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Postmortem Distribution and Redistribution of Nitrobenzodiazepines in Man

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ABSTRACT: The distribution of the nitrobenzodiazepines, flunitrazepam, clonazepam and nitrazepam, and their respective 7-amino metabolites were examined in blood, serum, vitreous humor, liver, bile and urine of decedents taking these drugs. Peripheral blood, serum and liver concentrations were not significantly different to each other. However, vitreous concentrations were one-third of blood, while bile concentrations were 5–12 fold higher. Blood, serum and vitreous contained predominantly the 7-amino metabolite, liver contained only the metabolite, while bile contained significant concentrations of both the parent drug and the 7-amino metabolite. Urine contained only small concentrations of parent drug, however, as expected a number of metabolites were detected. Redistribution studies compared the drug concentrations of femoral blood, taken at body admission to the mortuary, with femoral blood taken at autopsy approximately 39 h later in 48 cases. The concentrations of 7-amino metabolites were not significantly different, however the concentrations of parent nitrobenzodiazepines were significantly higher in the admission specimens. In 6 cases in which subclavian blood was taken, the concentrations were not significantly different to the concentrations in admission blood. Similar findings were observed when femoral and subclavian blood concentrations were compared in 6 cases. There was also no apparent difference in total blood concentrations of nitrobenzodiazepines when blood concentrations taken in hospital shortly prior to death were compared to postmortem blood. Postmortem diffusion into peripheral blood is therefore not a confounding factor in the interpretation of nitrobenzodiazepine concentrations.

KEYWORDS: forensic science, forensic toxicology, benzodiazepines, distribution, redistribution, human toxicology

The benzodiazepine family of drugs are the leading group of prescription drugs for the management of anxiety throughout the world, and are frequently detected in cases of sudden and unexpected death (1). The group of benzodiazepines containing a nitro group on the 7-position of the A-ring are known generically as nitrobenzodiazepines. This group has many features in common including their metabolic profile and include the drugs nitrazepam, clonazepam and flunitrazepam. They are prescribed widely in Australia for either sleep disorders, anxiety or epilepsy. They are most commonly administered orally and are rapidly and totally absorbed from the gastrointestinal tract (2–4).

Bacteria are known to metabolize these drugs postmortem to their respective 7-amino metabolite (5). Consequently, both the parent drug and this metabolite tend to be measured in postmortem cases involving these drugs. In life, the concentrations of the 7-amino metabolites in blood often parallel the concentrations of parent drug (3,6). There is little data concerning the distribution of these drugs in various tissues and whether the measurement in various tissues offers any advantages over blood alone. Unfortunately, there is also little known about the effect of the postmortem interval on the concentration of these drugs. Data tends to be restricted to isolated case reports (1). The interpretation of toxicological results is therefore limited by this lack of scientific knowledge.

It was the aim of this study to investigate the distribution of nitrobenzodiazepines in various postmortem specimens and assess if the measurement of the concentrations in other specimens can assist in the interpretation of toxicological data. The effect of the postmortem interval on the concentration of these drugs in peripheral blood was also assessed.

Materials and Methods

Reagents and Glassware

All drugs and metabolites were obtained from the curator of standards at the Australian Government Analytical Laboratories. Sodium carbonate (Na_2CO_3) and potassium dihydrogen orthophosphate (KH_2PO_4) were of analytical reagent grade (Ajax Chemicals, Australia). Acetonitrile (Mallinckrodt, Australia), butyl chloride (Fisons, UK) were of HPLC grade.

Extraction tubes were silanized by immersing the glassware in a 5% solution of Surfasil (Pierce Chemical Company, U.S.A) in toluene for 1 h, followed by rinsing in methanol. These were then dried before use.

Standards and Controls

Stock drug solutions were prepared in methanol at a concentration of 1 mg/mL. Working standard solutions were prepared by adding dilutions of the stock solutions with methanol to the relevant blank tissue to give final concentrations ranging from 0.01–0.60 mg/L.

Blood specimens prepared with known concentrations of nitrobenzodiazepines and metabolites were assayed in duplicate in each experiment to provide a measure of quality assurance. These were prepared in-house by the QC officer. Target concentrations were 0.10 and 0.40 mg/L with an acceptance range of $\pm 20\%$. Negative controls were also run with each assay.

