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Case Report

A Fatal Case of Pentedrone and α-Pyrrolidinovalerophenone Poisoning

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We report a fatal case of combined α-pyrrolidinovalerophenone (α-PVP) and 2-(methylamino)-1-phenylpentan-1-one (pentedrone) poisoning. A 28-year-old man was taken to hospital in asystole. Despite resuscitation efforts over 30 min, he died. The forensic autopsy showed pulmonary edema and moderately advanced atherosclerotic lesions of the arteries. Microscopic observation revealed chronic changes in the heart. Confirmation of the presence of pentedrone, α-PVP, and its metabolite 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol (OH-α-PVP) in tissues and fluids were achieved using gas chromatography–mass spectrometry analysis after liquid–liquid extraction. A quantitative validated liquid chromatography–mass spectrometry method was used to determine the concentrations of the above designer drugs in postmortem samples. Pentedrone, α-PVP, and OH-α-PVP concentrations were 8,794, 901 and 185 ng/mL in whole blood, respectively; 100,044, 2,610 and 2,264 ng/g in the liver, respectively; 22,102, 462 and 294 ng/g in the kidney, respectively; 13,248, 120 and 91 ng/g in the brain, respectively and 500,534, 4,190 and 47 ng/g in the stomach contents, respectively. This is the first known reported death attributed to the combined use of α-PVP and pentedrone. Additionally, this article is the first to report the distribution of pentedrone in postmortem human samples.

Introduction

α-Pyrrolidinovalerophenone (α-PVP) and 2-(methylamino)-1-phenylpentan-1-one (pentedrone) are sympathomimetic drugs related to cathinone, the primary psychoactive alkaloid in khat (*Catha edulis*). α-PVP is a pyrrolidine *N*-substituted cathinone. Pentedrone is the α-pentyl-β-keto analog of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) (1–3).

Because pentedrone and α-PVP are still legal substances in many countries, including Poland, they are provided readily through the Internet, without legal issues. These substances, which are increasingly popular among teenagers and young adults, are available typically online as 'legal highs', 'bath salts', 'collector's items' or 'research chemicals' and are labeled 'not for human consumption'. Various routes of administration of these substances include nasal insufflations, oral ingestion, smoking and intravenous injection.

Limited data are available on the pharmacokinetics and pharmacodynamics of pentedrone (2, 4) and α-PVP (1–5). Furthermore, no literature data are available on the clinical effects, toxicological symptoms, addictive nature of or acute overdose potential of pentedrone after administration. The information is limited mainly to user reports, on Internet discussion forums. To our knowledge, fatal intoxication as a result of pentedrone has not been previously reported.

α-PVP is a stronger inhibitor of dopamine, serotonin and norepinephrine transporters than other cathinone derivatives (3). The metabolic pathways of α-PVP have been studied both *in vitro* and *in vivo* (3, 5–8). The most common signs of intoxication of α-pyrrolidinophenone derivatives include cardiovascular and neurological symptoms, such as tachycardia, chest pain, hypertension, agitation, combative behavior, paranoia, insomnia, myoclonus, mydriasis, delusions/hallucinations, hyperthermia and excited delirium syndrome (3, 9). Few fatal cases induced by α-PVP intoxication have been reported (10–14).

In this article, we present a fatal case of combined α-PVP and pentedrone poisoning and the resulting disposition of these drugs in blood and key tissues. In addition, 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-ol (OH-α-PVP), a metabolite of α-PVP, was identified and quantified in postmortem human tissues and blood.

Case history

A 28-year-old man, with a history of designer drug use over several months, was brought to hospital in asystole. Despite resuscitation efforts over 30 min, he died. A small plastic bag, containing a white powder labeled 'α-PVP', was found in his jacket. In addition, a material safety data sheet for pentedrone and α-PVP was found in the trouser pocket of the deceased.

