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CASE REPORT

TOXICOLOGY

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Death of a 10-Month-Old Boy After Exposure to Ethylmorphine

ABSTRACT: Ethylmorphine, an opiate that is partially metabolized to morphine, is a common ingredient in antitussive preparations. We present a case where a 10-month-old boy was administered ethylmorphine in the evening and found dead in bed the following morning. Postmortem toxicological analyses of heart blood by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry revealed the presence of ethylmorphine and morphine at concentrations of 0.17 μM (0.054 mg/L) and 0.090 μM (0.026 mg/L), respectively. CYP2D6 genotyping showed that the deceased had an extensive metabolizer genotype, signifying a "normal" capacity for metabolizing ethylmorphine to morphine. The autopsy report concluded that death was caused by a combination of opiate-induced sedation and weakening of respiratory drive, a respiratory infection, and a sleeping position that could have impeded breathing. This is the first case report where the death of an infant has been linked to ethylmorphine ingestion.

KEYWORDS: forensic science, forensic toxicology, ethylmorphine, morphine, death, infant, child, postmortem, blood concentration

Ethylmorphine is an opiate that is used mainly as an antitussive agent in liquid preparations. The molecular structure is similar to morphine, the only difference being an additional ethyl group at the 3-position. The affinity of ethylmorphine to the opiate μ receptor is only 1/300 of the affinity of morphine (1). Approximately 5–20% of an ethylmorphine dose is metabolized to morphine by the genetically polymorph hepatic cytochrome P450 isoenzyme 2D6 (CYP2D6). It is believed that most of the pharmacological effects of ethylmorphine are mediated through bioconversion to morphine (2). The further elimination of morphine depends on glucuronidation to the metabolites morphine-6-glucuronide (M6G, active) and morphine-3-glucuronide (M3G, inactive), which are excreted in the urine.

There are few accounts of ethylmorphine-related deaths in the literature, and no information on ethylmorphine-related deaths in children. The distribution of ethylmorphine in various bodily fluids and tissues in a death attributed to ethylmorphine overdose in an adult male has been reported. The femoral blood concentration in this case was 0.49 μg/mL (3). A Swedish study of medicolegal autopsies in adults reported 14 cases with ethylmorphine concentrations above the upper therapeutic range of 0.3 μg/mL. In eight of these cases, fatal poisoning was considered to be the cause of death. Among these, ethylmorphine was judged to be the main causative agent in two cases and assumed to have contributed to a deadly outcome in the remaining six cases. The authors discussed the fact that ethylmorphine is partly metabolized to morphine, but their toxicological interpretation did not take into consideration that ethylmorphine must be converted to morphine to cause major effects (4).

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Case Report

A 10-month-old boy was found dead in bed, lying on his stomach. Ambulance personnel and the attending general practitioner swiftly arrived at the scene and initiated resuscitation, although the child on their arrival already showed marked cutaneous discoloration and signs of initial rigor mortis. Revival attempts were terminated half an hour later. In retrospect, the child was assumed to have been dead for several hours.

Inquiries revealed that the boy had been having symptoms of an airway infection with coughing, intermittent fever, and increased mucus secretion for several weeks previously. The night before he was found dead, the boy's older half sister had reportedly given him "one teaspoon of cough medicine," to ease his symptoms. The cough suppressant was not prescribed for the child, but had been obtained by the mother for her own use at a previous occasion. The police report noted that a teaspoon and two bottles, one containing an unspecified cough mixture and one containing paracetamol (acetaminophen) mixture, were found on a table beside the boy's bed. Five milliliters of Cosylan® or Solvipect®, the two available antitussive preparations containing ethylmorphine, would amount to 8.5 or 12.5 mg of ethylmorphine, respectively.

