toxicology service provides legal protection for both individuals and society and has an increasing impact on welfare and health as drug use is becoming more prevalent. During the last decades there has been considerable progress in many facets of the discipline, including development of analytical methods, understanding of post-mortem changes, and interpretation of results.¹ Current quality-assured analytical results and their evidence-based interpretation make medico-legal cause-of-death investigation more reliable and improve the quality of death certificates. As national mortality statistics are based on death certificates, the information obtained from high-quality death certificates will, in turn, help authorities and policymakers to recognize trends of drug misuse and abuse and carry out the necessary interventions, thus improving drug safety.²⁻⁴

In cause-of-death investigation, clinical history, autopsy findings and the totality of laboratory results have to be interpreted together. PM concentrations of drugs and poisons play a major role in the interpretation, but it is important to realize that reference ranges for PM concentrations are only one of the crucial elements in the process. Laboratories usually possess in-house databases of varying size with data gathered from case work. In addition, published case notes or small case series, as well as compilations collected from literature sources are available,⁵ but these data are often heterogeneous in terms of the sampling site, the analytical methods used, and the number of cases involved. There may even be a bias of publishing mainly cases with exceptionally high concentrations.

The fact that PM drug concentrations are not necessarily the same as those at the time of death, called the PM drug redistribution (PMR), was brought to attention by Prouty and Anderson in their two papers published in 1987 and 1990,^{6,7} as well as by Pounder and Jones in 1990,⁸ but similar observations had been made much earlier.⁹ Drug levels may vary according to the sampling site and the interval between death and specimen collection (PM interval). In optimal circumstances, a sample

of PM venous blood from a femoral vein is taken as soon as possible after death, as this procedure is considered to give results that are the least susceptible to PM change.^{10,11}

Systematic collection and evaluation of reference concentrations in PM femoral blood have been carried out by Swedish investigators,¹² taking advantage of the relatively high PM toxicology rate and uniform procedures in the country. In this approach, the cases are subdivided into poisonings by one specific substance only (Group A), multi-substance poisonings (Group B), and PM controls comprising deaths not involving incapacitation by substances (Group C). Moreover, the results are compared with data based on therapeutic drug monitoring and data collected from driving under the influence cases. This approach produces extremely valuable results, but the information retrieval is rather slow and laborious due to manual, multi-reviewer, case-by-case evaluation. Moreover, the number of cases especially in Group A may remain low, consisting of only a few concentration entries or no entries at all.

Another systematic approach that relies on a high PM toxicology rate is to utilize the PM concentrations that accumulate during case work without pre-selection for cause of death. This “all-causes-of-death approach”, introduced by Jones and Holmgren,¹³ is more straightforward and prolific regarding the number of cases and drugs involved, omitting the tedious manual case grouping step. Also based on the Swedish material, these authors published concentration distributions of 25 drugs most frequently identified in PM femoral blood.

Finland is another country with a high PM toxicology rate and a centralized laboratory investigation. According to the law, all sudden and unexpected deaths undergo a medico-legal investigation, initiated by the police and conducted by a forensic pathologist. Specific grounds for the investigation include an obvious or suspected accident, suicide, crime, poisoning, occupational disease or medical treatment. As a result, in nearly 20% of all deaths a medico-legal investigation is performed.

In our former paper, we followed the all-causes-of-death approach and published the PM median, mean, and upper percentile (90th, 95th, 97.5th) concentrations calculated for 129 drugs based on 57 903 Finnish autopsy cases with PM toxicology executed.¹⁴ In the present study, our main objective was to make the results of the original study more complete by extending the range to cover 183 drugs and metabolites, based on an even larger amount of accumulated data as a basis for the PM concentrations. Another objective was to compare our results with those published by the Swedish investigators.

