Case Report

A Fatality Due to an Accidental Methadone Substitution in a Dental Cocktail

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Abstract

A 6-year-old male child was scheduled for a dental procedure requiring conscious sedation. Prior to the procedure, the child was administered a dental cocktail containing chloral hydrate, hydroxyzine, and methadone. After returning from the dentist, the child appeared groggy and was allowed to sleep. A few hours later, he was found unresponsive, and following resuscitation attempts at a local medical center, he was pronounced dead. Toxicological analyses of femoral blood indicated the presence of hydroxyzine at less than 0.54 µg/mL, trichloroethanol (TCE) at 8.3 µg/mL, and methadone at 0.51 µg/mL. No meperidine was detected. The cause of death was reported to be due to the toxic effects of methadone. The toxicological analysis was corroborated by the analysis of the contents of the dental cocktail, which revealed the presence of hydroxyzine, chloral hydrate, and methadone. Residue from a control sample obtained from the same pharmacy, but administered to a different subject, was found to contain hydroxyzine, chloral hydrate, and meperidine. This report represents the first known fatality due to accidental substitution of methadone in a dental cocktail.

Introduction

Methadone, a synthetic opioid, was originally synthesized as a morphine substitute in Germany during World War II and approved by the U.S. Food and Drug Administration (FDA) in 1947 for use as an analgesic (1). By 1950, methadone was being prescribed for the treatment of withdrawal symptoms associated with heroin and other opioids (1). Methadone is an effective treatment of opioid addiction and moderate to severe pain due to its long duration of action. When compared to morphine, methadone’s higher bioavailability and longer half-life make it an attractive choice for pain management (2). The plasma half-life of methadone is widely variable among individuals, but can be from 13 to 58 h, permitting a once-a-day dosage regimen (3,4). Death from methadone toxicity is primarily the result of respiratory depression, although cardiac arrhythmias have been reported in people receiving extremely high methadone maintenance doses (5,6). Methadone-related fatalities have dramatically increased in Oklahoma, likely due to illicit use and misuse of the drug for pain management (7). Methadone’s increasing popularity in treating withdrawal and pain has led to a rise in methadone preparations being dispensed by pharmacies. This report describes the case of the mysterious death of a child administered methadone in a dental drug cocktail meant to contain meperidine, hydroxyzine, and chloral hydrate.

Case History

A 6-year-old male Caucasian child weighing 55 lb and with a medical history of asthma was scheduled for a dental procedure requiring conscious sedation. A drug mixture of meperidine (50 mg), hydroxyzine (41 mg), and chloral hydrate (375 mg) was prescribed for sedation and analgesia during the procedure. On the morning of the appointment, the mother of the child picked up the “dental cocktail” from the pharmacy and delivered the syringe containing the compounded drugs to the dentist. The child was subsequently administered the dental cocktail orally, along with nitrous oxide gas, and the dental procedure was completed uneventfully. No additional postoperative medications were prescribed or administered. Following the procedure, the child appeared responsive but groggy. He was taken home and left to sleep on a couch. A few hours later,
the boy was found unresponsive and was transported to a nearby medical center. Resuscitation attempts were unsuccessful, and the boy was pronounced dead.

A complete autopsy was performed at the Eastern Division of the Office of the Chief Medical Examiner in Tulsa, OK. The autopsy findings were essentially unremarkable with sections of lung showing focal mild peribronchial inflammation rich in eosinophils and thickened basement membrane, both of which were consistent with the stated history of asthma. Samples of blood, vitreous, urine, liver, brain, and gastric contents were sent to the toxicology laboratory in Oklahoma City for analysis. The dentist’s office provided two syringes containing some drug residue to a private laboratory for chemical analysis. One syringe (syringe A) was administered to the deceased child, and the other syringe (syringe B) was used in another patient and purportedly contained the same dental cocktail (pimozide, hydroxyzine, chloral hydrate), thereby serving as a control. Both syringes were compounded by the same pharmacy within days of each other.