Autopsy was performed 2 days after death. The examination revealed no signs of physical abuse. Macroscopically, scattered petechiae were found on the thymus and on the pleural surface. Both main bronchi were partially obstructed by moderate amounts of mucus. Microscopy of the lungs showed slight hyperemia and occasional edema. In sections taken from both lungs, neutrophilic granulocytes were found in large bronchi, and there were also areas with aggregates of granulocytes in alveolar tissue, suggestive of bronchopneumonia. No other relevant findings were made at

autopsy. Microbiology cultures of nasopharyngeal secretion revealed the presence of *Streptococcus pneumoniae* as well as respiratory syncytial virus.

Heart blood was obtained at autopsy for toxicological analyses. No other specimens were collected for evaluation. Analyses were carried out for alcohols (ethanol, methanol, isopropanol, acetone) using a headspace gas chromatography-mass spectrometry (GC-MS) method, and for opiates (morphine, codeine, ethylmorphine, oxycodone, M3G, M6G) and paracetamol using specific liquid chromatography-mass spectrometry (LC-MS) methods. Alcohols or paracetamol were not detected. Ethylmorphine, morphine, and M3G were measured at concentrations of 0.17 μM (0.054 mg/L), 0.090 μM (0.026 mg/L), and 0.13 μM (0.060 mg/L), respectively. The active morphine metabolite M6G was not detected.

In the method used for detecting opiates, 1 mL blood and 50 μL d3-morphine (internal standard, IS) were mixed with 2.0 mL 10 mM $(NH4)_2CO_3$. The mixture was eluted through a SPE Chromabond C18 column (Machery Nagel, Düren, Germany) previously preconditioned with methanol, water, and 10 mM ammonium carbonate, respectively. After washing with 3.0 mL 10 mM ammonium carbonate, the column was eluted with 0.5 mL methanol:0.5 M acetic acid (9:1). After evaporation of the eluent, the residue was reconstituted in 50 μL 50 mM ammonium carbonate pH 7.0, transferred to vials and injected on an Agilent MSD 1100 LC-MS system (Agilent, Palo Alto, CA). The LC-MS system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a G1316A column oven, and a G1946A mass spectrometer. Separation was performed on a Zorbax Eclipse XDB-C8 (4.6 × 150 mm) column with a mobile phase consisting of methanol/ammonium formate/ammonium acetate (3/6/91) with a total runtime of *c.* 6 min. Ethylmorphine was monitored after positive electrospray ionization at m/z 314.0, while the IS d3-morhine was monitored at m/z 289. The calibrated range was 0–10 μM, and linearity was demonstrated over this interval. Six quality control samples covering the range from 0.005 to 5 μM were analyzed with every batch of unknown samples. Between-day coefficient of variation calculated from quality control samples was better than 14.8% at 0.010 μM and 4.8% at 0.1 μM. The limit of quantitation of the method was 0.005 μM.

The small volume of blood obtained (only 2 mL) precluded further specific analyses, but the blood was screened against a comprehensive drug library (National Institute of Standards and Technology mass spectral reference library, version D.05.00 G1033A, June 2005) with a GC-MS method, which did not indicate the presence of any other drugs or substances. This screening method is valuable in identifying unknown substances, but may fail to identify significant concentrations of drugs that are pharmacologically active at low concentrations (such as fentanyl), and may also overlook highly polar substances (such as amphetamines).

CYP2D6 genotyping of blood from the deceased showed two functional copies of the CYP2D6 gene (*CYP2D6**1/*1). This corresponds to the extensive metabolizer phenotype, which is the "regular" (*c.* 90%) variant with average to slightly above average ethylmorphine metabolizing capacity. In brief, genotyping was performed by isolating genomic DNA from peripheral leukocytes using a Qiagen Blood and Cell Culture DNA kit (Qiagen, Hilden, Germany), according to the manufacturer's guidelines. The inactivating alleles *3, *4, and *5 were determined by allele-specific polymerase chain reaction (PCR) analysis and restriction fragment length polymorphism (RFLP). The sample was also tested by long-PCR for the duplicated/multiduplicated gene (the *2Xn mutation). Alleles in which none of these mutations were found were classified as *1 (wild-type) alleles.