Collection of Specimens

Femoral or sub-clavian blood, vitreous humor, liver, bile and urine were all acquired at the time of autopsy and stored at $-20°C$

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until assay. Blood tubes contained 1% sodium fluoride/potassium oxalate as preservative. Plasma was separated from femoral blood, by centrifugation, and stored at −20°C until assay.

Admission blood was removed from the femoral region when the body arrived at the mortuary and was stored at −20°C until assay. The admission tubes also contained 1% sodium fluoride/potassium oxalate as preservative. In some cases blood was taken from both the subclavian and femoral regions. In some cases specimens (blood or plasma) taken before death in hospital were also obtained.

Identification and Quantification of Benzodiazepines

The nitrobenzodiazepines flunitrazepam, clonazepam and nitrazepam and the corresponding 7-amino-metabolites were identified in blood by capillary gas chromatography using nitrogen-phosphorous detection, and occasionally mass spectrometry (7). These drugs were quantified in the tissues by HPLC, as described previously (8).

Statistics

Mean ± standard deviation are shown in the text. Statistical evaluation of these data was conducted using the In Stat 2.01 program run on an Apple Macintosh personal computer. Statistical analysis for comparing autopsy blood to other tissues was conducted using ANOVA and the Wilcoxon test. Other tests used are described in the text. Statistical significance was assumed at alpha ≤ 0.05.

Results

Blood

Nitrobenzodiazepines were detected in 71 cases (Table 1). 7-Amino flunitrazepam was detected in 30 of the cases at a mean concentration of 0.06 mg/L, 7-amino clonazepam was detected in 28 cases at a mean concentration of 0.40 mg/L and 7-amino nitrazepam was detected in 23 cases at a mean concentration of 0.32 mg/L. A combination of two 7-amino metabolites were detected in the same blood specimen on 10 occasions. Parent drug was not detected without the presence of the respective 7-amino metabolite in any specimen.

The parent nitrobenzodiazepines nitrazepam and clonazepam were detected in 12 and 14 specimens, respectively. They were both detected at a mean concentration of 0.07 mg/L, and were usually associated with the ingestion of high concentrations of nitrobenzodiazepines. Flunitrazepam was not detected in any specimen.

Plasma

Nitrobenzodiazepines were detected in 25 of the plasma specimens (Table 1). The 7-amino metabolites were detected in all specimens in concentrations and ranges similar to corresponding blood specimens ($p > 0.05$).

In 5 cases a combination of two 7-amino metabolites were detected. Nitrazepam was detected in 2 cases. The mean concentration of nitrazepam found was approximately twice that found in the corresponding autopsy blood cases. Clonazepam was detected in 3 specimens and had a mean concentration of approximately 2.4 fold higher than the corresponding blood specimens. In no case was the parent drug detected without its respective 7-amino metabolite.

TABLE 1—*Concentrations of 7-amino nitrazepam (7AN), nitrazepam (N), 7-amino clonazepam (7AC), clonazepam (C), 7-amino flunitrazepam (7AF) and flunitrazepam (F) in various toxicological specimens.*

Specimen	*n*	Drug	Mean ± SD (mg/L)	Range (mg/L)
Autopsy Blood (*n* = 71)	23	7AN	0.32 ± 0.48	0.02–2.0
	28	7AC	0.40 ± 0.55	0.01–2.5
	30	7AF	0.06 ± 0.06	0.01–0.23
	12	N	0.07 ± 0.05	0.02–0.16
	14	C	0.07 ± 0.07	0.01–0.24
	ND	F	ND	
Plasma (*n* = 25)	7	7AN	0.37 ± 0.44	0.06–1.2
	10	7AC	0.45 ± 0.64	0.05–2.2
	13	7AF	0.06 ± 0.07	0.01–0.29
	2	N	0.10 ± 0.01	0.09–0.10
	3	C	0.17 ± 0.19	0.02–0.39
	ND	F	ND	
Vitreous humor (*n* = 52)	11	7AN	0.11 ± 0.15*	0.01–0.50
	21	7AC	0.13 ± 0.17*	0.01–0.69
	21	7AF	0.02 ± 0.02*	0.01–0.06
	2	N	0.01 ± 0.01	0.01–0.01
	4	C	0.03 ± 0.02	0.02–0.06
	ND	F	ND	
Urine (*n* = 19)	3	7AN	0.32 ± 0.06	0.28–0.39
	7	7AC	1.2 ± 1.7*	0.10–5.0
	10	7AF	0.38 ± 0.51*	0.04–1.6
	1	N	0.05	0.05
	2	C	0.17 ± 0.03	0.15–0.19
	1	F	0.01	0.01
Bile (*n* = 19)	4	7AN	0.88 ± 0.78*	0.17–1.8
	5	7AC	1.7 ± 1.8*	0.14–4.3
	10	7AF	0.88 ± 1.1*	0.06–3.2
	3	N	0.57 ± 0.43*	0.14–1.0
	3	C	4.1 ± 3.8*	0.52–8.7
	4	F	0.71 ± 0.86	0.05–1.9
Liver (*n* = 21)	8	7AN	0.20 ± 0.20*	0.01–0.35
	7	7AC	0.18 ± 0.19*	0.01–0.30
	7	7AF	0.11 ± 0.10*	0.01–0.18
	ND	N	ND	
	ND	C	ND	
	ND	F	ND	

