Postmortem redistribution of triazolam, alprazolam, delorazepam (chlordesmethyldiazepam) and zolpidem in a suicide case

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Abstract: Postmortem drug redistribution (PMR) is a well-recognized phenomenon which affect the concentration of drugs inside the various body tissues and organs, possibly determining misled interpretation of postmortem drug concentrations. In contrast, drug levels in peripheral blood are commonly considered to be comparable with ante-mortem concentrations. The difference between central and peripheral blood concentrations is known as the "central to peripheral ratio" (C/P). Drugs with high C/P ratios are associated with potential for PMR. In several forensic cases, PMR should be taken into account for the correct estimation of drug blood levels at the moment of death, especially when multiple psychotropic drugs have been co-ingested.
In the case reported hereby, the PMR of several benzodiazepines including triazolam, alprazolam, and delorazepam (chlordesmethyldiazepam) plus zolpidem was evaluated in a fatal multidrug suicide case. A 38-year-old man was found dead in his apartment. On the scene, many packaging of pharmaceutical drugs were found. During the autopsy, no evidence of natural disease nor trauma was found to account for his death. Heart (central) and femoral (peripheral) blood, urine and vitreous humor were collected and submitted to toxicological analysis.
Delorazepam, triazolam and zolpidem were detected at therapeutic levels in peripheral blood while alprazolam and ethanol were found at toxic levels. The potential synergistic sedative effect of multiple benzodiazepines intake, combined to high ethanol concentration, produced a condition compatible with fatal intoxication. C/P ratio for the tested compounds ranged from 1.22 (alprazolam) to 1.47 (delorazepam) demonstrating moderate PMR for these drugs. This is the first report in which the PMR of delorazepam is discussed.

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Torino, October 2nd, 2015

Dr. Pascal Kintz
Editor
Toxicologie Analytique et Clinique

Dear Editor

I am pleased to submit the reviewed version of the manuscript n. TOXAC-S-15-00010 entitled "Postmortem redistribution of triazolam, alprazolam, delorazepam (chlordesmethyldiazepam) and zolpidem in a suicide case" for publication on Toxicologie Analytique et Clinique.

The manuscript was reviewed following all the Referees' comments and recommendations, consequently the references were updated.
All the revisions in the text and Tables were marked using a yellow highlighting. The answers to the Referees' comments are listed below:

Reviewer #1 comments:

1) *[...], the state of decomposition of the decedent has not been described; the position of the decedent has not been described; when the decedent was last seen has not been described; the ambient temperature has not been described; etc. All these parameters can and often do affect postmortem drug concentrations and without these a paper cannot accurately describe PMR in the year 2015.*

Authors' response: More information and parameters useful to evaluate PMR were added to the text.

2) *[...], the authors only seem to describe the literature that makes their point - for example, only a poor literature review would allow one to think that ethanol does not suffer PMR.*

Authors' response: Other literature data regarding the PMR of ethanol were added and discussed in the text. Consequently, the references were updated.

3) *[...], the total volume of gastric contents were not collected nor they were properly analyzed for drug concentrations.*

Authors' response: The total volume of gastric content was added in the text. Moreover, gastric content was analyzed for drug concentrations, but tested negative.

4) *Even for the specimens that were collected, the authors fail to describe how they were collected (e.g. scooping up blood, squeezing blood out of the heart, ligating the peripheral vessel), how they were preserved and stored and how long were they in storage before analysis.*

Authors' response: All these additional data were added in the text.

5) *On the blood determinations described in this manuscript, the authors appear to have utilized the same technique for screening and for confirmation/quantitation. This practice is forensically unacceptable.*

Authors' response: In the text was clarified how screening and confirmation analyses on blood samples were performed.

6) *The authors are also able to determine a large amount of ethanol consumed by the decedent based on his measured concentrations in central blood and urine but ignore the discrepancy of ethanol results between peripheral blood, central blood, urine and vitreous humour and instead only list their findings in Table 2 without comments. This discrepancy has the potential of severely undermining their theory of concomitant use of ethanol and drugs by this decedent and should have been further explored.*

Authors' response: Ethanol was additionaly quantified in peripheric blood at 3.17 g/L. This finding demonstrated no discrepancy in ethanol concentration between central and peripheral blood. Consequently, new data were added in the text and Table 2 was updated.