Autopsy findings

A full autopsy was performed, and an internal examination revealed pulmonary edema and moderately advanced atherosclerotic lesions of the arteries. Microscopic observation revealed chronic changes in the heart (uneven staining pattern of the myocardium, fragmentation and waviness of fibers, perivascular connective tissue growth, intramuscular fibrosis and scarring, disintegration of cardiomyocytes, nuclear disintegration, loss of cross-striations and thickening of blood vessel walls) and the presence of hemosiderin-laden pulmonary macrophages (heart failure cells). For toxicological analysis, we collected femoral blood and also liver, kidney, brain and stomach contents. The samples were stored at −10°C, until further analysis, with no addition of preservative agents.

Materials and methods

Reagents and materials

Pentedrone hydrochloride (1 mg/mL in methanol), α-PVP hydrochloride (1 mg/mL in methanol), OH-α-PVP trifluoroacetate (10 mg/mL in methanol) and amphetamine-d5 (1 mg/mL in methanol) were obtained from LGC Standards (Dziekanow Lesny, Poland). Acetonitrile [liquid chromatography–mass spectrometry (LC–MS) grade], dichloromethane [high-performance liquid chromatography (HPLC) grade], methanol (HPLC grade) and trifluoroacetic acid were obtained from Sigma-Aldrich (Poznan, Poland). All other chemicals of analytical grade were obtained from Avantor (Gliwice, Poland). Standard solutions of the

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target drugs (100, 10, 1 and 0.1 μg/mL) were prepared in methanol. Amphetamine-d5 (internal standard, IS) was diluted in methanol to a final concentration of 10 μg/mL. All stock solutions and standard solutions were kept in amber glass vials at −10°C, until further use. Drug-free control blood samples, used for method development and validation and the preparation of controls, were obtained from LGC Standards (Dziekanow Lesny, Poland). Pig livers were purchased from a local supermarket and their suitability for use as a blank matrix for toxicological drug screening was verified.

Sample preparation

A total of 1 mL of whole blood, 1 g of solid tissue (homogenized) or 1 g of stomach contents were added to clean, labeled glass tubes and fortified with 50 μL of 10 μg/mL amphetamine-d5 (IS). A total of 100 μL of 1 M sodium hydroxide (NaOH) and 5 mL of dichloromethane were added to all samples. The mixtures were shaken for 20 min and centrifuged for 10 min at 1,000 × *g*. The organic phase was then transferred to a 7-mL polypropylene tube and evaporated to dryness under a stream of nitrogen at 25°C. The resulting residue was reconstituted in 200 μL of methanol and transferred to a glass insert vial. Samples that were found to contain analyte concentrations above the upper limit of the calibration curve were diluted appropriately and re-extracted.

Qualitative analysis of α-PVP in the white powder by gas chromatography–mass spectrometry

A 10 mg sample of the white powder from the plastic bag was weighed out and dissolved in 1 mL of methanol. The resulting solution was further diluted 1:100 v/v with methanol and then analyzed by gas chromatography–mass spectrometry (GC–MS). Confirmation of the white powder as α-PVP was based on comparison against the retention time (10.3 min) and spectrum of an α-PVP reference standard.

GC–MS conditions

A GCMS-QP2010 Ultra gas chromatograph–mass spectrometer (Shimadzu, Kyoto, Japan) was operated in the electron ionization (EI) mode, using a Zebron ZB-5MS Guardian capillary column (30 m × 0.25 mm, 0.25 μm; Phenomenex, Torrance, USA). The temperatures of the injection port and interface were set at 250°C. Sample injection (1 μL) was in splitless mode. Helium was used as the carrier gas at a flow rate of 0.55 mL/min. The temperature program consisted of four steps: the initial column temperature of 80°C was maintained for 1 min, then increased linearly by 15°C/min up to 200°C, then further increased linearly by 10°C/min up to 300°C and maintained for 3 min. The mass detector was set to EI mode, with the electron beam energy at 70 eV. The mass detector was operated in a full-scan mode (mass range m/z 40–600). Acquisition and analysis of data were carried out with GCMS Solution Version 2.72 (Shimadzu, Kyoto, Japan).