Materials and methods

Toxicological analysis

The Finnish medico-legal system and the PM toxicology services were described in detail in our previous paper.¹⁴ Briefly, the concentration data were acquired from femoral venous blood taken at autopsy, the samples containing 1% NaF and stored at 4°C prior to analysis. The blood samples were quantitatively monitored for about 200 drugs on a routine basis using three comprehensive methods. For acidic and neutral drugs, dual-column gas chromatography with nitrogen phosphorus detection (GC-NPD)¹⁵ was used until replaced in February 2007 by a method based on GC coupled with mass spectrometry (GC-MS).¹⁶ For benzodiazepines, a GC method with electron capture detection (GC-ECD)¹⁷ was used until March 2010, after which a method based on GC and negative-ion chemical ionization MS (GC-NCIMS)¹⁸ was adopted for routine use. A dual-column GC-NPD method was used for basic drug screening¹⁹ until December 2014, when a method based on ultra-high-performance liquid chromatography with a photodiode array detector and a corona charged aerosol detector (UHPLC-DAD-CAD) was put into operation.²⁰ Digoxin was analysed with an immunological method using Siemens Immulite 1000 or 2000XPi analyzers. Lithium was analysed by inductively coupled plasma mass spectrometry (ICP-MS) until February 2014, followed by a

method based on an ion-selective electrode. Confirmation and additional determinations were carried out by GC-MS and LC-MS/MS for drugs not covered by the comprehensive quantitative monitoring methods described above. All the concentration results were obtained by using quality-controlled and mostly accredited methods that relied on calibration with appropriate reference standards. Along with the changes in the analytical methods, the lower limit of quantification (LOQ) changed for some compounds (Table 2).

Data refining

During the period between 1 January 2000 and 31 December 2017 the results from quantitative analyses of drugs in PM femoral venous blood from 122 234 autopsy cases were entered into the toxicology database (Table 1). From this material, those drugs that had been quantified at least 18 times in PM blood were selected, and the median, mean, and upper percentile (90th, 95th, 97.5th) concentrations (mg/L) were calculated from the findings (Table 2).

Comparison to literature reference concentrations

In Table 2, a one point reference concentration value in living persons' plasma (C_{plasma}) was given for each drug to enable instant comparison with the PM concentrations. In most cases, the C_{plasma} values represented the upper limit of plasma/serum concentrations (in general, trough at steady state) observed following therapeutically effective doses.²¹

Comparison to the PM concentrations from the Swedish investigators' studies²²⁻²⁶ was based on the following concentration percentile ratios obtained from the two databases (Swedish/Finnish): median/median, 90th percentile/median, 90th /90th percentile, and 90th /97.5th percentile. First, the concentration percentile ratios were calculated for individual drugs, and second, the medians of these ratios were calculated and presented in Table 3.

Results and discussion

Table 1 shows demographics of the 122 234 autopsy cases from the 18-year study period for which a comprehensive PM drug analysis was completed. The number of autopsies, the mean age, and the mean blood alcohol concentration (BAC) in cases where it exceeds the LOQ of 0.2‰ (g/kg) are given separately for males and females. The number of accumulated autopsy cases forming the basis of the concentration data is about twice the size of that in our original study,¹⁴ while the concentration data presented in that study forms a part of the present data. The demographics of the cases are fairly similar between these two studies in terms of gender distribution, age, and proportion of alcohol-positive cases. Males and females represented 74 and 26% of the subjects, respectively, and the median age was 58 and 64 years, respectively. The prevalence of alcohol-positive cases was 36% and the median BAC was 1.6‰. These figures showed little difference from the original study.¹⁴

Table 2 shows the concentration distributions in PM femoral venous blood for the 183 drugs and metabolites most frequently found in autopsy cases in alphabetical order, comprising 221 780 individual concentration entries. There is an increase of 54 substances relative to the original study. Indicated are the number of cases, the LOQ, the PM mean, median, and upper percentile (90th, 95th, 97.5th) concentrations. As stated in the original study, the median PM concentrations are likely to give an idea of the ‘normal’ PM concentration range, and the upper percentile concentrations indicate possible overdose levels. This judgment is supported by the fact that the manner of death is natural in approximately 55% of all PM toxicology cases in Finland, and the proportion of fatal drug poisonings in the present material was on average 8%. However, this concept of normal and overdose levels cannot be applied to each drug in a mechanical manner.

