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Post mortem tissue distribution of quetiapine in forensic autopsies

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ABSTRACT

The antipsychotic drug quetiapine is widely used, and increasingly prescribed off-label. Furthermore, quetiapine use has been linked to increased mortality rates, most likely due to a range of cardiovascular and metabolic adverse effects. This makes quetiapine a relevant substance in forensic toxicology casework. Quetiapine is believed to undergo significant post mortem redistribution. Herein, we present tissue distribution and concentration levels of quetiapine in post mortem whole blood, brain tissue, skeletal muscle, and liver tissue in a series of 14 quetiapine-implicated forensic autopsy cases along with the quetiapine concentrations determined in femoral whole blood in conjunction with the autopsies. Quantification was performed using liquid-liquid extraction and a validated UPLC-MSMS method. Six deaths were attributed to intoxication with quetiapine in combination with other substances; there were no quetiapine monointoxications. In eight cases, death was attributed to other causes than drug toxicity. In a majority of the cases, liver tissue contained the highest quetiapine concentrations, while whole blood levels were the lowest. Central (heart) blood concentrations were generally higher than peripheral (femoral) blood levels. Quetiapine concentrations in femoral blood correlated most strongly with concentrations in skeletal muscle. Otherwise, there was no consistent hierarchy of quetiapine tissue concentrations, and the tissue distribution showed no clear relationship with the length of the post mortem interval.

1. Introduction

Quetiapine is an atypical antipsychotic drug used in the treatment of schizophrenia and bipolar disorder [1]. Due to its property of producing sedation at low doses, quetiapine is frequently used off-label as a substitute for conventional sedative drugs. Thus, the number of quetiapine users per capita in Norway has increased exponentially over the past decade concomitant with a substantial decrease in prescribed doses [2]. A similar trend has been reported in a number of other Western countries [3–6]. This development is a cause for concern, as in addition to sedation, quetiapine may induce a range of adverse effects, including weight gain, hyperlipidemia and potentially fatal cardiac arrhythmias [7–10]. Indeed, data suggest a higher mortality risk in quetiapine users compared to users of other atypical antipsychotic drugs [11].

Psychopharmaceuticals tend to be highly protein-bound and possess large apparent volumes of distribution [12], and quetiapine is no exception. Quetiapine is therefore likely to undergo significant post mortem redistribution, an assumption supported by previous studies of post mortem quetiapine concentrations [13–17]. The extent of this phenomenon has not been well characterized, and this may hamper the interpretation of post mortem quetiapine levels.

Herein, we present concentrations levels and distribution of quetiapine in whole blood, brain, muscle and liver tissue from a series of 14 quetiapine-positive forensic autopsy cases.

2. Materials and methods

2.1. Forensic autopsies

The Department of Pathology at St. Olav University Hospital routinely conducts forensic autopsies upon request from the local police. Norwegian law obliges the police to request forensic autopsies in cases of suspected homicide or unidentified corpse. The law also advises the police to request forensic autopsies in cases of sudden, unexpected death, i.e. suicides, accidents, intoxications, deaths occurring in prisons, etc. [18]. Nationally, about 10 % of deaths are subjected to autopsy, and forensic autopsies constitute 40 % of these [19]. St. Olav University hospital serves four counties in Central Norway (population approx. 750.000) and conducts approximately 300 forensic autopsies annually.

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All forensic autopsies conducted between September 2006 and August 2014 at St. Olav University Hospital in which toxicological analysis was positive for quetiapine were selected for this study. Of the 20 cases that met these criteria, there were 14 from which biological material was available for further analysis.

Specimens of central (heart) blood and peripheral (femoral vein) whole blood, brain tissue (right frontal lobe) and liver tissue (right and left liver lobes) were acquired where available. Samples from all relevant matrices were available in nine cases. In eight cases, tissue from both the left and right liver lobes had been sampled. Peripheral blood samples were missing in two cases, and the reanalyzed peripheral blood concentration of quetiapine was below the lower limit of quantification (LLOQ) in one case which originally yielded a positive screening result for quetiapine in splenic tissue. In total, 11 samples of central blood, peripheral blood and muscle tissue, 12 samples of brain tissue, 13 samples of liver tissue (right lobe) and 8 samples of liver tissue (left lobe) were obtained.

All samples were collected in accordance with established quality procedures aimed at minimizing the risk of contamination and other systematic and random errors. This included specific instructions with regard to clean instruments, uniform and rigorous procedures for sampling, registration and labelling, as well as transport and storage of specimens at −80 °C.