Methods

Postmortem drug analysis
Alcohols were analyzed in heart blood by headspace gas chromatography. Alcohols were identified via retention time and quantitated by comparing to standards. Testing for alkaline drugs was performed on heart blood with a liquid–liquid extraction modified from a previously published method (8,9). The alkaline drug extracts were analyzed by gas chromatography with a nitrogen-phosphorus detector (GC–NPD) and by GC–mass spectrometry (MS). Acidic/neutral drugs were analyzed by GC with flame-ionization detection (FID) and GC–MS using a modified, previously published method (10). Heart blood samples were also screened for common drugs of abuse (methamphetamine, amphetamine, benzoylecgonine, opiates, phencyclidine, barbiturates, and benzodiazepines) using enzyme-linked immunoassay (ELISA).

Quantitation of trichloroethanol (TCE), the major active metabolite of chloral hydrate, was confirmed and quantitated with liquid–liquid extraction followed by analysis using GC with electron capture detection (ECD). One-tenth milliliter of internal standard solution (1.0 mg/mL ethchlorvynol in methanol) was added to 1.0 mL case femoral blood. Toluene (2.0 mL) was added, and the tubes were rotoextracted for 10 min, followed by centrifugation to separate the layers. A 1.0-µL aliquot of the toluene extract was injected onto an Agilent 6890 GC equipped with an FID and a RTx200 capillary column (15 m × 0.25 mm, 0.25-µm film thickness, Restek). GC conditions were as follows: injector temperature, 250°C; detector, 320°C; initial column temperature, 50°C; and oven ramp, 50–120°C at 10°C/min. Identification by retention time and quantitation by peak area were accomplished by comparison of case blood to a standard curve covering a range of 1–16 µg/mL TCE.

Hydroxyzine was extracted from femoral blood, liver, and gastric contents using the alkaline drug screening method described. Internal standard (propranol) was added to 1.0 mL femoral blood, liver homogenate (1:4 with water) or diluted gastric contents (1:100 with water). Standards were prepared from a methanolic stock solution of hydroxyzine to construct a standard curve of 0.125–2.0 µg/mL. Samples and standards were analyzed on an Agilent 6890 GC equipped with an FID (column: RTx-50, Restek, 15 m × 0.25 mm × 0.25-µm film thickness). Chromatograph temperatures were as follows: injector temperature, 250°C; detector, 320°C; initial column temperature, 200°C; and oven ramp, 200–300°C at 10°C/min (final hold time = 5 min). Identification (retention time) and quantitation by peak area were accomplished by comparison of case blood to a standard curve covering a range of 0.125–2.0 µg/mL hydroxyzine.

Methadone was extracted from femoral blood, liver, and gastric contents using the described alkaline drug screening method. Internal standard (maprotiline) was added to 1.0 mL femoral blood, liver homogenate (1:4 with water), or diluted gastric contents (1:100 with water). Standards were prepared from an aqueous stock solution of methadone to construct a standard curve. The method is linear over the range of 0.062–2.0 µg/mL. Samples and standards were analyzed on an Agilent 6890 GC equipped with an FID (column: RTx-50, Restek, 15 m × 0.25 mm × 0.25-µm film thickness). Chromatograph temperatures were as follows: injector temperature, 250°C; detector, 320°C; initial column temperature, 150°C; and oven ramp, 150–300°C at 20°C/min. Identification (retention time) and quantitation by peak area were accomplished by comparison of case blood to the standard curve.

Analysis of contents of the syringes
The two syringes contained only trace amounts of the compounded preparation remaining within the bore. Extraction was achieved by reconstituting the remnants of the syringe with 5 mL nanopure water, followed by sonication for 5 min to ensure complete dissolution. Exactly 250 µL of the reconstituted solution was then extracted with three 10-µL aliquots of chloroform. The extracts were combined for each syringe and then evaporated down with nitrogen gas. These were then reconstituted in 100 µL chloroform. A 1-µL portion of each was injected separately into an HP 5890 series II GC (column: 30 m × 0.25-µm df × 15 m) equipped with an HP 5790 mass selective detector. Initial oven temperature was 33°C with a 5-min hold time, and the temperature was increased at the rate of a 35°C/min to a final oven temperature of 300°C. The injection temperature was 175°C with a detector temperature of 300°C.