7) *On line 116, the authors state that drug quantitation in urine were performed but do not explain what the usefulness in a postmortem case report or scientific purpose of quantifying drugs in a waste product such as urine that can accumulate substances over days can possibly be.*

Authors' response: Drugs in urine are normally quantified in postmortem cases. Usefulness is poor, as remarked by the reviewer. However, the panel of detected substances can assist the identification of the compounds consumed by the deceased before the death.

Reviewer #3 comments:

a. *General: considerations about the in vitro instability (or not ?) of the substances of interest should be added together with references.*

Authors' response: Additional literature data about the in vitro stability of the benzodiazepines were added and discussed in the text. Consequently, the references were updated.

b. *General: "<mu>g/L" instead "ng/mL" as Liter is the international unit for volume*
Authors' response: the unit was modified thorough the manuscript

c. *Line 113: mass spectra library used for the GC-MS screening method should be added.*

Authors' response: MS libraries used for the qualitative identification of the compounds were added in the text.

d. *Line 157: The agreement between the authoptic (???) examination and toxicological findings is consistent with a suicidal hypothesis: please, explain!*

Authors' response: the sentence was modified. As a matter of fact, the suicidal hypothesis is not proved by the authoptic examination.

e. *Line 102 : "in" instead of "on urine"*

Authors' response: the text was modified

f. *Could you give the nature of the conservative used for blood specimen sampling?*

Authors' response: the information was provided in the paragraph 2.1

Abstract

Postmortem drug redistribution (PMR) is a well-recognized phenomenon which affect the concentration of drugs inside the various body tissues and organs, possibly determining misled interpretation of postmortem drug concentrations. In contrast, drug levels in peripheral blood are commonly considered to be comparable with ante-mortem concentrations. The difference between central and peripheral blood concentrations is known as the "central to peripheral ratio" (C/P). Drugs with high C/P ratios are associated with potential for PMR. In several forensic cases, PMR should be taken into account for the correct estimation of drug blood levels at the moment of death, especially when multiple psychotropic drugs have been co-ingested.

In the case reported hereby, the PMR of several benzodiazepines including triazolam, alprazolam, and delorazepam (chlordesmethyldiazepam) plus zolpidem was evaluated in a fatal multidrug suicide case. A 38-year-old man was found dead in his apartment. On the scene, many packaging of pharmaceutical drugs were found. During the autopsy, no evidence of natural disease nor trauma was found to account for his death. Heart (central) and femoral (peripheral) blood, urine and vitreous humor were collected and submitted to toxicological analysis.

Delorazepam, triazolam and zolpidem were detected at therapeutic levels in peripheral blood while alprazolam and ethanol were found at toxic levels. The potential synergistic sedative effect of multiple benzodiazepines intake, combined to high ethanol concentration, produced a condition compatible with fatal intoxication. C/P ratio for the tested compounds ranged from 1.22 (alprazolam) to 1.47 (delorazepam) demonstrating moderate PMR for these drugs. This is the first report in which the PMR of delorazepam is discussed.

1. Introduction

Postmortem redistribution (PMR) is a complex biological process by which the concentration of drugs in the body is modified by their diffusion along a concentration gradient, generally from various organs toward the circulatory central system, resulting in a biased increase of blood drug levels. Mainly, this diffusion from sites of higher to lower drug concentration involves tissues, organs and body fluids (1,2), and occurs in the interval elapsed between death and autopsy. This important issue raises the question of whether or not the drug levels determined in post-mortem biological samples properly reflect their concentrations at the time of death (3). Generally, the rate and extent of PMR varies according to several factors, including the nature of the drug and the time interval between death and postmortem specimen collection (2). More specifically, this process is related to the volume of distribution for each drug, lipophilic drugs having higher tendency to be redistributed than hydrophilic drugs (4-6) due to their previous accumulation in lipophilic organs.