NOTE—That more than one benzodiazepines were detected in some cases, hence individual totals do not add up to the total number of cases.
*$p < 0.05$ compared to matched blood concentrations.
ND-Not detected.
†-Matched to corresponding blood specimens.

Vitreous Humor

Vitreous humor, contained the least amount of drug of all tissues. The parent drug concentration and 7-amino metabolite concentrations were, on average, one-third of autopsy blood ($p < 0.05$) (Table 1). In 15% of cases, where the 7-amino metabolites were detected in blood, 7-amino metabolites were not detected in the vitreous. In only 10% of cases were the parent nitrobenzodiazepines detected in vitreous.

In 11 cases parent nitrobenzodiazepines were detected in the blood specimens and not in the corresponding vitreous specimen. In 7 of these cases death resulted from an acute ingestion of high concentrations of nitrobenzodiazepines, often in combination with other drugs. The mode of death in the remaining 4 cases were accidents and were not related to acute drug toxicity. In 9 cases neither parent nitrobenzodiazepines nor metabolite were detected in vitreous. The modes of death in 3 of these cases were from acute ingestion of high doses of nitrobenzodiazepines. The deaths in the remaining two thirds of cases were not apparently related to acute drug toxicity.

Bile

In bile the concentration of both the nitrobenzodiazepines and the 7-amino metabolites were similar to each other (Table 1). The mean concentration of the parent nitrobenzodiazepines was statistically different from that obtained in autopsy blood ($p < 0.05$) as was the 7-amino metabolites ($p < 0.05$). On average, the sum of the parent and 7-amino metabolites were 5 times the sum for blood for nitrazepam, 12 times for clonazepam and flunitrazepam. The 7-amino metabolites were detected in 95% of bile specimens while parent drug was detected in 55% of specimens.

Liver

In liver only the 7-amino metabolite was detected (Table 1). The concentrations of 7-amino metabolites were not significantly different from the corresponding blood concentrations ($p > 0.05$).

In one case a combination of two 7-amino metabolites were detected. In five specimens no drug was detected, although they were detected in the corresponding blood specimen. The deaths all involved low concentrations of nitrobenzodiazepines (i.e., less than 0.05 mg/L) and were not related to any particular mode of death.

Urine

Urine contained high concentrations of 7-amino metabolites with little parent drug. Urine was the only tissue examined which contained detectable metabolites other than 7-amino metabolites. In cases containing flunitrazepam, 67% of specimens contained 7-amino-desmethyl flunitrazepam at concentrations similar to those of the 7-amino metabolite. Metabolites other than the 7-amino metabolites of nitrazepam and clonazepam were not examined. Urinary 7-amino metabolites were detected in all cases, while parent drug was detected in only 33% of cases. The mean concentration of both the parent drug and 7-amino metabolites in urine were approximately 3.5 fold higher than in autopsy blood.

In two cases, parent drugs were detected in urine but not in the corresponding blood specimens. These were both cases of death resulting from ingestion of high doses of nitrobenzodiazepines.

Correlation of Nitrobenzodiazepine Concentrations

The concentration of nitrobenzodiazepines in various specimens were regressed with the concentrations in corresponding blood specimens using the parametric (Pearson) linear correlation. The two-tailed *P* value was significant for all comparisons (Table 2). The best correlation was found for the metabolites with all coefficients greater than 0.75.

