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CASE REPORT

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Fatal Mephenesin Intoxication

ABSTRACT: This report describes a death related to the abuse of and intoxication by mephenesin. To the best of our knowledge, this is the first report case of lethal intoxication involving solely mephenesin and reporting mephenesin blood concentrations. The victim was a 48-year-old woman found unconscious at home. Resuscitation was unsuccessful. Toxicological analysis was performed on a blood sample collected during resuscitation. The results being negative, the body was exhumed for an autopsy, which revealed bronchial inhalation syndrome. Analysis in a second laboratory has revealed the presence of mephenesin in samples collected during autopsy. No other drug/toxin was found, and alcohol was negative. Reanalysis of the peripheral blood collected during resuscitation found a mephenesin concentration of 15.81 μg/mL (15-fold greater that the maximum concentration that would result from a single intake of a 500 mg formulation). The pathologist has concluded on a bronchial inhalation syndrome consecutive to a mephenesin overdose as the cause of death. The manner of this death is discussed in the light of the toxicological hair analysis and the medical past of the victim.

KEYWORDS: forensic science, mephenesin, toxicology, exhumation

Mephenesin (o-cresoxy-3 propanediol-1-2), see Fig. 1, is the historical and chemical leading centrally acting muscle relaxant. It also shows local anesthetic properties due to the participation of a membrane-stabilizing action in spinal reflex inhibition (1,2). It is metabolized to the inactive metabolites β-(o-tolyoxy)lactic acid and β-(2-methyl-4hydroxyphenoxy)lactic acid. Less than 2% is excreted in urine as an unchanged drug (3). First used in the management of tetanus (4,5) strychnine poisoning (6), and also as an anxiolytic (7), it is currently prescribed in many countries for muscle contracture or as a local muscular analgesic. Although it has been in clinical use for over 50 years, there have been few reports implicating it in intoxication. Newhouse (8) described two deaths following tetanus spasm treatment by mephenesin. In one case, death was attributed to respiratory complications without implicating mephenesin, which at that time was not thought to be a respiratory depressant. In the other case, the local anesthetic action of the molecule was thought to have caused inhalation of mephenesin elixir and then lung complications as a cause of the death. In the sole case of voluntary intoxication, in a subject who had been prescribed mephenesin as an anxiolytic, the quantities involved were estimated to be between 5.5 and 11 g (7); the victim presented coma and respiratory distress secondary to intercostal muscular paralysis; assisted respiration and stomach-wash enabled recovery of consciousness more than 7 h after initiation of treatment. The author concluded that mephenesin could have caused respiratory depression and deep sedation. None of these reports mentioned the blood concentration of the mephenesin. The present case is, to the best of our knowledge, the first lethal intoxication by mephenesin for which quantitative toxological analysis has been reported.

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Case History

The victim was a 48-year-old nurse, married without children. She had been out of work for several years because of depression, for which she took bromazepam as an anxiolytic. On February 21, 2005, she was found by her family unconscious, in bradypneia, in a fetal position on the living room floor, and the emergency services were called in. On arrival, the physician reported cardiorespiratory arrest and performed external cardiac massage and intracardial adrenalin injection and set up jugular venous and right radial catheters for bicarbonate perfusion. Death was certified after 45 min resuscitation and the death-certificate signed, requiring burial to be suspended. At police request, a blood sample was taken via the right radial catheter. No forensic evidence of suicide (suicide note or blister-packs, etc.) or of homicide emerged. The *Procureur* (District Attorney) authorized burial, but asked for toxicological analysis of the blood sample. Initial analysis was negative; this apparently inexplicable sudden death led to an official investigation, with exhumation on May 11 and autopsy on May 13, 2005.

Autopsy

Radiography ahead of autopsy failed to show any traumatic lesion or suspect foreign body. External examination found putrefied teguments, with no visible traumatic lesion. Macroscopic examination found a fractured sternum and laterocervical and right radial hematoma sustained during resuscitation, along with bilateral bronchial inhalation syndrome and generalized organ putrefaction. Histology confirmed the presence of food in the distal bronchi. During autopsy, toxicological samples of gastric content, pericardial, and pleural liquid and hair were taken. The blood

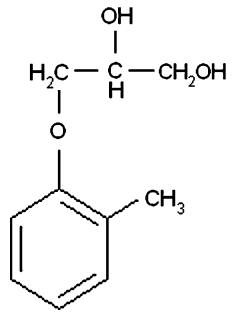

FIG. 1—*Mephenesin structure.*

sample taken by the emergency intervention physician after attempted resuscitation was also submitted for re-examination.