Liquid chromatography–electrospray ionization–mass spectrometry conditions

Samples were analyzed, using an Agilent Technologies 1100 series liquid chromatograph connected to an 1100 MSD single quadrupole mass spectrometer (Agilent Technologies, Waldbronn, Germany) equipped with an electrospray interface. Chromatographic separation of analytes was performed after injection of 10 μL of each extracted sample onto a Zorbax Eclipse XDB-C8 column (150 × 4.6 mm; 5 μm; Agilent Technologies) maintained at 25°C, with the compounds of interest eluted with acetonitrile–0.1% trifluoroacetic acid (70:30, v/v) at a flow rate of 0.4 mL/min. Amphetamine-d5 was used as the IS. The following mass spectrometer parameters were used: fragmentor voltage: 70 V, capillary voltage: 4,000 V, nitrogen flow rate: 12 L/min, temperature of the drying gas (nitrogen): 250°C and nebulizer pressure: 30 psi. Qualitative analysis was carried out in scan mode (mass range m/z 50–600). Quantitative results were obtained in selected ion monitoring (SIM) mode for m/z 192 for pentedrone, m/z 232 for α-PVP, m/z 234 for OH-α-PVP and m/z 141 for the IS. The retention times of pentedrone, α-PVP, OH-α-PVP and the IS were set at 7.3, 9.7, 10.7 and 5.2 min, respectively. LC–MS data acquisition and integration were performed, using LC-MSD ChemStation® chromatographic analysis software (Agilent Technologies, Waldbronn, Germany).

Method validation for LC–ESI–MS analysis

Method validation was conducted according to the guidelines established by Peters *et al.* (15) for methods used in case reports. Blood and liver were chosen as the target matrices for method validation. The following parameters were determined for the validation of pentedrone, α-PVP and OH-α-PVP in blood and liver: selectivity, linearity, limit of quantitation (LOQ), limit of detection (LOD), interday and intraday precisions, accuracy, matrix effect and extraction recovery. Whole blood and liver fortified with pentedrone were prepared in triplicate at eight different concentrations (10, 100, 200, 500, 1,000, 5,000, 7,000 and 10,000 ng/mL or ng/g). In addition, whole blood and liver fortified with α-PVP and OH-α-PVP were prepared in triplicate at eight different concentrations (1, 10, 50, 100, 500, 1,000, 2,000 and 3,000 ng/mL or ng/g). Calibration curves for solid tissues were constructed using pig liver as the blank matrix. Calibration curves were obtained by plotting the peak area ratio of the drug to IS against the drug concentration. The intraday and interday precisions were determined at two concentrations. Intraday precision analysis was performed on a single day of analysis ($n = 5$), whereas interday precision analysis was performed over three consecutive days. The analyses were carried out on three replicates for each day ($n = 3 \times 3$). Accuracy is expressed as a percent deviation from the theoretical concentration. The LOD was defined as the lowest concentration which could be detected with a signal-to-noise (S/N) ratio of 3 and was determined using an empirical method. Three different samples of blank matrix of both blood and liver, fortified with decreasing concentrations, were analyzed in duplicate (two separate samples) for three runs. The LOD met the predetermined acceptance criteria (retention time within 2% of reference standards, ion ratios within 20% and peaks meeting the chromatography criteria). The LOQ was the lowest concentration that met the LOD criteria, and a S/N ratio of 10, a precision coefficient of variation (CV) lower than 20% and an accuracy between 80 and 120%. The LOQ was determined using five replicates on three different days ($n = 5 \times 3$) with blank matrix samples (blood, liver) from different sources. Interference and specificity studies were conducted by analyzing eight different sources of blank samples (blood and liver), without the addition of analytes and IS. There was no interference

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from matrix components at the retention times of the analytes which in any way affected the assay. Moreover, specificity was evaluated by comparing the chromatograms of eight different batches of blank samples (blood and liver) fortified with IS (amphetamine-d5) and that fortified with 1,000 ng/mL of the analytes. The IS and analytes also gave rise to no interfering peaks. Specificity studies were conducted by spiking blank samples (blood and liver) with high concentrations (1,000 ng/mL) of potentially interfering drugs and metabolites. A total of 64 drugs that included analytes of similar molecular weight (including positional isomers of pentedrone and

Table I

Validation Data for the Liquid Chromatography–Mass Spectrometry Method Established in This Study

Item for validation	Pentedrone		α-PVP		OH-α-PVP	
	Blood	Liver	Blood	Liver	Blood	Liver
LOD ng/mL (ng/g)	5.0	5.0	0.5	0.5	0.5	0.5
LOQ ng/mL (ng/g)	10.0	10.0	1.0	1.0	1.0	1.0
Range of linearity (ng/mL, ng/g)	10–10,000	10–10,000	1–3,000	1–3,000	1–3,000	1–3,000
Correlation coefficient (r)	0.998	0.998	0.999	0.997	0.997	0.998
Recovery (%) ($n = 5$)						
100 ng/mL (ng/g)	92.8	83.2	95.5	90.0	100.3	91.4
1,000 ng/mL (ng/g)	100.8	89.6	99.6	100.8	96.4	99.6
Matrix effects (%) ($n = 5$)						
100 ng/mL (ng/g)	91.2	82.5	87.6	100.8	88.5	95.4
1,000 ng/mL (ng/g)	97.2	99.9	108.2	102.2	88.8	93.9

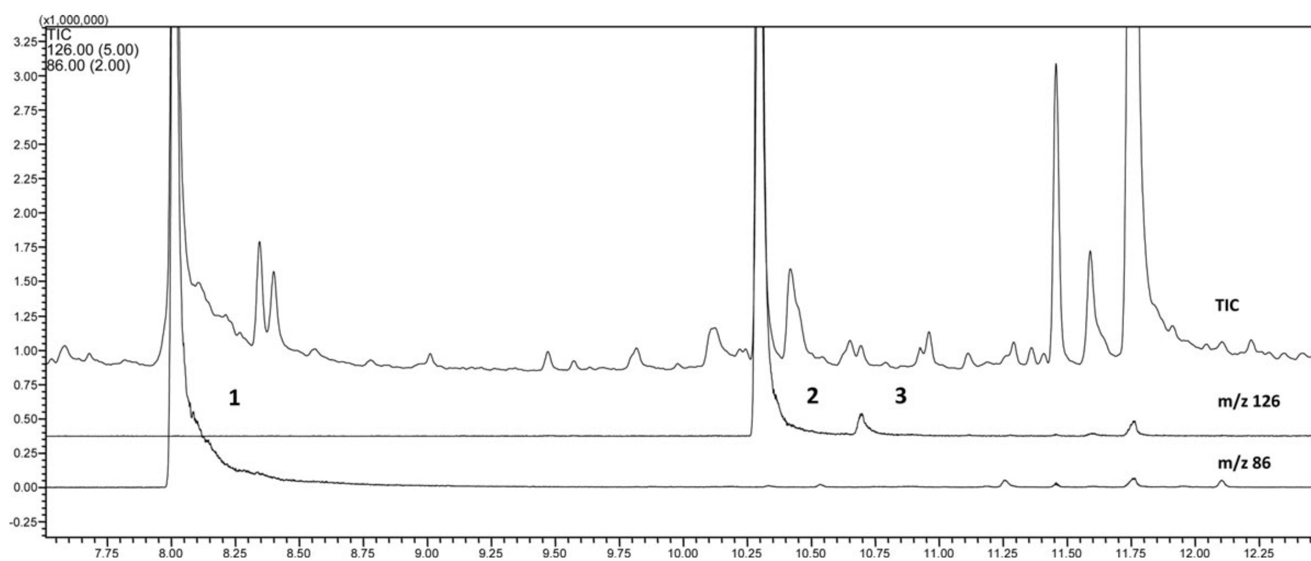

Figure 1. GC–MS chromatogram of the blood sample of the deceased. Peak identification: pentedrone (1), α-PVP (2) and OH-α-PVP (3).

Table II

Intraday and Interday Assay Precision and Accuracy of Pentedrone, α-PVP and OH-α-PVP at Two Different Concentrations

Fortified concentration (ng/mL, ng/g)	Blood				Liver			
	Precision (RSD %)		Accuracy (%)		Precision (RSD %)		Accuracy (%)	
	Intraday ($n = 5$)	Interday ($n = 9$)	Intraday ($n = 5$)	Interday ($n = 9$)	Intraday ($n = 5$)	Interday ($n = 9$)	Intraday ($n = 5$)	Interday ($n = 9$)
Pentedrone								
100	5.0	7.9	4.4	5.0	6.8	10.1	10.8	8.5
1,000	4.2	6.4	6.7	6.5	3.0	6.0	1.9	9.8
α-PVP								
100	3.9	7.3	5.2	−1.8	2.6	5.9	2.7	0.4
1,000	6.7	8.1	5.3	10.1	2.3	7.7	7.9	1.6
OH-α-PVP								
100	2.4	5.7	2.7	2.0	5.5	5.6	−0.8	−0.9
1,000	6.9	6.5	3.7	6.8	1.9	5.7	6.9	9.2

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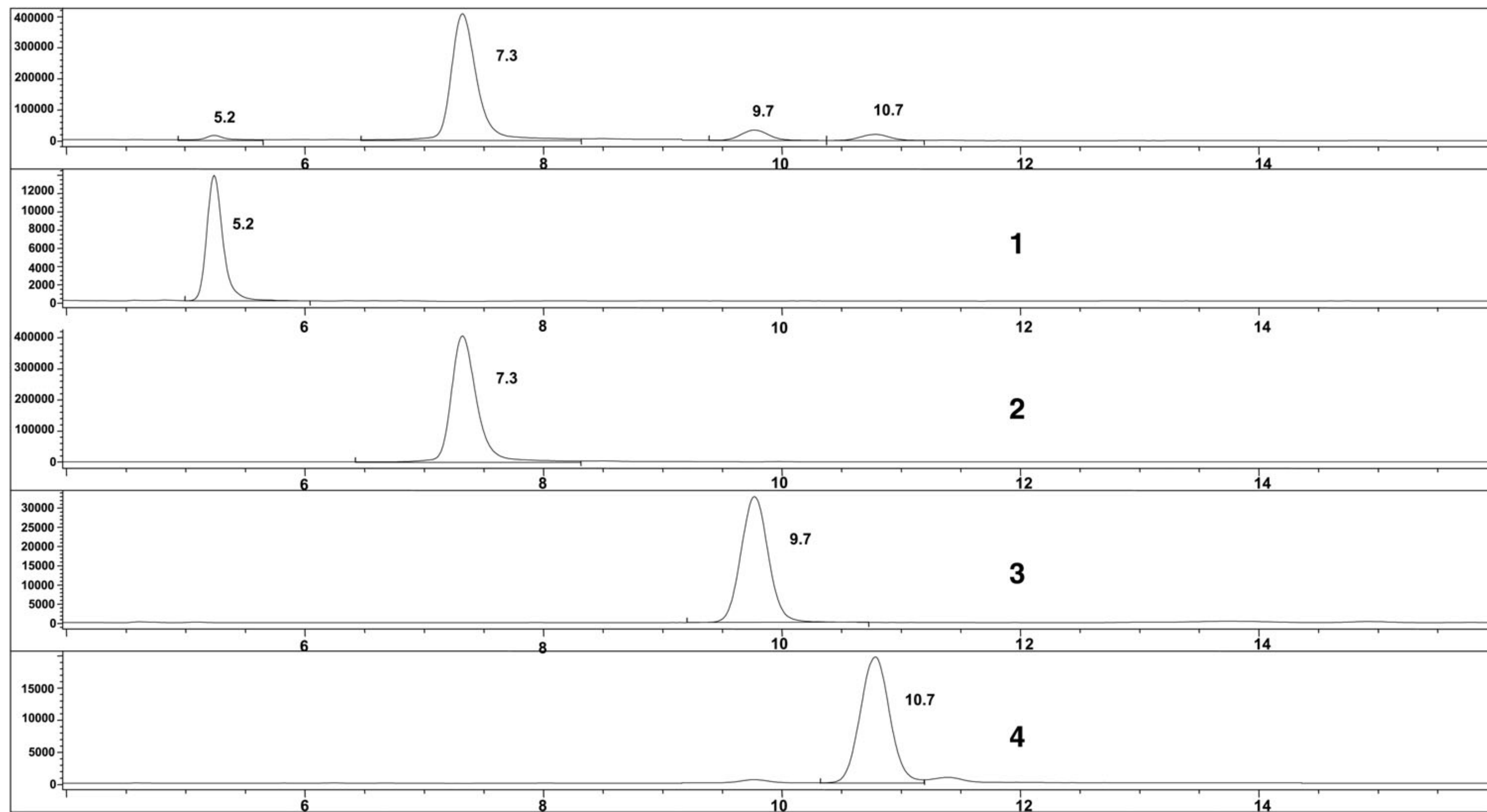