2.2. Toxicological analysis

In the initial toxicological analysis performed in conjunction with the forensic autopsies, blood specimens collected between September 2006 and December 2013 were subjected to specific analyses for alcohols (ethanol, methanol, isopropanol, acetone) using a headspace GC–MS method, and specific analyses for benzodiazepines (diazepam, desmethyldiazepam, oxazepam, nitrazepam, 7-aminonitrazepam, flunitrazepam, desmethylflunitrazepam, 7-aminoflunitrazepam, clonazepam, 7-aminoclonazepam, alprazolam, midazolam), opioids (oxycodone, codeine, ethylmorphine, morphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G)) and amphetamines (amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA)) using LC–MS methods. In addition, blood specimens were screened against comprehensive drug libraries (National Institute of Standards and Technology Mass Spectral Library, Forensic Toxicology Retention Time Locking Database/Library and Pfleger/Maurer/Weber Drugs and Pesticides Library for Toxicology) with a GC–MS method. For samples collected after December 2013 blood specimens were subjected to specific analyses for alcohols (ethanol, methanol, isopropanol, acetone) using the same methodology. In addition, blood specimens were screened against a database of ~10,000 known substances using an LC–QTOF–MS method, and the positive findings were confirmed with specific LC–MS/LC-MSMS methods. In all cases, urine specimens (when available) were also screened for drugs of abuse using LC–MS/LC-MSMS methods. Positive screening results or suspicion of substance intake based on information from the police or the medical history of the deceased instigated analyses with specific LC–MS/LC-MSMS or GC–MS methods.

All quantitative analyses of quetiapine were performed with a validated ultra-high performance liquid chromatography-tandem mass spectrometry method for simultaneous determination of quetiapine, clozapine and mirtazapine concentrations in whole blood, brain, muscle and liver tissue. This method is described in detail elsewhere [20]. The validated analytical range for quetiapine was 4–1500 ng/mL. Sample pretreatment for brain, muscle and liver tissue included homogenization of 0.5 g of matrix with 1 mL buffer so that the actual lower limit of quantification was 12 ng/mL for these matrices. Samples containing quetiapine above the validated concentration range were diluted during homogenization until the quetiapine concentration in the homogenate was within the validated range.

Our laboratory participates in international interlaboratory comparisons and proficiency testing programs, and is accredited by the Norwegian body for accreditation of laboratories, sampling organizations, etc. (Norwegian Accreditation, Lillestrøm, Norway; www.akkreditert.noen).

2.3. Ethics

This study is part of an ongoing project in which post mortem toxicological specimens are coupled to information from forensic autopsies performed in Central Norway in a regional research biobank [21]. The project has been approved by the Regional Committee of Research Ethics (2015/212/REK midt) and the Director General of Public Prosecution.

3. Results

Brief demographic data, quetiapine femoral blood concentrations included in the coroners' report, additional toxicological findings, post mortem interval (PMI) and the pathologist's conclusion as to the cause of death are shown in Table 1. Among the 14 forensic autopsy cases in which quetiapine was detected, 6 deaths were classified as mixed intoxications due to the presence of quetiapine and other potentially toxic substances, and 8 deaths were attributed to non-toxicological causes (other causes of death), e.g. motor vehicle accident, suicide and homicide. In one case (case #10), a subtherapeutic concentration of olanzapine was the only additional finding in blood, along with a potentially lethal concentration of quetiapine.

In Table 2, the concentrations of quetiapine in each matrix from each case are presented along with the peripheral blood concentration provided in the coroner's report and the time between autopsy and reanalysis. The femoral blood concentration appeared to have decreased modestly and by 8–31 % for most cases, while cases #12, #11, #9 and #1 showed apparent concentration increases of 8%, 33 %, 99 % and 208 %, respectively (Table 2).

The tissue distribution of quetiapine is shown in Table 3 as individual ratios of the quetiapine concentrations found in central whole blood, brain, muscle and liver tissue and relative to the quetiapine concentrations in peripheral whole blood. The ratios of quetiapine concentrations in brain and muscle tissue relative to peripheral blood were in the 1.6–11 and 1.0–17 ranges, respectively. Quetiapine concentrations in muscle showed a stronger linear correlation with peripheral blood concentrations ($r = 0.93$) than the concentration in brain tissue ($r = 0.83$). The mean ratio between quetiapine concentrations in liver tissue and femoral blood was 17 (range 1.7–58, $n = 10$) and 13 (range 2.8–28, $n = 7$) for the right and left liver lobes, respectively. Quetiapine concentrations in liver tissue (right lobe) showed the strongest linear correlation with quetiapine concentrations in peripheral blood ($r = 0.97$).