Toxicological Analysis

Toxicological screening was performed on biological liquids using liquid chromatography with photodiode array detection (HPLC/DAD) and gas chromatography with mass spectrometry detection (GC/MS). Samples (blood: 1 mL, gastric content: 0.1 mL, pericardiac and pleural liquid: 0.1 mL), spiked with phenazine as internal standard, were extracted by using Toxitube A™. For HPLC/DAD analysis, the dry residue was dissolved in 100 µL HPLC initial mobile phase (described below) and 60 µL was injected. The HPLC chain was an Agilent serie 1100. The analytical column was a 250 × 4.6 mm ID Uptisphère C_8 Interchrom, 5 µm particle size. The solvent gradient program, composed of a mixure of acetonitrile/phosphate buffer 50 mmol, pH 3.6, was as follows: initial acetonitrile was held at 15% for 2 min, linearly increased to 65% for 13 min, and to 80% for 10 min. The identification of the compounds was performed by using the library "UV spectra of toxic compounds" from F., Pragst, M. Herzler, S. Herre, B.-T. Erxleben, M. Rothe (Berlin, Germany). For GC/MS, the dry residue was acetylated by using the method described by Maurer (9) and modified as follows: 200 µL of pyridine/acetic anhydride mixture (40/60, v/v) was added to dry residue for 30 min at 60°C, then evaporated and redissolved in 100 µL ethyl acetate, and 1 µL was injected. The GC/MS chain was an Agilent 6890 GC with a mass spectra detector 5973. The column was an HP5MS (length 30 m, 0.25 mm ID, film thickness 0.25 µm). The gas vector was helium at 1 mL/min flow. Temperature injector was 260°C. The oven temperature gradient program was as follows: initial temperature 90°C, held 1 min, linearly increased to 200°C (20°C/min) and increased to 300°C (15°C/min). The identification of compounds was performed by using four spectra libraries: Wiley, NIST 02, Pfleger Maurer Weber V3, and a home-made library. For screening of toxin in hair, after decontamination with water then dichloromethane, hair were cut into 1 cm segments and powdered with a ball mill. Fifty milligrams of pulverized hair was incubated 16 h with 2 mL HCl 0.1 M at 60°C. This preparation was neutralized with 2 mL NaOH 0.1 M, and extracted with a Toxitube A™. The dry residue was analyzed by GC/MS as described above for biological liquid.

For each detected drugs, quantitation was performed by using the same HPLC/DAD technique as for biological liquids and GC/MS for hair, with multipoint calibration tables build by spiked blank blood and hair. Limits of quantitation of mephenesin were 0.01 µg/mL in biological fluids (linearity range tested 0.01–20 µg/mL) and 1 ng/mg (linearity range tested 1–100 ng/mg) in hair. Analysis of blood alcohol concentration was performed by Head-space gas chromatography with a flame ionization detector (HS/GC/FID). Autopsy sample analysis found nothing except mephenesin by GC/MS and HPLC/DAD. The concentrations found by HPLC/DAD were 3.50 µg/mL in the gastric content, 69.75 µg/mL (after dilution) in pericardiac liquid, and 73.97 µg/mL (after dilution) in pleural effusion liquid. Analysis of the blood sample taken at the time of death by HPLC/DAD confirmed the above findings, with an isolated mephenesin concentration of 15.81 µg/mL. Hair analysis by GC/MS on six consecutive 1 cm segments (S1–S6) from the root showed mephenesin absorption over the 6 months preceding death (Table 1). Alcohol was tested negative.

TABLE 1—*Mephenesin levels in hairs of the victim.*

Segment	Length (cm)	Estimated Period of Exposure to Mephenesin	Mephenesin Concentration (ng/mg)
S1	1	January 21 to February 20, 2005	47
S2	1	December 21, 2004, to January 20, 2005	93
S3	1	November 21 to December 20, 2004	63
S4	1	October 21 to November 20, 2004	50
S5	1	September 21 to October 20, 2004	24
S6	1	August 21 to September 20, 2004	14

Discussion

Determining the cause of death in this case was difficult for a number of reasons. As there had been no initial autopsy, exhumation was required, which inevitably entailed a certain loss of information but did allow an isolated bronchial inhalation syndrome to be established. This observation was suggesting an intoxication, which was confirmed on subsequent analysis despite the initially negative findings. This discrepancy between the results of two laboratories using the same analytic techniques was probably due to mephenesin being absent from the ultraviolet and mass spectrum libraries used by the first of the two.

Another problem arose due to the relative lack of literature data on the toxic concentration for mephenesin. Literature reports of mephenesin intoxication (7,8) lacked any blood concentration data, probably due to technical limitations at the time. Two blood concentration reference lists give toxic thresholds of 10 µg/mL (10) and 20 µg/mL (11), respectively, for mephenesin, the authors urging caution and a case-by-case approach in their use, further observation being liable to revise these threshold values. Pharmacokinetic data allowed more precise interpretation of results. A bio-equivalence study carried out by the manufacturer on 18 subjects quotes mean maximum blood concentrations (C_{max}) of 0.97 µg/mL (± 0.12) 0.5 h after absorption of one 500 mg dose of mephenesin, with an elimination half-life of $T_{1/2} = 0.82$ h (± 0.02) (unpublished study). Another study, in a single subject, reported a 0.036 µg/mL concentration 4 h after absorption of a 500 mg dose (12). Working from the former study, and given that death ensued at the peak concentration time, the present observed concentration is 15-fold greater than the maximum concentration that would result from a single intake of a 500 mg formulation. Moreover, this concentration may have been underestimated. Indeed, as is often the case with CNS depressants, death probably occurred sometime after absorption, so that, given mephenesin's short half-life, the 15.81 µg/mL concentration was probably below the maximum level reached before death. The bicarbonate perfusion may further have reduced the level measured at the time of death. In the light of all these factors and in the absence of any

other explanation, fatal mephenesin intoxication inducing a bronchial inhalation syndrome was given as the cause of death.

The final difficulty lay in determining the forensic cause of death. Hair toxicology revealed an unaccountable chronic intake of mephenesin over at least the 6 months preceding death. The victim's medical records allowed the hypothesis of undetected pharmaco-dependence: there was in fact mention of unexplained malaise due to acetaminophen intoxication, before an episode of fulminant hepatitis. It was established that the victim had secretly been taking acetaminophen for anxiety, without any medical advice. This was not self-destructive behavior, to judge from what she had said to her psychiatrist. It seems likely that she had repeated this pattern of secret intake with mephenesin, no pack of which was found in the scene of death. The inquiry ruled out a criminal act; so, taken together, these elements combined to suggest accidental lethal mephenesin intoxication.

Whatever the clinical presentation, death from natural causes is a diagnosis to be made by a process of elimination and only after forensic autopsy and analyses carried out by competent laboratories. Failure to follow this rule can have serious implications, even if such was not the case in the present instance.

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