Postmortem drug concentration in peripheral blood is generally supposed to reflect ante-mortem drug concentration. Therefore, femoral venous blood represents the specimen of choice for postmortem toxicological analyses (1-3, 7). On the other hand, several PMR cases have been documented for various drugs, in which their concentrations proved to be several fold higher in the central vessels and heart than in peripheral blood (4,8). Differently, ethanol usually does not show significant PMR phenomena because of its even distribution into the total body water (9) and previous studies have demonstrated no significant differences between its concentration in peripheral and central blood (10, 11). In some cases, ethanol postmortem distribution from the stomach to the left cardiac chambers can occur, especially when high levels of ethanol were detected in the gastric content (12) or by diffusion from suctioned vomit containing high quantities of ethanol (13). To understand whether PMR phenomena had occurred, postmortem blood specimens should be collected from at least two different sites of the corpse, namely a peripheral and a central area (often the heart), so that a comparison can be made (14). The difference between

the central and the peripheral blood concentrations is known as the central to peripheral ratio (C/P) (2). Generally, drugs with high C/P ratios are associated with potential for redistribution (8), while C/P ratio values close to 1 indicate limited PMR of the drug.

Aim of this study was to evaluate to what extent PMR for alprazolam, triazolam, delorazepam (also known as chlordesmethyldiazepam or with the acronym CDDZ) and zolpidem occurred in a real case of fatal multidrug intoxication, and to compare the results obtained in the present case with those available in the scientific literature. Notably, the PMR for delorazepam has never been described before, to the best of our knowledge.

2. Case history

A 38-year-old man (weight 55 kg, height 167 cm) with previous history of chronic depression was found dead in his bed, laying in fetal position, in a condition of slight rigor mortis. The room temperature was 18°C while the body temperature was 29°C (rectal) and no signs of body decomposition were present. On the scene, many packaging of psychoactive drugs were found, suggesting the occurrence of drug-related suicidal death. Specifically, the police seized: 4 empty bottles of alprazolam, 1 empty bottle of delorazepam, and 12 empty blister packs of zolpidem. Moreover, 3 empty bottles of beer and 2 empty bottles of wine were found in the kitchen. The seized material did not allow a direct estimate of the amount of drugs possibly ingested by the victim the day of his death. No letters to account for a suicide were found in the apartment. The death was reported to the Public Prosecutor's office which took jurisdiction of the case.

2.1 Autopsy findings

At the autopsy, the decedent did not show any specific pathology and appeared well-nourished. Internal examination presented a general pulmonary edema and multi-visceral congestion; no evidence of any trauma was found to account for his death, supporting the hypothesis that acute drug intoxication had occurred. Therefore, our laboratory received the responsibility to determine

whether massive drug assumption could be accounted for the death. The specimen sampled during the autopsy included heart (central) and femoral (peripheral) blood, urine, gastric content (3 mL of brown liquid), bile, hair, and vitreous humor from right and left eye. Central blood was collected from the heart with a scoop, while peripheral blood was obtained from the femoral vein. Blood samples were collected in tubes containing sodium fluoride/EDTA as preservatives. All the specimens were stored at –20°C before analysis.

3. Equipment and methods

3.1 Chemical and Reagents

Alprazolam, delorazepam, triazolam, zolpidem and nitrazepam-d_5 were purchased from Cerilliant/Sigma-Aldrich (Milan, Italy). Sodium hydrogen carbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), sodium phosphate dibasic dihydrate ($Na_2HPO_4 \cdot 2 H_2O$), potassium phosphate monobasic (KH_2PO_4), methanol, formic acid, t-butyl methyl ether (TBME), and β-glucuronidase (from Escherichia coli) were obtained from Sigma-Aldrich (Milan, Italy). Phosphate buffer was prepared by dissolving 4.63 g of KH_2PO_4 and 11.75 g of $Na_2HPO_4 \cdot H_2O$ in 1 L of deionized water. The carbonate buffer was prepared by dissolving 2.12 g of Na_2CO_3 and 6.72 g of $NaHCO_3$ in 1 L of deionized water. Deionized water was obtained from a Milli-Q system (Millipore Corporate Headquarters, Billerica, USA).