4. Discussion

According to a review from the German Center for Drug information and Pharmacy Practice, the reference range for therapeutic concentrations of quetiapine in plasma is 0.1–0.5 mg/L, based on steady-state samples from patients subjected to therapeutic drug monitoring. Concentration levels in plasma above 1.0 mg/l are considered toxic, but this threshold has determined simply by doubling the upper limit of the therapeutic range. The lowest toxic quetiapine concentration in plasma based on case reports is 1.8 mg/L, while coma and fatalities have been reported at

Table 1
Toxicological findings and case details provided in the coroner's report.

Case #	Sex	Age	Quetiapine concentration in femoral blood (mg/L)	Other toxicological findings (mg/L except where noted otherwise)	Post mortem interval	Cause of death
1	F	29	7.7	Ethanol 6.6 mg/100 mL (vitreous fluid), amphetamine 0.31, valproate 1.8, fluoxetine 2.5, norfluoxetine 2.5, levomepromazine 0.014, ibuprofen (+)	Uncertain	Mixed intoxication
2	F	51	0.24	Morphine 0.057, codeine 1.2, morphine-3-glucuronide 0.97, morphine-6-glucuronide 0.35, oxazepam 0.01, diazepam 0.06, desmethyldiazepam 0.15, paracetamol 89, venlafaxine 0.39, o-desmethylvenlafaxine 1.2, mirtazapine 0.32, pregabalin 0.021, zopiclone 1.9	Hours	Mixed intoxication
3	F	55	0.012	Ethanol 13 mg/100 mL, diazepam 0.010, desmethyldiazepam 0.017, 7-aminoclonazepam 0.040, paracetamol 10, tramadol 0.40, mirtazapine 0.082	Hours	Other cause of death
4	M	26	18	Ethanol 8.8 mg/100 mL	2 days	Mixed intoxication
5	M	36	10	Methamphetamine 0.63, amphetamine 0.026, ethanol 16 mg/100 mL, lamotrigine 18	Uncertain	Mixed intoxication
6	M	59	0.049	Oxazepam 0.25, mianserin 0.16, desmethylmianserin 0.015, tramadol 0.34, zopiclone 0.028	Uncertain	Other cause of death
7	M	60	0.016	Oxazepam 0.012, paracetamol 48, metoprolol 0.27	Hours	Other cause of death
8	M	77	0.032	Morphine 0.043, morphine-3-glucuronide 0.24, morphine-6-glucuronide 0.06, midazolam 0.098, mirtazapine 0.19	Hours	Other cause of death
9	M	64	0.012		Hours	Other cause of death
10	M	39	7.3	Olanzapine 0.0040	2 days	Mixed intoxication
11	M	20	0.18	Olanzapine 2.2	Hours	Mixed intoxication
12	M	57	0.15	Citalopram 0.32, alimemazine 0.095, hydroxyzine 0.45, metformin (+), cetirizine (+)	Uncertain	Other cause of death
13	F	48	0.088*	Ethanol 2.3 mg/100 mL (vitreous), amphetamine 0.091, methamphetamine 1.2, diazepam 0.043 (spleen), desmethyldiazepam 0.009 (spleen)	5 days	Other cause of death
14	M	32	**	Ethanol 11 mg/100 mL, paracetamol (+)	Hours	Other cause of death

* Concentration measured in spleen. **GC–MS screen-positive.

Table 2
Concentrations of quetiapine in central and femoral blood, brain, muscle and liver tissue, femoral blood concentrations of quetiapine measured in conjunction with the autopsy and the duration of storage at −80 °C before reanalysis.

Case #	Quetiapine concentrations (mg/L)						Femoral blood concentration change from autopsy report findings (%)	Time between autopsy and reanalysis (years)
	Central blood	Femoral blood	Brain	Muscle	Liver (right)	Liver (left)		
1	93.4	23.7	47.4	35.0	149	108	+208	10
2	.056	–	0.30	0.623	1.54	2.19	–	10
3	0.010	0.011	0.018	<LOQ	0.179	0.203	−8	9
4	94.6	12.4	34.3	34.4	84.5	118	−31	8
5	11.8	7.55	12.0	7.76	12.5	21.2	−24	8
6	0.035	0.040	0.074	0.049	0.703	0.341	−18	6
7	0.019	0.014	0.037	0.022	0.242	0.317	−13	5
8	0.014	0.026	0.047	0.031	0.807	0.725	−19	5
9	–	0.016	0.169	0.02	0.077	–	+33	5
10	15.8	5.37	47.4	–	–	–	−26	5
11	5.61	0.358	1.07	0.494	2.82	–	+99	5
12	0.458	0.157	0.931	2.66	9.08	–	+8	5
13	–	–	<LOQ	<LOQ	0.013	–	–	4
14	<LOQ	<LOQ	<LOQ	<LOQ	0.056	–	–	4

concentrations of 1.9 mg/l and above [22]. Langman et al. [23] and Skov et al. [15] presented quetiapine monointoxications with concentration levels of 7.2 mg/l and 9.0 mg/L, respectively, in femoral blood. Our study included 10 cases with femoral blood concentrations within or below the therapeutic range determined for plasma, and 4 cases with potentially lethal femoral blood concentrations.

Overall, the concentration levels of quetiapine (Table 2) and the ratios of quetiapine concentrations between different matrices (Table 3) showed large inter-case variability, with no clearly discernable distribution patterns. Since the analyses were conducted with a rigorously validated method in a nationally accredited laboratory with strict quality control, it is unlikely that this variability can be explained by analytical error. The concentration levels of quetiapine in whole blood, brain and muscle tissue were predominantly within the same order of magnitude for each case, which suggests that the rates of *in vivo* accumulation and post mortem redistribution of quetiapine in these matrices are similar. Despite considerable variability, there appeared to be some trends in the post mortem tissue distribution.

Firstly, the ratios of quetiapine concentrations in central blood relative to peripheral blood had a mean value of >1, which may imply that quetiapine is subject to post-mortem redistribution. Elevated central-to-peripheral blood concentration ratios are usually interpreted as the result of diffusion from tissues in which a drug has accumulated before death [24]. The ratio was <1 for

Table 3
Ratios of reanalyzed quetiapine concentrations in central blood (CB), brain tissue (BR), muscle tissue(MU), liver tissue (right lobe (LR)) and liver tissue (left lobe (LL)) to the reanalyzed femoral blood concentration (PB) for each case, along with the correlation coefficient (r) for the compared matrices.

Case #	CB/PB	BR/PB	MU/PB	LR/PB	LL/PB
1	3.9	2.0	1.5	6.3	4.6
2	–	–	–	–	–
3	0.91	1.6	–	16	18
4	7.6	2.8	2.8	6.8	9.5
5	1.6	1.6	1.0	1.7	2.8
6	0.88	1.9	1.2	18	8.5
7	1.4	2.6	1.6	17	23
8	0.54	1.8	1.2	31	28
9	–	11	1.3	4.8	–
10	2.9	8.8	–	–	–
11	16	3.0	1.4	7.9	–
12	2.9	5.9	17	58	–
13	–	–	–	–	–
14	–	–	–	–	–
r	0.91	0.83	0.93	0.96	

three of the 10 sample pairs. This is consistent with the results from a case series by Mikkelsen et al. [13] which showed a median central-to-peripheral concentration ratio of 1.2 (range 0.34–14, n = 46), and a case series by Parker et al. [25] which found higher mean concentrations of quetiapine in central blood than in peripheral blood, with only 5 of 17 sample pairs showing a central-to-peripheral concentration ratio <1. Another study of 20 cases by Flammia et al. [17] included only one case where both central and peripheral blood concentration of quetiapine were reported, and the central-to-peripheral concentration ratio in that case was 2.1. In our material, the mean central-to-peripheral blood concentration ratio was 3.8 (range 0.54–16), which corroborates the large inter-individual variation reported in existing literature.

Secondly, liver tissue contained the highest quetiapine concentration in 12 of the 13 cases where material/data were available. Elevation of the liver-to-peripheral blood concentration ratio has been proposed as a marker of a drug's propensity for post mortem redistribution [26]. Quetiapine accumulation in liver tissue has previously been reported in forensic toxicological casework [17,27,28], and a study by McIntyre with 65 quetiapine-positive cases found liver-to-peripheral blood ratios averaging 18 [29], which is consistent with our results. Post mortem redistribution from the biliary system may also contribute to the apparent accumulation in hepatic tissue; quetiapine accumulation in bile has been proposed to occur due to enterohepatic circulation of the drug by Hopenwasser et al. [28]. It has previously been reported in that the left lobe of the liver could be more susceptible than the right lobe to post mortem redistribution of zopiclone [30], isobutanol and toluene [31] due to its anatomical proximity to the ventricle. This presupposes the presence of a drug in the gastric contents during the post mortem interval, which could be expected in cases of massive overdoses administered *per os*. In the 7 paired samples of liver tissue from the right and left liver lobes, there was no apparent trend of greater quetiapine accumulation in either lobe. In our material, higher concentration levels of quetiapine in the left lobe of the liver compared to the right lobe did not appear to be associated with overall quetiapine concentration levels indicative of large overdoses.