Table 2 also lists clinical C_{plasma} values to roughly illustrate how the median PM femoral blood drug concentrations relate to the therapeutic ranges reported mainly in an established data compilation by Schulz *et al.*²¹ Calculating the PM median/ C_{plasma} ratio one can get an idea of the PM behavior for a

particular drug. Apart from the PMR, exceptionally high PM median/ C_{plasma} ratio values may arise from a high intrinsic clinical blood/plasma ratio and/or a high volume of distribution, as exemplified by dextromethorphan and hydroxychloroquine, or from the high proportion of poisonings by a particular drug in the database, as exemplified by dextropropoxyphene and promazine. Correspondingly, exceptionally low values may arise from a low clinical blood/plasma ratio, as exemplified by aripiprazole, warfarin, and some benzodiazepines. Obviously, the representativeness of the C_{plasma} values plays a role in the relevance of the ratio. The association between the pharmacological characteristics remarked above and the PM concentration levels has been discussed in more detail in our previous study.¹⁴

Table 2 shows the relative differences in the PM median concentrations between the present database and the original database. For 18 drugs, the median concentration in the present database was more than 10% higher, and for 38 drugs it was more than 10% lower than in the original database. The mean (median) difference in the PM median concentrations between the databases was -5% (0%), and the mean (median) difference in the absolute values was 13% (8%). These findings suggest that the PM median concentrations are largely reproducible over the course of time, though there were some exceptions concerning individual drugs. The reasons for a more prominent change include a relatively low or a much changed number of cases, changed clinical prescription practices or changed abuse patterns. While LOQ is an important factor relative to the statistical concentration distribution, the current changes in LOQ were generally associated with only minor effects on the results.

Table 3 shows the comparison of selected concentration percentiles in PM femoral venous blood between the present study, involving all causes of death (N = 144 034), and the five Swedish studies (N = 9436), employing grouping according to the cause of death.²²⁻²⁶ A moderate correspondence was obtained between Swedish group C and our median concentration, both representing a 'normal' PM concentration. The median ratios of Swedish group C median to our median and Swedish group

C 90th percentile to our median were 0.6 and 1.7, respectively. For example, in case of the antipsychotic drug olanzapine, our median concentration was 0.20 mg/L, while the Swedish group C median and 90th percentile were 0.10 mg/L and 0.20 mg/L, respectively.²⁵ A correspondence also existed between the Swedish group A and B 90th percentiles and our 97.5th percentile (ratios 1.2 and 0.9, respectively), representing lethal concentrations for most substances. Similarly, as exemplified by olanzapine, our 97.5th percentile concentration was 2.4 mg/L, while the Swedish group A and B 90th percentile concentrations were 2.71 mg/L and 0.90 mg/L, respectively.²⁵ These comparisons illustrate how the PM concentration values between the subgroups of the two large databases may or may not match, giving additional grounds for interpretation.

Drug metabolites may have similar (e.g. *N*-desmethyramitriptyline) or different (e.g. *N*-desmethylclomipramine) pharmacodynamic properties than their respective parent compounds, or they may be pharmacologically inactive (e.g. *N*-desmethylcitalopram).²⁷ For those drugs with similar properties, the sum of the concentrations of parent drug and active metabolite can be used for interpretation. Even non-active metabolites are important from a pharmacokinetic perspective, because the metabolite-to-parent drug ratio (MPR) can be used for differentiating between acute and chronic intake.²³ MPR sometimes allows identification of abnormal metabolism caused by pharmacokinetic interactions or genetic abnormalities,²⁸ especially when compared with established ratios from therapeutic drug monitoring.²⁷ As has been pointed out earlier, the PM concentrations of drugs of abuse, such as parenterally administered strong opioids^{12,29,30} and stimulants,³¹ are of limited value in assessing the cause of death because individual tolerance, route of administration, and poly-drug abuse are more important factors in these cases. However, MPR can be decisive in interpreting the role of drugs in abuser deaths.³² In this study, we were able to report the PM concentrations of a limited number of drug metabolites, but we acknowledge that a wider range of metabolites is needed.

Interest is currently focused on the quantification of drugs in PM materials other than blood, including bile, brain, liver, muscle, and vitreous humor.³³⁻³⁸ However, while these alternative materials show promising results with individual drugs or in specific circumstances, femoral venous blood still represents the most viable material for interpretative purposes in PM toxicology, with a more extensive range of reference concentrations published in the literature.

Conclusions

We have provided an extended list of drug concentration distributions in PM femoral venous blood, accumulated during an 18-year period by using quality-controlled and mostly accredited methods. The data are intact in the sense that no preselection of cases has occurred according to the cause of death or any criterion other than the number of qualified findings per drug. Hence, there is no prior interpretation by a pathologist or toxicologist that might create a bias. The reader should use the data in case work with consideration and taking into account all of the necessary circumstantial and contributory factors related to the case. The strength of the present all-causes-of-death approach is that it provides abundant data for a statistically reliable basis for 'normal' PM drug concentrations in blood and even offers potential for answering the question 'was it a poisoning?' – but only in the right context.

