Fatal Cold Medication Intoxication in an Infant

Diane M. Boland*, Joseph Rein, Emma O. Lew, and W. Lee Hearn
Miami-Dade Medical Examiner Department, Toxicology Laboratory, 1851 NW 10th Avenue, Miami, Florida 33136

Abstract
The case history and toxicological findings of an infant fatality involving pseudoephedrine, brompheniramine, and dextromethorphan are presented. Concentrations of brompheniramine and dextromethorphan were measured in both postmortem blood and liver specimens using a gas chromatograph equipped with a nitrogen-phosphorus detector. Brompheniramine and dextromethorphan were 0.40 mg/L and 0.50 mg/L, respectively, in the blood sample and 0.16 mg/kg and 0.57 mg/kg in the liver sample. The concentration of pseudoephedrine in blood and liver specimens was measured using gas chromatography-mass spectrometry and was determined to be 14.4 mg/L in the blood and 16 mg/kg in the liver. Additionally, a baby bottle allegedly administered to the infant was collected as evidence and sent to the Medical Examiner's Office for evaluation. The amounts of total brompheniramine, dextromethorphan, and pseudoephedrine remaining in the baby bottle were 1.4 mg, 9.4 mg, and 40 mg, respectively.

Case History
A two-month-old black female appeared to have a cold and was crying off and on until approximately 2:00 a.m. The mother reportedly fed the infant a bottle containing water and a small amount of Tylenol. The infant fell asleep and woke again at approximately 4:30 a.m., at which time the mother placed her in a prone position with her head to one side. At 7:30 a.m., the infant's mother went to check on her and found her unresponsive. The mother contacted emergency personnel, who responded and pronounced the infant dead at the scene. Upon arrival of the Medical Examiner, the decedent was observed lying in a prone position in her crib. Three blankets were located underneath the decedent, and one was covering her back up to her shoulders. At the head of the crib were two bottle caddies containing empty bottles and two soft plastic containers containing a couple of pairs of socks. Items received by the Medical Examiner's Office included Infants' