CASE REPORT

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A Fatal Case of Methotrimeprazine Overdose

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ABSTRACT: Fatal ingestion of methotrimeprazine is unusual, and while therapeutic drug levels are established as concentrations between 0.02 to 0.14 mg/L, fatal levels are not. The following describes a case of fatal suicidal ingestion of methotrimeprazine in which the measured concentration of methotrimeprazine in the blood was 4.1 mg/L. In addition, the major metabolites of methotrimeprazine, desmethylmethotrimeprazine, and methotrimeprazine sulfoxide were also measured at 2.0 and 1.8 mg/L, respectively. Methotrimeprazine and its metabolites were also measured in urine, bile, and vitreous humor. These results are compared with other case reports of methotrimeprazine fatalities reported in the literature.

KEYWORDS: forensic science, forensic toxicology, drug overdose, methotrimeprazine, suicide

Methotrimeprazine (Nozinan®) is a phenothiazine derivative used in clinical practice since 1958 (1). It is a neuroleptic with sedative and analgesic properties more widely used in Europe than in North America. Methotrimeprazine and its metabolites have been measured in clinical samples by gas chromatography (GC) methods using different detectors (2–4) and lately by high performance liquid chromatography (HPLC) (5). Methotrimeprazine has also been detected and quantitated in fly larvae using HPLC (6). Although there are a number of papers dealing with the concentrations of methotrimeprazine and its metabolites in living patients, only two reports involving four fatalities cite fatal concentrations of methotrimeprazine (7,8). The following describes a fatal case of methotrimeprazine overdose in which the blood concentration of methotrimeprazine is lower than previously reported in the absence of multiple drug ingestion. The concentrations of methotrimeprazine and its two metabolites in the various biological fluids are also given.

Case History

The deceased, a 42-year-old male, had been living with his mother since separating from his common law wife. On the day of his death, a call was received by a local hospital stating that the deceased had been found unresponsive on the floor with three empty bottles of medication lying next to him. The deceased was a manic depressive taking several medications including methotrimeprazine. Although there were several types of medication present at the scene, all three empty medication containers had contained methotrimeprazine. The remainder of the scene examination was unremarkable.

Autopsy showed a well-nourished 42-year-old male with no remarkable external features. Internal examination revealed mild to moderate atherosclerosis of the left anterior descending coronary artery not exceeding 50% narrowing. The heart was otherwise normal with no evidence of ischemic damage. The lungs showed evidence of an early aspiration pneumonia. Examination of the liver showed mild fatty change.

Body fluids including blood, bile, urine, and vitreous humor were recovered for toxicological analysis, the stomach was empty at the time of autopsy. Methotrimeprazine and its metabolites were present in all body fluids tested (Table 1). No other drugs were identified. Alcohol analysis was negative. The cause of death was listed as methotrimeprazine overdose, the manner of death was recorded as a suicide.

Method of Analysis

One half mL of biological fluid (bile diluted 1:25 with distilled water before extraction) was mixed with 1 mL of phosphate buffer pH 10 and extracted with 7 mL of n-butyl chloride. The organic layer was evaporated to dryness under a stream of dry nitrogen. The residue was dissolved in 30 μL of ethyl alcohol. One microliter of each of the reconstituted extracts was injected into a GC equipped with a nitrogen phosphorus (NP)detector. The GC was fitted with a capillary column (DB-1, 0.32 mm I.D., film thickness 0.25 μm). The oven temperature was programed from 110°C to 320°C at a rate of 8°C/min. Helium flow was set at 1 mL/min.

TABLE 1—*Methotrimeprazine and its metabolites in body fluids (mg/L).*

	Blood	Urine	Bile	Vitreous Humor
Methotrimeprazine	4.1	0.80	70	0.25
Desmethylmethotrimeprazine	2.0	1.2	35	0.20
Methotrimeprazine sulfoxide	1.8	8.9	26	0.90

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Injector and detector temperatures were 250°C and 300°C, respectively. Prazepam was used as an internal standard. Methotrimeprazine, desmethylmethotrimeprazine, and methotrimeprazine sulfoxide were detected at the following retention times: 15.4, 15.6, and 18.8 min, respectively. The presence of methotrimeprazine and its two metabolites were confirmed by mass spectrometry (MS). Standard curves for determining the concentrations of the drug and metabolites were prepared by adding a known amount of these compounds to drug free bovine blood (for blood analysis) or distilled water (for other biological fluids). Standards of methotrimeprazine, methotrimeprazine sulfoxide, and desmethylmethotrimeprazine were obtained from Rhône Poulenc Rorer of Mississauga, Ontario, Canada. All analyses were carried out in duplicate.

Discussion

Drug overdose as a cause of death is not uncommon, fatal ingestion of methotrimeprazine, however, is unusual. Although blood concentrations of methotrimeprazine between 0.02 to 0.14 mg/L are reported by Winek as within the therapeutic range (9), lethal blood concentrations of methotrimeprazine have not yet been firmly established. Table 2 shows the fatal concentrations of methotrimeprazine reported in the literature. Freislederer et al. (7) describes three lethal cases of methotrimeprazine poisoning, all of which involved consumption of ethyl alcohol (EtOH). In the first two cases, low concentrations of EtOH were detected (200 mg/L), whereas in the third case, EtOH was quite elevated (2480 mg/L). Furthermore, in the first case, diazepam and nordiazepam were detected in concentrations of 0.8 and 0.04 mg/kg, respectively, and in the third case, prazepam and nordiazepam were found in concentrations of 0.2 and 0.4 mg/kg, respectively. Methotrimeprazine is known to have a potentiating effect on the central nervous system (CNS) depressant effects of alcohol and other CNS depressants (10), thus, the combined ingestion of such drugs may result in death at lower concentrations than may occur in toxicity from methotrimeprazine alone. Only Bonnichsen et al. (8) reports a case in which methotrimeprazine was the only drug detected and in a concentration higher than reported in this case. The fatal concentration of methotrimeprazine reported in this case is the lowest documented in the absence of polydrug ingestion. Because all drugs have a range of fatal concentrations rather than a single fatal concentration, the level reported in this case may represent the lower end of the fatal range so far established for methotrimeprazine. It should be noted, at the same time, that the bile concentration determined is the highest ever reported, but may simply reflect chronic ingestion of methotrimeprazine because the individual had been prescribed methotrimeprazine on a regular basis. No information is available as to the compliance of the victim in this case. Because the postmortem distribution of the two major active metabolites of methotrimeprazine (desmethylmethotrimeprazine and methotrimeprazine sulfoxide) is also given, it provides a more complete picture of methotrimeprazine poisoning.

TABLE 2—*Fatal concentrations of methotrimeprazine reported in the literature (mg/L or mg/kg).*

Blood	Urine	Bile	Liver	Other Drugs Found in Blood	Reference
3.0	3.0	16	10	Diazepam (0.8) Nordiazepam (0.04) EtOH (200)	8
7.5	5.0	46	8	EtOH (200)	8
0.7	0.2	3.3	1.2	Prazepam (0.2) Nordiazepam (0.4) EtOH (2480)	8
8.0	—	—	160	—	9

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