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Table 1. Demographics and mean blood alcohol concentration for autopsy cases with comprehensive post-mortem drug analysis completed.

Sex	N	Age, years Mean (median) highest	N ^a	Blood ethanol, ‰ (g/kg) Mean (median) highest
Male	90,398 (74%)	56.5 (58) 103	35,889 (81%)	1.71 (1.60) 7.7
Female	31,836 (26%)	61.9 (64) 105	8,243 (19%)	1.64 (1.50) 8.5
Both sexes	122,234 (100%)	57.9 (59) 105	44,132 (100%)	1.70 (1.60) 8.5

^aBlood ethanol \geq 0.2‰

Table 2. Descriptive statistics for concentrations of drugs determined in post-mortem (PM) femoral blood representing all causes of death.

Drug	PM cases	PM LOQ mg/L	PM mean mg/L	PM median mg/L	Upper PM percentiles mg/L			Therapeutic concentration in plasma (C _{plasma}) ^a mg/L	Previous PM median ^b mg/L	Difference in PM median from previous data ^c %
					90 th	95 th	97.5 th			
Acebutolol	115	0.25	11	0.77	23	72	100	2	0.84	-8
Alfentanil	119	0.00005	0.029	0.016	0.08	0.10	0.16	0.60		
Alprazolam	2234	0.02	0.06	0.033	0.12	0.20	0.33	0.05	0.05	-34
Alprazolam, 1-hydroxy-	821	0.001	0.005	0.002	0.010	0.018	0.028	0.003 ³⁹		
Aminophenazone, 4-methyl-	599	2/3 ^d	21	12	50	67	96	10 ^e	15	-20
Amiodarone	137	0.4	3.9	1.8	8.0	11	18	2	1.8	0
Amitriptyline	2604	0.1	1.3	0.40	2.6	4.6	7.9	0.30	0.40	0
Amitriptyline, <i>N</i> -desmethyl-	1347	0.1	0.59	0.30	1.3	2.0	3.0	0.25 ⁴⁰		
Amlodipine	3081	0.006	0.09	0.055	0.16	0.21	0.28	0.015	0.07	-21
Amphetamine	1087	0.04	0.80	0.26	1.9	2.9	4.4	0.10	0.28	-7
Aripiprazole	199	0.1	0.29	0.15	0.51	0.71	0.86	0.50		
Atenolol	668	0.2	1.5	0.69	2.6	4.3	6.1	1.0	0.64	9
Betaxolol	156	0.003	0.20	0.10	0.31	0.40	0.43	0.05	0.10	0
Biperiden	38	0.1	0.20	0.10	0.30	0.32	0.46	0.10	0.10	0
Bisoprolol	7570	0.01	0.11	0.05	0.18	0.28	0.45	0.10	0.05	0
Bupivacaine	99	0.2/0.05 ^d	1.5	0.36	1.3	3.3	4.7	1.5	0.40	-10
Buprenorphine	1549	0.0002	0.0033	0.0013	0.0059	0.0095	0.019	0.015	0.0012	8
Buprenorphine, nor-	1251	0.0002	0.0038	0.0012	0.0078	0.014	0.025	0.005 ⁴¹		
Bupropion	204	0.1	3.7	0.28	7.2	17	42	0.10		
Buspirone	27	0.05	0.083	0.050	0.23	0.30	0.33	0.01 ⁴²		
Caffeine	32721	1/3 ^d	4.7	3.9	8.5	11	14	10	3.0	30
Candesartan	291	0.005	0.12	0.03	0.20	0.40	0.64	0.18		
Carbamazepine	2228	1/0.3 ^d	7.6	6.3	13	18	26	8.0	6.2	2
Carbamazepine, 10,11-dihydro-10-hydroxy-	834	5/3 ^d	27	22	50	62	80	35	22	0
Carvedilol	253	0.003	0.040	0.018	0.080	0.13	0.30	0.15	0.02	-10
Celiprolol	177	0.03	3.3	0.27	2.7	5.3	8.7	0.50	0.28	-4
Cetirizine	112	0.001	0.67	0.11	0.90	1.9	3.0	0.30	0.10	10
Chlordiazepoxide	2408	0.2	1.4	0.61	3.0	4.8	6.9	3.0	0.70	-13
Chloroquine	59	0.2	10	0.67	39	55	67	0.50	1.3	-48
Chlorpromazine	291	0.05	0.95	0.30	2.1	3.9	6.5	0.10	0.30	0
Chlorprothixene	755	0.1	1.8	0.30	2.6	5.0	9.0	0.30	0.30	0
Citalopram	5800	0.1	0.87	0.40	1.3	2.1	4.5	0.40	0.40	0
Citalopram, <i>N</i> -desmethyl-	892	0.5/0.05 ^d	0.39	0.21	0.83	1.1	1.7	0.15 ⁴³		
Clobazam	42	0.1/0.05 ^d	0.35	0.20	0.71	1.3	1.6	0.61 ⁴⁴		
Clobazam, <i>N</i> -desmethyl-	101	0.2/0.05 ^d	1.6	0.90	3.4	5.5	8.6	1.5 ⁴⁵		
Clobutinol	23	0.2/0.05 ^d	0.54	0.30	0.87	1.4	2.1	0.20		
Clomipramine	155	0.1	1.0	0.60	2.2	3.4	4.0	0.40		
Clomipramine, <i>N</i> -desmethyl-	81	0.5/0.05 ^d	2.7	1.2	4.8	7.1	20	1.0 ⁴⁶		
Clonazepam	315	0.01	0.030	0.011	0.041	0.080	0.10	0.08	0.03	-63