3.2 Sample preparation

Authoptic samples were thawed at +4°C one day before analyses. Toxicological analyses were performed six days after the autopsy. General screening analysis was executed on 2 mL of urine, buffered at pH 7.4 with 2 mL of 0.1 M phosphate buffer and deconjugated with the addition of 30 µL of β-glucuronidase from E. coli prior of incubating the mixture at 55°C for 1 h. The sample was subsequently extracted under alkaline conditions (pH 9.6) by adding 2 mL of a 0.1 M carbonate

buffer and then 10 mL of TBME. After shaking the mixture in a multimixer for 10 min, the organic layer was separated and dried under a gentle flow of nitrogen. The resulting residue was reconstituted with 50 µL of methanol. Lastly, a 1 µL aliquot was injected (splitless mode) into the gas chromatography/mass spectrometry (GC/MS) system. In addition, the heart blood sample was screened with a method for the detection of about ninety pharmaceutical drugs and metabolites routinely employed in our laboratory (15). For the quantitative determination of benzodiazepines and zolpidem in blood, 250 µL of sample was added with 250 µL of water:methanol 5:1 (v:v) solution and transferred into a 1.5 mL vial. After the addition of nitrazepam-d_5 as the internal standard (60 µg/L final concentration) and vortex mixing for 10 seconds, 100 µL were transferred in a new 1.5 mL vial and diluted with 200 µL of acetonitrile. Afterwards, the sample was incubated at –20°C for 15 min and then centrifuged at 14000 rpm for 15 min. A 50 µL aliquot of the organic phase was transferred into a new vial from which 1 µL was directly injected into the UHPLC-MS/MS system.

3.3 Apparatus and Methods

Preliminary screening analyses in urine for amphetamines, barbiturates, benzodiazepines, cannabinoids, methadone, cocaine and opiates were performed by the Enzyme Multiplied Immunoassay Technique (EMIT, Abbott Laboratories, IL, USA). The ethanol concentration in blood, urine and gastric contents was determined by headspace-GC-MS. Screening analysis for unknown substances was performed using a 6890N GC apparatus (Agilent Technologies, Milan, Italy) equipped with a 17 m fused-silica capillary column (J&W Scientific HP-5) with a 0.2-mm inner diameter and 0.33-µm film thickness. Helium was employed as the carrier gas at a constant pressure of 23.24 psi. The GC oven temperature was set at 90°C for 1 min and then raised to 180°C with a 30°C/min heating rate. The oven temperature was maintained at 180°C for 7 min and then raised to 315°C with a 15°C/min heating rate. The GC injector and transfer line were maintained at 280°C. Full scan spectra in the interval 40-650 amu were acquired using a 5975 inert mass-selective

detector (Agilent Technologies, Milan, Italy) operating in the EI mode at 70 eV. The qualitative identification of the compounds was performed by comparing the full scan spectra obtained with those recorded in the updated spectra libraries (PMWTox2, SWGDRUG version 1.7, AAFS2012, CaymanSpectraLib). An additional screening for the determination of pharmaceutical drugs and metabolites in blood was conducted by means of an updated UHPLC-MS/MS method, previously described (15). Quantitative analysis for zolpidem and benzodiazepines in urine was performed by an analytical method described in another study (16).

The quantitation of benzodiazepines and zolpidem in central and peripheral blood, vitreous humor and gastric content was executed by means a UHPLC-MS/MS procedure developed and validated on purpose. The chromatographic separation was performed using a Shimadzu LC-30A series system (Shimadzu, Duisburg, Germany) equipped with a Acquity UPLC BEH C18 column (1.7 µm × 2.1 mm × 100 mm) protected by a guard column. The elution solvents were water/formic acid 5mM (solvent A) and acetonitrile/formic acid 5 mM (solvent B). After an initial isocratic condition at 90% A for 0.5 min, the mobile phase composition was varied by a linear gradient (A:B; v/v) from 90:10 to 24:76 in 4.0 min; followed by isocratic elution at 95% B for 1.0 min. The flow rate was 0.6 mL/min and the total run time was 7.0 min including re-equilibration at the initial conditions before each injection. Detection was carried out by an API 5500 triple quadrupole mass spectrometer (ABSCIEX, Foster City, CA, USA) equipped with turbo ion spray source, operating in the positive ionization mode. Best results were obtained using a source block temperature of 550°C. Data were recorded in the selected reaction monitoring (SRM) mode. In order to establish appropriate SRM conditions, the analytes and internal standard were individually infused into the electrospray ionization (ESI) capillary, and the cone voltage (CV) was adjusted to maximize the intensity of the deprotonated molecular species. The collision energy voltage (CE) was selected to preserve approximately 10% of precursor ion. Nitrogen was employed as the collision gas (5×10^{-3} Pa). Optimized chromatographic and mass-spectrometric conditions for targeted molecules and IS are presented in Table 1.