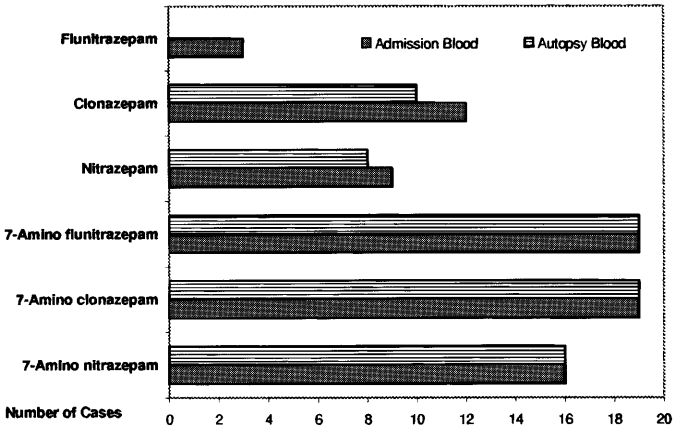

FIG. 1—*Frequency of nitrobenzodiazepine detections in 48 matched autopsy and admission specimens found to contain nitrobenzodiazepines.*

Comparison of Concentrations in Admission and Autopsy Blood Specimens

The time interval between collection of a blood specimen on admission of the body to the mortuary and collection at autopsy was 39 ± 19 h (range 3 to 94 h). The average length of time from death until admission to the mortuary, for 35% of cases, was 8 h ± 5 h ranging from 3 h to 20 h. In the remaining cases the time of death was uncertain since the deceased persons had died alone. Most of these cases were suicide deaths, and none were grossly decomposed.

For 48 paired cases for all drugs the concentration of the 7-amino metabolites in admission blood was similar ($p > 0.05$) to autopsy blood (Fig. 1).

The concentration of the parent nitrobenzodiazepines in admission blood was, however, double that found in femoral blood at autopsy ($p < 0.05$) (Table 3). This was also reflected in the proportion of cases in which parent drug was detected, 44% in admission blood compared to 32% in autopsy blood.

In 6 cases, blood collected at autopsy was from the subclavian region, and not from the femoral region. Of the 6 subclavian specimens collected at autopsy, 5 contained nitrazepam and/or 7-amino nitrazepam. The other specimen contained both 7-amino clonazepam and 7-amino flunitrazepam, with no respective parent drug detected (Fig. 2).

Nitrazepam and 7-amino nitrazepam concentrations, detected in admission blood (femoral blood), were compared statistically to concentrations detected in corresponding subclavian blood specimens collected at autopsy from the same cadaver. There was no significant difference ($p > 0.05$) between the nitrobenzodiazepine concentrations found in femoral blood and subclavian blood, for either the parent nitrobenzodiazepines or the 7-amino metabolites.

TABLE 2—*Nitrobenzodiazepine correlations (as r-value) between blood and various postmortem specimens.*

Specimen	Parent Nitrobenzodiazepines	7-Amino Metabolites
Plasma ($n = 25$)	1.000	0.979
Vitreous humor ($n = 52$)	0.626	0.764
Urine ($n = 19$)	0.571	0.834
Bile ($n = 19$)	0.695	0.829
Liver ($n = 21$)	ND	0.809

TABLE 3—*Concentrations of nitrobenzodiazepines in autopsy and admission blood in cases, either found, or not found to contain, nitrobenzodiazepines in stomach contents.*

Nitrobenzodiazepines Present in Stomach	Admission Blood	Autopsy Blood
All Cases ($n = 22$)	0.29 ± 0.29	0.27 ± 0.26
Drug in Stomach ($n = 13$)	0.35 ± 0.32	0.32 ± 0.30
No drug in stomach ($n = 9$)	0.22 ± 0.25	0.19 ± 0.21

Values expressed as the mean (mg/L) ± SD.