Clonazepam, 7-amino-	1790	0.005	0.17	0.094	0.38	0.56	0.83	0.14 ⁴⁷		
Clozapine	880	0.1	2.7	1.1	4.3	8.7	16	0.60	1.1	0
Codeine	3633	0.02	0.65	0.14	1.4	2.7	4.6	0.25	0.16	-13
Cyclizine	62	0.005	1.1	0.30	1.2	2.3	5.9	0.25	0.30	0
Demoxepam	727	0.1	1.1	0.80	2.5	3.1	4.0	2.8 ⁴⁸		
Desloratadine	56	0.001	0.071	0.031	0.13	0.24	0.44	0.006		
Dextromethorphan	91	0.1	0.57	0.30	1.5	1.9	2.5	0.04	0.40	-25
Dextropropoxyphene	270	0.1	6.6	2.6	12	18	41	0.30	2.6	0
Diazepam	11831	0.02	0.17	0.090	0.40	0.60	0.80	2.0	0.09	0
Diazepam, <i>N</i> -desmethyl-	15945	0.02	0.21	0.10	0.50	0.70	0.99	0.80	0.10	0
Diclofenac	69	0.5/0.3 ^d	2.2	1.1	5.6	6.9	8.3	3.0	1.3	-15
Digoxin	2578	0.0005	0.0028	0.0018	0.0045	0.0063	0.0086	0.002		
Diltiazem	422	0.1	2.4	0.30	1.8	7.8	22	0.13	0.30	0
Diphenhydramine	122	0.005	0.36	0.20	0.80	0.90	1.3	0.10	0.20	0
Dixyrazine	57	0.003	0.79	0.10	1.9	5.7	6.9	0.30	0.10	0
Donepezil	560	0.003	0.23	0.20	0.40	0.49	0.59	0.075	0.20	0
Doxepin	902	0.05	2.2	0.60	6.3	10	15	0.20	0.60	0
Doxepin, <i>N</i> -desmethyl-	254	0.2/0.05 ^d	0.73	0.40	1.6	2.3	3.2	0.20		
Duloxetine	320	0.01	0.40	0.15	0.63	1.2	2.7	0.12	0.14	7
Enalapril	115	0.01	0.10	0.032	0.16	0.47	0.66	0.10		
Ephedrine	357	0.04	0.50	0.20	0.90	1.5	2.3	0.20	0.21	-5
Ethylmorphine	116	0.02	0.42	0.10	1.2	2.7	2.9	0.60	0.10	0
Etoricoxib	141	0.5	2.9	1.5	5.0	6.3	8.6	3.6	1.2	25
Felodipine	141	0.001	0.017	0.0020	0.040	0.060	0.15	0.012		
Fentanyl	1074	0.0001	0.010	0.0042	0.019	0.030	0.047	0.01	0.0058	-28
Flecainide	166	0.2	4.1	1.8	8.7	16	23	0.80	1.9	-3
Fluconazole	443	0.1	7.8	4.3	20	29	37	5.0	3.8	13
Fluoxetine	868	0.2	0.84	0.50	1.9	2.8	3.7	0.50	0.50	0
Flupentixol	43	0.001	0.020	0.0070	0.056	0.087	0.099	0.01		
Fluvoxamine	96	0.03	2.4	0.70	7.3	8.4	19	0.23	0.70	0
Furosemide	310	0.1	2.5	0.90	5.5	9.1	16	5.0	0.90	0
Gabapentin	541	1	27	12	58	93	145	6.0	11	9
Galantamine	88	0.01	0.22	0.14	0.40	0.54	0.76	0.06	0.11	27
Glibenclamide	45	0.08	0.28	0.09	0.31	0.63	0.69	0.20		
Glimepiride	211	0.01	0.27	0.03	0.21	0.38	1.0	0.50	0.03	0
Haloperidol	335	0.003	0.02	0.009	0.03	0.046	0.12	0.017	0.01	-10
Hydrochlorothiazide	581	0.05	0.34	0.23	0.69	0.99	1.3	2.0		
Hydroxychloroquine	394	1	12	8.0	26	33	45	0.10	10	-20
Hydroxyzine	434	0.2	0.61	0.30	1.1	2.0	3.1	0.10	0.30	0
Ibuprofen	1973	10	18	14	35	49	70	30	19	-26
Indomethacin	51	0.5	1.3	1.0	2.1	3.0	3.9	1.0	1.1	-9
Ketamine	358	0.1	0.82	0.44	1.5	2.4	4.1	6.0	0.50	-12
Ketoprofen	249	0.3	3.3	1.2	5.7	10	21	3.7	1.3	-8
Labetalol	216	0.01	0.12	0.059	0.25	0.35	0.42	0.18	0.09	-34
Lacosamide	57	1	8.9	6.0	16	23	27	10		