4. Results and discussion

The presence of alprazolam, delorazepam, triazolam and zolpidem was ascertained in central and peripheral blood. All of these drugs were also found in vitreous humor at concentrations generally lower than in blood, while no presence of benzodiazepines and zolpidem was found in the gastric content. Furthemore, the detection of these drugs in urine indicates the occurrence of extensive excretion before death. High levels of ethanol were found in central and peripheral blood and urine samples, at concentrations of 3.28 g/L, 3.17 g/L and 3.65 g/L respectively. All the toxicological results, including C/P ratio, are reported in Table 2. With respect to in vitro stability of the detected compounds, several studies demonstrated that benzodiazepines are relatively stable up to six months, provided that the biological samples are stored at -20°C (17,18). Consequently, the storage conditions adopted for the preservation of the authoptic samples in the present case, and the interval time elapsed between autopsy and the toxicological analyses, allow us to assume that degradation phenomena were avoided and drugs concentrations in the collected specimens were accurately estimated.

Although intoxication by benzodiazepines is rarely cited as the cause of death, the correct estimation of their blood levels is of utmost relevance in several forensic cases, especially when the concurrent intake of other psychotropic drugs is involved. As a matter of fact, the chance of provoking adverse effects from benzodiazepines gets substantially increased when more than one substance is administered. Despite the fact that benzodiazepines are relatively safe drugs, as is attested by their wide therapeutic index, several cases of intoxication have been reported, particularly when alcohol was co-ingested (19). In the present case, the peripheral blood concentrations of delorazepam (68 µg/L), triazolam (5 µg/L) and zolpidem (190 µg/L) appear to be comprised within their respective therapeutic ranges (20-22), while the high alprazolam concentration (67 µg/L) is consistent with a possible state of intoxication (20-22). Therefore, the concomitant presence of delorazepam, triazolam and zolpidem at therapeutic levels, together with

toxic levels of alprazolam and ethanol may have collectively contributed to the fatal event. The potential synergic sedative effect of multiple benzodiazepines intake combined to the observed high level of blood ethanol appears to be fully compatible with the occurrence of an acute intoxication leading to death. In conclusion, the scene examination and the toxicological findings are coherent with a suicidal hypothesis.

Despite the widespread therapeutic use of benzodiazepines and zolpidem and their frequent detection in postmortem cases, few studies report information about the PMR for these compounds. Furthermore, the available data are often controversial. Benzodiazepine concentrations are supposed to show variable changes in the immediate postmortem period, although the reported magnitude of these changes is generally modest, due to their relatively low volume of distribution (5). Triazolam and alprazolam are expected to exhibit a measurable PMR, as their C/P averaged, respectively, 2.8 (range, 1.0–7.5) in 4 deaths and 1.5 (range, 1.0–2.8) in 4 fatal cases (8,22). In other studies, alprazolam and triazolam were reported to have minimal PMR, that correspond to C/P values ranging from 1.00 to 1.61 for triazolam, and 0.9 for alprazolam (3,23,24). Shiota et al. (25) indicated that diazepam and triazolam diffuse from the gastrointestinal tract into the surrounding tissues after death.

To the best of our knowledge, delorazepam is approved for marketing only in Italy, making postmortem cases that involve this molecule extremely rare, while its possible PMR has never been investigated before. Delorazepam is rapidly metabolized to lorazepam, which in turn does not apparently exhibit any PMR (3,8). On the other hand, delorazepam can also be present in biological fluids as an active metabolite of the designer benzodiazepines diclazepam and cloxazolam (26,27).