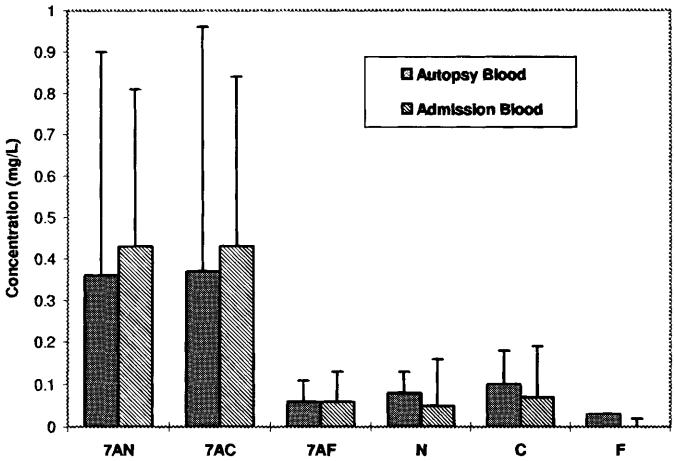

FIG. 2—*Concentrations (mg/L) of nitrobenzodiazepines detected in 6 matched postmortem subclavian and femoral blood. 7AN = 7-aminonitrazepam, 7AC = 7-aminoclonazepam, 7AF = 7-aminoflunitrazepam, N = nitrazepam, C = clonazepam and F = flunitrazepam.*

In cases found to contain nitrobenzodiazepine residues in the stomach contents, the concentrations of drug were compared between the time of body admission and the time of autopsy. When compared to cases not found to contain nitrobenzodiazepines in the stomach contents, there was no significant difference observed ($p > 0.05$), (Table 3).

Comparison of Subclavian and Femoral Blood Concentrations

In 6 cases, blood was collected at autopsy from both subclavian and femoral regions. In 5 cases nitrazepam and/or 7-amino nitrazepam were detected. The other case contained both 7-amino clonazepam (0.02 mg/L in both femoral and subclavian specimens) and 7-amino flunitrazepam (0.03 mg/L in both subclavian and femoral specimens). Due to the low sample size, only the concentrations of 7-amino nitrazepam were compared statistically between the blood for the two sites. The concentrations of 7-amino nitrazepam in femoral and subclavian specimens were 0.75 ± 0.3 mg/L and 0.90 ± 0.46 mg/L, respectively ($p > 0.05$, student's t-test).

Comparison of Antemortem and Postmortem Concentrations

Six antemortem specimens were found to contain nitrobenzodiazepines and were included separately in this study.

The concentration of nitrobenzodiazepines detected in the antemortem blood specimens were compared to the concentrations detected in the corresponding postmortem blood. Table 4 describes the concentrations of the parent nitrobenzodiazepines and 7-amino metabolites in the antemortem specimens and postmortem specimens, collected at various times relative to the time of death.

In cases 1, 3, and 5, the concentration of the analytes in the final antemortem specimen were similar to those detected in the admission blood (taken up to 10 h later) and autopsy blood specimens (taken up to 158 h later, $p > 0.05$). In case 4, the concentration of metabolite was disproportionately higher in postmortem specimens than in any of the antemortem specimens. This patient died approximately 7 h after the final antemortem specimen was collected. Cases 2 and 6 did not have admission blood collected.

In cases 3 and 4, parent nitrobenzodiazepines were detected in the last antemortem specimen collected prior to death, however only case 3 contained detectable parent nitrobenzodiazepines in postmortem specimens.

Discussion

Femoral blood, the most commonly analyzed specimen by our laboratory for quantification of nitrobenzodiazepines was used as a reference specimen in order to relate the concentration found in other tissues. Femoral vein blood is considered to be the most accurate representation of drug concentration at the time of death (9).

The range of nitrobenzodiazepine and 7-amino metabolite concentrations detected in the autopsy blood of the paired cases was very large, reflecting both therapeutic and toxic concentrations. Except for bile all other tissues contained relatively low concentrations of the parent benzodiazepine, or none at all (liver). This lack of parent drug may be a result of postmortem bioconversion to its respective 7-amino metabolite (5). Hence laboratories not able to detect the 7-amino derivatives of nitrobenzodiazepines are not likely to detect cases of nitrobenzodiazepine usage, even in toxic concentrations.

The concentration of nitrobenzodiazepines and 7-amino metabolites in postmortem plasma were found to be statistically no different from autopsy blood. This similarity was reinforced by the strong positive correlation for the two tissues. In liver, the concentrations of nitrobenzodiazepines species were based exclusively on the 7-amino metabolite. The concentrations were also not significantly different from blood.