Lamotrigine	691	1/0.5 ^d	4.9	3.0	10	15	24	14	3.8	-21
Levetiracetam	457	3	28	18	61	78	90	40	15	20
Levomepromazine	2274	0.1	1.1	0.31	1.9	3.2	5.1	0.025	0.40	-23
Lidocaine	3853	0.1	0.75	0.34	1.7	2.5	3.9	5.0	0.40	-15
Lithium	223	0.5	3.9	2.5	7.5	11	19	8.0	2.0	25
Lorazepam	1676	0.01	0.04	0.02	0.07	0.10	0.20	0.25	0.03	-33
Losartan	720	0.005	0.13	0.03	0.27	0.48	0.80	0.65		
Losartan, carboxylic acid (EXP3174)	602	0.005	0.12	0.05	0.26	0.52	0.79	0.60 ⁴⁹		
MDA	47	0.05	0.13	0.07	0.19	0.45	1.0			
MDMA	139	0.04	1.1	0.49	3.0	3.7	5.0	0.35	0.30	63
Meloxicam	40	0.2	2.2	1.4	5.5	9.0	9.1	2.00		
Melperone	174	0.05	1.6	0.40	3.4	9.4	16	0.10	0.40	0
Memantine	302	0.02	0.74	0.48	1.6	2.0	2.4	0.15		
Meprobamate	194	10	18	3.3	52	72	83	10	28	-88
Mesoridazine	88	0.2	0.74	0.50	1.2	1.6	2.6	1.0	0.50	0
Metformin	3386	1	14	5.1	34	61	92	1.0	6.0	-15
Methadone	466	0.05	0.63	0.50	1.4	1.7	2.0	0.50	0.40	25
Methamphetamine	185	0.04	0.86	0.18	1.2	2.1	2.8	0.10	0.18	0
Methylphenidate	30	0.05/0.1 ^d	0.20	0.10	0.28	0.38	0.83	0.06		
Metoclopramide	1209	0.05	0.21	0.10	0.40	0.60	0.80	0.15	0.10	0
Metoprolol	3681	0.05	0.90	0.20	1.1	1.9	4.0	0.50	0.20	0
Mianserin	487	0.05	0.37	0.20	0.70	1.1	2.0	0.13 ⁴⁰	0.20	0
Mianserin, <i>N</i> -desmethyl-	130	0.1	0.47	0.30	0.80	1.1	1.5	0.08 ⁵⁰		
Midazolam	445	0.02	0.12	0.046	0.24	0.46	0.60	0.10	0.07	-34
Midazolam, 1-hydroxy-	621	0.002	0.053	0.008	0.10	0.18	0.30	0.40 ⁵¹		
Mirtazapine	3820	0.05	0.45	0.19	0.70	1.5	2.7	0.08	0.20	-5
Moclobemide	177	0.1	14	1.9	36	49	120	1.0	1.9	0
Morphine	2134	0.02	0.21	0.070	0.35	0.61	0.95	0.10	0.07	0
Naloxone	167	0.0006	0.0082	0.0020	0.013	0.023	0.033	0.03		
Naproxen	847	10	33	23	66	89	110	50	33	-30
Nifedipine	74	0.02	0.20	0.067	0.29	0.53	0.73	0.15	0.10	-33
Nitrazepam	86	0.05	0.080	0.034	0.20	0.30	0.49	0.10	0.06	-43
Olanzapine	2215	0.05	0.45	0.20	0.80	1.4	2.4	0.08	0.20	0
Orphenadrine	551	0.1	0.94	0.34	1.8	3.3	5.9	0.20	0.30	13
Oxazepam	9467	0.02	0.28	0.072	0.69	1.2	1.9	1.5	0.07	3
Oxcarbazepine	269	0.3	1.6	0.70	3.4	5.6	8.6	2.0	0.60	17
Oxycodone	3114	0.02	0.29	0.08	0.45	0.80	1.5	0.10	0.10	-20
Paliperidone (9-hydroxyrisperidone)	193	0.002	0.021	0.013	0.040	0.060	0.10	0.06 ²⁷		
Paracetamol	9579	5/10 ^d	36	18	67	120	200	25	15	20
Paroxetine	482	0.004	0.69	0.24	1.2	2.0	3.4	0.05	0.24	0
Pentobarbital	38	0.5	7.3	2.5	26	27	30	5.0		
Perphenazine	477	0.005	0.070	0.010	0.070	0.17	0.36	0.02	0.01	0
Pethidine	59	0.1	0.52	0.30	1.1	1.3	1.8	0.80	0.30	0
Phenazepam	116	0.03	0.090	0.050	0.21	0.29	0.38	0.04	0.09	-45
Phenobarbital	46	10	20	16	45	53	55	30	30	-47