The autopsy report concluded that death was caused by an unfortunate combination of three factors; lung infection with partial airway obstruction, opiate-induced sedation and weakening of respiratory drive, and a sleeping position that could have impeded breathing.

Discussion

To our knowledge, this is the first report of a death linked to the ingestion of ethylmorphine in a child. Three case reports have previously described deaths in children exposed to opiates. A 13-day-old boy died with a blood morphine concentration of 0.25 μM (0.070 mg/L) after having been breastfed by his mother, who had been ingesting codeine. She was later found to have a CYP2D6 ultrarapid metabolizer genotype, thereby producing unusually large amounts of morphine from codeine (5). A 7½-month-old boy died after having been administered repeated doses of morphine rectally for postoperative analgesia. A serum morphine concentration of 0.33 μM (0.094 mg/L) was measured in a sample taken shortly before death (6). Finally, an 8-year-old girl was administered a high dose of morphine by mistake after tonsillectomy and was found dead the next morning, with a postmortem morphine blood concentration of 0.45 μM (0.13 mg/L) (7). In the cases where morphine was measured in postmortem blood (5,7), the sampling site (femoral vein, heart, other) was not reported.

In all the aforementioned case reports, morphine concentrations were considerably higher than in the present case. However, a study of neonates, infants, and children who were given morphine under controlled conditions after cardiac surgery showed that some degree of respiratory depression would be expected in most patients at morphine serum concentrations above 0.070 μM (0.020 mg/L). The respiratory response was highly variable, and even at serum levels below 0.020 mg/L, some of the subjects showed signs of respiratory depression (8). In light of this, we believe it is justified to conclude that ethylmorphine ingestion contributed to death in the present case.

The morphine-to-ethylmorphine concentration ratio in blood from the deceased was 0.53, which is higher than one would expect after the exclusive ingestion of ethylmorphine. There are several possible explanations for this. First, the metabolism of ethylmorphine involves both the de-ethylation to morphine by CYP2D6 and the conjugation to glucuronide by the glucuronosyltransferase UGT2B7. The activity of these enzymes varies because of genetic factors and is also influenced by age. Infants have lower glucuronidation capabilities than adults. One study of developmental pharmacokinetics of morphine showed that infants reach 80% of the adult glucuronidation capacity by the age of 6 months (9). However, the interindividual variability is pronounced, and in some infants, glucuronidation capacity may remain at a relatively low level throughout the first year of life. On the other hand, CYP2D6 activity reaches adult levels around the age of 2 months and may even exceed adult levels in infancy (10). High or normal CYP2D6 activity combined with low glucuronidation capacity may have caused some degree of accumulation of morphine after the ethylmorphine intake. Second, we cannot exclude the possibility of additional morphine administration; however, there is no circumstantial evidence to support this. A third possible explanation to the high morphine-to-ethylmorphine ratio might have been ultrarapid CYP2D6 metabolism. This was excluded by genotyping.

In the present case, heart blood rather than femoral venous blood was analyzed. Hence, the possible influence of postmortal redistribution on the measured drug concentrations cannot be ruled out. However, a majority of available data suggests that extensive postmortal

redistribution of morphine does not occur (11,12). According to one study, the postmortem morphine concentrations in heart blood were higher than in peripheral blood, but this only applied to the cases where heart blood concentrations were higher than 0.30 mg/L. At lower concentrations, there was no significant difference between heart and femoral blood concentrations (12). Thus, the possibility that our measurement represents an overestimation of the actual blood concentration at the time of death seems unlikely.

In conclusion, we have presented the first case in which the death of an infant has been linked to the ingestion of ethylmorphine. Clinicians, toxicologists, and pathologists should beware the possibly lethal effects of even small doses of opiates in infants, especially in the presence of respiratory infections or other possible impediments of lung function.

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