In contrast, the concentrations in vitreous humor were lower, on average by one-third. The lower concentrations in vitreous humor will reduce the value of this tissue in cases of advanced putrefaction and decomposition, when vitreous may be less affected than blood. There was however, a reasonable positive correlation with blood results, suggesting this tissue may still be useful.

In bile both the parent drug and 7-amino metabolite were generally present in significant concentrations. The sum total of the two species were ~5–12 fold higher in bile than for blood. The bile results suggest that nitrobenzodiazepines may be present in bile when not present in blood and liver. This would therefore be similar to morphine. Agarwal and Lemos (10) also found high concentrations of diazepam and flurazepam in bile.

The reasonable positive correlations found for all tissues with blood would suggest that quantification in more than one tissue would increase the ability to predict more accurately the significance of the postmortem concentrations of nitrobenzodiazepines over quantification in one tissue alone.

Urine is often qualitatively used to determine the presence of benzodiazepines, although it is rarely used for quantification. The presence of relative high concentrations in urine compared to blood therefore confirms this suitability, particularly since the metabolites were the predominant species detected. Urine was the only specimen where metabolites other than the 7-amino metabolites were found. Care must always be exercised if urine is the only specimen used to screen for the presence of a drug overdose, since urine will sometimes not contain drug if death occurs shortly after administration.

There were no apparent differences in the distribution of nitrobenzodiazepines and the corresponding 7-amino metabolite in cases where the concentrations were considered therapeutic and in those where the concentrations were considered higher than therapeutic.

Few studies have assessed if benzodiazepines in general undergo postmortem redistribution. Pulmonary concentrations of flurazepam has been shown to be almost 7-fold higher than concentrations

TABLE 4—*Drug concentrations in matched admission blood, autopsy blood and antemortem blood specimens.*

Case-Drug	Antemortem Specimens	Admission Specimen	Autopsy Specimen
1-Flunitrazepam	0 (0.01) {−26 h}		
	0 (0.01) {−2 h}	0 (0.01) {4 h}	0 (0.02) {56 h}
2-Flunitrazepam	0 (0.02) {−34 h}		
	0 (0.01) {−10 h}	Not collected	0 (0.02) {158 h}
3-Clonazepam	0.03 (0.09) {−35 h}		
	0.04 (0.13) {−24 h}		
	0.04 (0.10) {−11 h}		
	0.04 (0.11) {−5 h}	0.01 (0.15) {33 h}	0 (0.13) {112 h}
4-Nitrazepam	0.31 (0.16) {−31 h}		
	0.26 (0.16) {−14 h}		
	0.13 (0.14) {−7 h}	0 (0.46) {52 h}	0 (0.49) {129 h}
5-Flunitrazepam	0.04 (0.07) {−42 h}		
	0.01 (0.03) {−34 h}		
	0 (0.01) {−10 h}	0 (0.01) {20 h}	0 (0.01) {43 h}
6-Flunitrazepam	0.06 (0.09) {−11 h}		
	0.07 (0.15) {−7 h}	Not collected	0 (0.13) {55 h}

Values expressed as concentration (mg/L), 7-amino metabolites concentrations are shown in parentheses. The time, in hours, is the time either prior to, or post death, and are shown in the curved parentheses.

in subclavian or femoral blood (11). In contrast, diazepam concentrations were only slightly elevated in cardiac blood compared to peripheral blood (12). The similarity in blood concentrations (sum of species detected) taken at body admission to the mortuary and autopsy some 30 h later, and a comparison of subclavian and femoral blood concentrations, would suggest that postmortem redistribution is not a significant factor when blood is taken peripherally. This would also be consistent with their relatively low volumes of distribution which does not favor significant redistribution (13).

In the studies reported here there was, however, a significant loss of parent drug to the 7-amino metabolite. This has previously been interpreted as being due to postmortem metabolism (5).

Similar conclusions were drawn in the smaller number of specimens taken from the subclavian region and in comparisons with antemortem specimens. In cases in which significant residues were still present in the gastric contents there was also no apparent increase in blood concentrations of nitrobenzodiazepines and metabolites. Postmortem diffusion into peripheral blood is, therefore, not a confounding factor in the interpretation of nitrobenzodiazepine concentrations (14).

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