Phenylpropanolamine	156	0.04	0.31	0.12	0.55	1.1	1.4	0.50	0.14	-14
Phenytoin	355	10	8.6	7.8	16	20	25	15	13	-40
Pholcodine	84	0.02	0.37	0.17	0.82	1.1	1.6	0.20	0.19	-11
Pioglitazone	86	0.01	0.15	0.080	0.36	0.49	0.55	2.0 ⁵²		
Pregabalin	1619	0.2	18	8.8	39	60	91	8.3	8.0	10
Prilocaine	38	0.1/0.05 ^d	0.79	0.30	1.6	2.0	3.3	2.0		
Promazine	371	0.1	4.2	1.0	11	18	26	0.05	1.2	-17
Propofol	786	0.1/0.5 ^d	2.5	1.3	5.6	8.2	11	8.0	1.3	0
Propranolol	1805	0.02	1.5	0.13	4.7	8.5	14	0.30	0.13	0
Pseudoephedrine	254	0.04	0.71	0.26	1.5	2.4	4.1	0.80	0.24	8
Quetiapine	1792	0.2	3.5	0.51	6.4	13	25	0.50	0.90	-43
Quinine	495	0.2	2.9	0.80	3.8	10	29	7.0	1.0	-20
Risperidone	973	0.002	0.010	0.004	0.021	0.040	0.070	0.006	0.004	0
Rivastigmine	79	0.003	0.030	0.010	0.051	0.090	0.13	0.02	0.01	0
Ropivacaine	118	0.1	2.0	0.70	2.8	3.8	6.6	1.5	0.70	0
Rosiglitazone	18	0.05	0.14	0.070	0.23	0.54	0.77	0.30		
Salicylic acid	1716	5/3 ^d	37	9.4	60	110	310	200	11	-15
Sertraline	760	0.1	0.54	0.30	1.0	1.6	2.3	0.25	0.30	0
Sildenafil	135	0.03	0.27	0.13	0.40	0.53	0.72	0.50	0.10	30
Sitagliptin	1339	0.01	0.65	0.40	1.4	2.0	2.9	0.38	0.36	11
Sotalol	169	0.25	3.0	2.0	5.8	9.0	13	3.0	2.0	0
Sulpiride	142	0.02	4.0	0.80	8.3	20	32	0.40	1.1	-27
Sumatriptan	32	0.01	1.4	0.28	2.4	5.2	11	0.06		
Telmisartan	93	0.005	0.41	0.19	1.0	1.4	3.0	4.0 ⁵³		
Temazepam	9545	0.02	0.35	0.09	0.88	1.5	2.4	0.15	0.09	0
Tetrahydrocannabinol	884	0.001	0.010	0.0024	0.0092	0.016	0.029	0.01	0.002	20
THC, 11-hydroxy-	60	0.003	0.015	0.006	0.020	0.030	0.050			
THC-COOH (11-nor-9-carboxy-THC)	310	0.003	0.030	0.018	0.070	0.10	0.14			
Theobromine	56	2	11	9.8	19	24	29	15		
Theophylline	388	10	16	11	24	45	84	15	15	-27
Thiopental	27	1	9.4	5.0	15	22	38	5.0		
Thioridazine	299	0.1	1.3	0.70	3.0	4.3	6.3	2.0	0.70	0
Tizanidine	214	0.003	0.14	0.026	0.21	0.45	0.93	0.015	0.02	30
Topiramate	137	1/3 ^d	16	10	24	33	47	10	8.8	14
Tramadol	2636	0.1	3.4	0.91	7.1	14	22	1.0	0.90	1
Tramadol, <i>N</i> -desmethyl-	843	0.2/0.1 ^d	1.1	0.42	2.3	4.1	6.0	0.30 ^{54,55}		
Tramadol, <i>O</i> -desmethyl-	951	0.2/0.1 ^d	0.78	0.40	1.7	2.4	3.8	0.30 ^{54,55}		
Trazodone	115	0.2	1.9	0.48	4.3	7.5	15	1.0	0.40	20
Trimethoprim	738	1	3.4	2.2	6.5	9.0	12	2.5	2.3	-4
Trimipramine	319	0.1	1.1	0.60	2.4	3.4	5.0	0.30	0.60	0
Trimipramine, <i>N</i> -desmethyl-	93	0.1/0.05 ^d	0.98	0.60	2.3	3.2	3.6	0.40 ⁵⁶		
Valproic acid	1859	1/3 ^d	50	30	75	99	193	100	28	7
Valsartan	103	0.005	1.5	0.36	4.2	5.8	13	6.0		
Venlafaxine	1609	0.1	4.1	0.60	5.4	16	36	0.40	0.70	0
Warfarin	2373	0.5	0.64	0.57	1.0	1.3	1.8	3.0	0.60	-19