The PMR for the benzodiazapine-like drugs, mainly used in the treatment of insomnia and commonly referred to as “z-drugs” (zolpidem, zopiclone and zaleplon), is also controversial. In the first investigation concerning three deaths, C/P for zolpidem ranged in the interval 0.8–0.9 (14,28), but more recent studies (3) reported scattered C/P, including high values, which ranged from 0.67

up to 13.25. Zaleplon exhibit significant PMR (29,30), unlike zopiclone for which low or negligible PMR was reported (31,32).

In the case presented hereby, all tested compounds yielded a C/P ratio within the range 1.2÷1.5, thus showing limited or moderate PMR. The C/P ratios for triazolam and alprazolam were 1.40 and 1.22 respectively, in agreement with previous studies (3,15,16). Similarly, C/P for zolpidem was 1.33. For the first time, we estimated the PMR for delorazepam. This compound showed a modest redistribution, corresponding to a C/P ratio of 1.47. This evidence is supported from the C/P ratio for its metabolite lorazepam, whose value was found to be 1.22. This finding is consistent with previous studies demonstrating that lorazepam does not exhibit significant PMR (3,8).

5. Conclusions

The investigation of postmortem cases is frequently problematic, especially when the death may be attributed to an hypothetical fatal intoxication arising from the synergetic effect of several drugs otherwise considered to be rather safe. In such cases, the clear evidence of all drugs simultaneously producing their pharmacological effect and the correct determination of drugs levels represent crucial elements to make up a reliable interpretation of toxicological findings. In the fatal case reported here, the demonstrated concomitant intake of benzodiazepines (alprazolam, delorazepam, triazolam), zolpidem and ethanol, combined with their concentration detected in peripheral blood, provide a comprehensive framework enabling us to suggest that the synergetic sedative effects of drugs and alcohol were likely to account for the death. In particular, the high blood levels of alcohol and alprazolam may have played the major role in the overall intoxication.

In order not to deduce biased evaluation of toxicological data, we carefully evaluated the chance that PMR of the molecules involved may have modified the actual drug concentrations in the biological specimen under study. In particular, we estimated for the first time the C/P ratio for delorazepam, showing modest redistribution of the drug in the postmortem interval. This

preliminary interpretation should be further supported by an adequate number of case reports and databases regarding toxic and lethal blood levels detected in the various sampling sites. In this respect, toxicologists should be encouraged to always evaluate the PMR of the tested compounds and report the observed results.

Table 1. Mass Chromatographic conditions for the tested benzodiazepines and zolpidem

Compound	RT (min)	SRM transitions (m/z)	CV* (V)	CE* (V)	CXP* (V)
Zolpidem	2.2	308.1 → 235.1	50	43	8
		308.1 → 236.0	50	38	17
		308.1 → 263.0	50	38	6
Alprazolam	3.1	309.0 → 281.1	60	47	6
		309.0 → 274.0	60	35	14
		309.0 → 205.0	60	47	13
Triazolam	3.2	343.0 → 239.0	73	54	5
		343.0 → 308.0	73	37	15
		343.0 → 314.9	73	39	7
Delorazepam	3.4	305.0 → 140.0	55	39	9
		305.0 → 206.1	55	46	8
		305.0 → 242.1	55	37	7
Nitrazepam-d5	3.0	287.1 → 185.0	70	50	6

*CV = cone voltage, CE = collision energy and CXP = Collision Cell Exit Potential.

Table 2. Victim's drugs concentrations (µg/L) detected in urine, humor vitreous, central and peripheral blood with respective C/P ratio.

	Specimens					
	Blood			Urine	Humor vitreous	
Drug	**Central**	**Peripheral**	**C/P**		**left eye**	**right eye**
Alprazolam	82	67	1.22	587 (146)[#]	29	29
Delorazepam	100	68	1.47	24	11	11
Lorazepam	11	9	1.22	502	2	2
Triazolam	7	5	1.40	25	1	1
Zolpidem	253	190	1.33	1800	135	143
Ethanol	3.28 g/L	3.17 g/L	1.03	3.65 g/L	n/d	n/d

[#]α-hydroxy-alprazolam