Since the data are not normally distributed it seems fallacious to place much emphasis on the Pearson's r values in Table 3, which describe how strongly the quetiapine concentration levels in peripheral blood correlate to the concentration levels in central blood, brain, muscle and liver tissue. It is interesting, however, that the linear correlation between quetiapine concentrations in peripheral blood and brain tissue is markedly weaker than the blood-muscle and blood-liver correlations. The brain is thought to be less vulnerable to redistribution phenomena due to its anatomical sequestration, delayed onset of putrefaction and lower rate of post mortem metabolism [32]. Thus, the comparatively weak linear correlation between quetiapine concentrations in brain tissue and peripheral blood may indicate that these two matrices approach a concentration equilibrium at a slower rate than blood and liver tissue or blood and brain tissue. Vice versa, diffusion from striated muscle, connective and adipose tissue is proposed to be a key source of post mortem drug redistribution to peripheral blood [33], and one would expect the drug concentrations in these matrices to approach one another as the PMI increases. However, our material did not show any such correlation between the PMI and the muscle-to-peripheral blood concentration ratio. Our results indicate that muscle may be a suitable alternative matrix to femoral blood in cases where the latter is not available. The large discrepancy between femoral blood and muscle quetiapine concentrations in case #12 may, however, raise concern about the possible occurrence of similar outliers.

The apparent 8–208 % increases in femoral blood concentrations of quetiapine since autopsy in cases #1, #6, #9 and #12 (Table 2) are remarkable, since one would expect a concentration decrease proportional to the storage time, as is evident in the remaining cases. Presuming that these anomalies have not been caused by analytical or reporting error, concentration differences between duplicate femoral blood samples may be culpable. When comparing drug concentrations in different matrices, variations in this order of magnitude have been documented and ascribed to post mortem redistribution by others [34,35]. In this study, however, a corresponding variation was observed between separate samples of the same matrix which have been collected simultaneously and analyzed years apart. This phenomenon is less commonly studied and acknowledged, but has previously been described in individual cases exposed to opioids [36].

Factors related to the cause and time of death are likely to affect the concentration levels of quetiapine in the various matrices. In cases of self-intoxication by ingestion of large amounts of pills, drug diffusion from reservoirs in the gastrointestinal tract to adjacent organs and tissues may occur post mortem [33]. Still, we did not observe any disproportionate elevation of liver-to-peripheral blood concentration ratios in cases where the manner of death could fit this scenario. According to Saar et al. [16], Brockbals et al. [37] and Gerostamoulos et al. [38] the length of the PMI correlates positively with the extent of drug diffusion post mortem, but no such correlation was evident in our data. In addition to putrefactive and autolytic processes, elevated ambient temperature during the PMI could possibly accelerate the rate of drug diffusion, and such phenomena may have obscured an eventual correlation between the length of the PMI and the extent of post mortem redistribution of quetiapine. Information about the progression of rigor mortis and putrefaction, the time of year, whether the deceased was found outdoors or indoors, attempts of resuscitation, body movement after death and additional pertinent information was generally available in the autopsy reports [33]. Although resuscitation attempts were accounted for in a number of the autopsy reports, inferences with regard to this should be made with caution in such a small and heterogeneous material.

5. Conclusion

To our knowledge, this is the first published account of simultaneous post mortem concentrations of quetiapine in whole blood, brain, muscle, and liver tissue. Our data showed large variability and inconsistent patterns in the quetiapine distribution that are unlikely to be explained by analytical error. Our findings are indicative of post mortem redistribution and hepatic

accumulation of quetiapine, phenomena which have been described in previous studies. Quetiapine concentrations in skeletal muscle correlated well with concentrations in femoral blood. From this we can infer that skeletal muscle may be a preferred matrix for analysis in the absence of blood. The large variability of the ratios between quetiapine concentration levels in different matrices may be related to (re)distribution phenomena occurring either *in vivo*, post mortem or both.

CRediT authorship contribution statement

Håvard Breivik: Investigation, Data curation, Writing - original draft. **Joachim Frost:** Conceptualization, Writing - review & editing, Supervision. **Trine N. Løkken:** Validation, Supervision. **Lars Slørdal:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

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