Figure 2. SIM chromatograms by LC–ESI–MS for the target cathinones extracted from the blood sample of the deceased. The ions monitored were: m/z 141 for the IS (1), m/z 192 for pentedrone (2), m/z 232 for α-PVP (3) and m/z 234 for OH-α-PVP (4).

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α-PVP), retention time and structure were analyzed. Specificity studies indicated no interferences from all 64 of the most frequently detected drugs in toxicology casework, including amphetamines, benzodiazepines, opiates, cocaine, sedatives, hypnotics, antidepressants and cathinones (*N*-ethylcathinone, 4-methyl-*N*-ethylcathinone, 4-ethylmethcathinone, 3,4-methylenedioxy-*N*-methylcathinone, 3,4-methylenedioxy-*N*-ethylcathinone, β-keto-*N*-methylbenzodioxolylbutanamine, methylenedioxypyrovalerone, 4-methylmethcathinone, 3-methylmethcathinone, 3,4-dimethylmethcathinone, 4-methoxymethcathinone and 4-fluoromethcathinone). Extraction recovery was determined by comparing the responses of the extracted samples (five replicates for blood and liver), initially fortified with the analytes at the final concentrations of 100 and 1,000 ng/mL (or ng/g), with the responses of blank samples in which analytes were added at the same concentration after the extraction step. Matrix effects were further evaluated by comparing the signal obtained when the analytes were added to the matrix extract with the response obtained from a methanolic solution containing the analytes at the same concentration.

Results and discussion

The assay data met all acceptable criteria for method validation and are summarized in Table I. The LOD was 5 ng/mL for pentedrone and 0.5 ng/mL for α-PVP and OH-α-PVP. The LOQs determined in blood and liver were 10 ng/mL (10 ng/g) for pentedrone, and 1 ng/mL (1 ng/g) for α-PVP and OH-α-PVP. Correlation coefficients for all calibration curves were greater than 0.997. The extraction recoveries were greater than 83.2% for all analytes. Results obtained for precision and accuracy are presented in Table II. The method demonstrated an intraday and interday precision CV of <10.8%.

Qualitative analysis by GC–MS showed that α-PVP was present in the methanolic solution of the powder recovered from the deceased. No other drugs in the panel routinely screened were detected in this sample. A standard postmortem toxicology panel was performed on the blood of the deceased, which included headspace GC volatile quantitation, an immunoassay blood drugs-of-abuse panel (amphetamines, benzodiazepines, opiates, cocaine and cannabinoids) and a full-scan GC–MS basic drug screen. No volatiles were detected and immunoassay results were negative. The full-scan GC–MS basic drug screen of the blood sample and solid tissues detected pentedrone, α-PVP and OH-α-PVP, which were identified based on their retention times and mass spectra, in comparison to those of reference standards of the three compounds. No other drugs were detected in these samples. Figure 1 shows total ion chromatograms of the whole blood sample from the deceased. Peaks for pentedrone, α-PVP and OH-α-PVP appeared at retention times of 8.0, 10.3 and 10.7 min, respectively.