Results

The toxicological analyses indicated the presence of hydroxyzine in blood at less than 0.54 µg/mL, TCE at 8.3 µg/mL, and methadone at 0.51 µg/mL (Table I). The cause of death was reported to be due to the toxic effects of methadone. Analysis of the contents of syringe A revealed the presence of hydroxyzine, chloral hydrate, and methadone. The control, syringe B,
was found to contain hydroxyzine, chloral hydrate, and meperidine.

Discussion

The combination of chloral hydrate, meperidine, and hydroxyzine is commonly used for conscious sedation in dentistry (11,12). Conscious sedation carries certain risks due to potential adverse effects of the medications. Chloral hydrate and meperidine, for example, have been associated with nausea and vomiting (11). The average elimination half-life of meperidine is 3.6 h with a range of 3.1 to 4.1 h. In the present case, however, no meperidine was detected (12). The unexpected presence of methadone raised the possibility of accidental substitution during the compounding of the cocktail. This was corroborated by the chemical analysis of the two syringes. The syringe administered to the decedent was found to contain methadone in substitution for meperidine.

Methadone-related deaths have shown a dramatic increase in recent years. (1,13–15). Some of the causes for this increased mortality include the wide interindividual variation in methadone’s pharmacokinetic parameters, long half-life, tendency to accumulate, and the potential for drug–drug interaction (16). Although many methadone-related deaths occur due to respiratory depression, fatal arrhythmias attributable to methadone-induced prolongation of QT interval have also been reported to occur frequently (16–21).

Dispensing errors leading to the accidental contamination of prescription drugs with methadone have been reported and a few case reports document methadone contamination of oral antibiotic preparations (22–24). The present case however represents the first known instance of accidental methadone substitution in a dental cocktail. The majority of methadone-related deaths typically include the presence of other CNS depressants such as other opiates or benzodiazepines (1,13–15,25,26). Postmortem interpretation of methadone concentrations can be challenging due to the presence of other drugs and the overlap between therapeutic and toxic concentrations (27).

The results of a toxicological analysis of deaths involving methadone found blood methadone concentrations ranging from 0.2 to 0.49 µg/mL in five children between 2 and 13 years of age (26). In the present case, the administered drugs (i.e., hydroxyzine and chloral hydrate) could potentially lead to additional respiratory depression when combined with methadone. However, the relatively high methadone concentration in the present case (0.51 µg/mL) is well within the range of reported fatalities due to methadone and would by itself contribute to significant adverse effects, especially considering the age of the subject and the lack of opioid tolerance (28).

Conclusions

It is the opinion of the authors that the cause of death was due to methadone toxicity. This opinion is based on the toxicological findings and further corroborated by the investigators. The toxicology results revealed the presence of hydroxyzine, TCE, and methadone in the decedent’s blood, liver, and gastric samples. The dental cocktail administered to the decedent contained hydroxyzine, chloral hydrate, and methadone and therefore could be linked to the toxicology results. In the present case, the methadone appeared to have been incorrectly substituted for meperidine at the pharmacy. These drugs were evidently placed on the shelf adjacent to each other. Both were 50-mg white tablets, thus potentially leading to the erroneous substitution. Furthermore, the consequences of the accidental administration of methadone to the child were further compounded by his age and lack of opioid tolerance. This report represents the first known case of accidental substitution of methadone in a dental cocktail.

Table 1. Postmortem Toxicological Analysis

<table>
<thead>
<tr>
<th>Sample</th>
<th>Methadone (µg/mL)</th>
<th>Hydroxyzine (µg/mL)</th>
<th>TCE (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td>0.51</td>
<td>&lt; 0.54</td>
<td>8.3</td>
</tr>
<tr>
<td>Liver</td>
<td>2.2</td>
<td>2.1</td>
<td>–</td>
</tr>
<tr>
<td>Gastic</td>
<td>&lt; 1.0</td>
<td>0.75</td>
<td>–</td>
</tr>
</tbody>
</table>

References