Venlafaxine, <i>N</i> -desmethyl-	36	0.05	0.47	0.40	0.96	1.3	1.4	0.50 ⁵⁷		
Venlafaxine, <i>O</i> -desmethyl-	362	0.1	0.85	0.47	1.6	2.6	3.8	0.50 ⁵⁷		
Verapamil	249	0.1	2.2	0.40	5.8	11	13	0.25	0.35	14
Vildagliptin	38	0.05	0.11	0.059	0.27	0.38	0.40	1.6 ⁵⁸		
Vortioxetine	43	0.003	0.14	0.090	0.17	0.29	0.47	0.07 ⁵⁹		
Xylometazoline	23	0.05	0.008	0.001	0.004	0.011	0.070			
Zolpidem	557	0.1	0.64	0.29	1.3	1.9	3.4	0.15	0.30	-3
Zopiclone	5778	0.02	0.33	0.08	0.66	1.3	2.5	0.05	0.10	-20
Zuclopenthixol	274	0.005	0.10	0.05	0.20	0.35	0.51	0.05	0.05	0

^aUpper limit of established therapeutic concentration in plasma (C_{plasma}) derived from Schulz *et al.* (ref. 21) unless another reference indicated as superscript

^bPM median concentration from previously published data by Launiainen and Ojanperä (ref. 14)

^cDifference in PM median concentration between current data and previously published data by Launiainen and Ojanperä (ref. 14)

^dData combined from two successive methods; validation parameters presented in order of appearance

^eFor parent drug metamizole