A validated LC–MS method was used to determine the concentrations of pentedrone, α-PVP and OH-α-PVP in postmortem samples. Figure 2 shows the chromatogram obtained from the blood sample. Table III shows the postmortem levels of pentedrone, α-PVP and its hydrogenated major metabolite OH-α-PVP in blood, stomach contents and solid tissues of the deceased. Pentedrone was found in all samples analyzed, with values ranging from 8,794 ng/mL (blood) to 100,044 ng/g (liver). The concentration of pentedrone in the biological samples appeared to be very high, although literature concentrations were not available for comparison.

Table III
Postmortem Concentrations of Pentedrone, α-PVP and OH-α-PVP in Blood, Stomach Contents and Solid Tissues of the Deceased

Biological material	Drugs detected (ng/mL, ng/g)		
	Pentedrone	α-PVP	OH-α-PVP
Blood	8,794	901	185
Liver	100,044	2,610	2,264
Kidney	22,102	462	294
Brain	13,248	120	91
Stomach contents (120 g)	500,534	4,190	47

In the present case, the blood concentration of α-PVP was 901 ng/mL, which is higher than those previously reported (10–13). Saito *et al.* (13) reported the first fatal case, in which α-PVP was the sole cause of death, where the whole blood concentration of the drug in the heart was 486 ng/mL. In another report of fatal poisoning with α-PVP, the concentration of α-PVP in a serum sample was reported to be 411 ng/mL (11), and the fatal outcome was attributed to heart failure. In our case, the microscopic observations of the heart specimen are consistent with these previous reports. In a fatal poisoning case, in which α-PVP was abused, the α-PVP levels in whole blood samples obtained from the right heart, left heart and femoral vein were 597, 635 and 580 ng/mL, respectively (12). Hasegawa *et al.* (10) reported data on the distribution of α-PVP and OH-α-PVP in body fluids and solid tissues in a fatal α-PVP poisoning case. High concentrations of OH-α-PVP, roughly comparable with those of α-PVP, were detected in tissue samples. The concentration of α-PVP in femoral venous blood was found to be 654 ng/mL, whereas the concentrations in solid tissue samples were 518 ng/g in the brain, 681 ng/g in the liver and 1,580 ng/g in the kidney. Moreover, the concentration of OH-α-PVP in femoral vein blood was 364 ng/mL. There was little difference in OH-α-PVP and α-PVP concentrations in the brain. The measured brain concentration of OH-α-PVP was 592 ng/g. High levels of OH-α-PVP were measured in the kidney (972 ng/g) and liver (1,080 ng/g) (10).

In the case presented here, unchanged α-PVP and its metabolite (OH-α-PVP) were detected in all of the samples. For both α-PVP and OH-α-PVP, the levels in the liver were higher than those in the femoral venous blood sample. In our case, the relatively high concentration of α-PVP and pentedrone in the stomach contents suggests the oral intake of both compounds, caused the victim's death.

Conclusion

To our knowledge, this is the first report describing the distribution of pentedrone in postmortem human tissues and blood. The fatal case reported in this study, involving the concomitant intake of α-PVP and pentedrone, suggests that synergistic pharmacological effects of the two drugs are likely to account for the fatal outcome. Moreover, the blood concentration found for α-PVP appears to be fully consistent with an acute intoxication, leading to death, whereas pentedrone is more likely to have played a secondary role in the fatality. It can also be hypothesized that α-PVP and pentedrone acted synergistically on the heart to cause a

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cardiac rhythm disturbance. The pathologist in this case reported that the cause of death was attributed to multiple drug toxicity associated with α-PVP and pentedrone use.

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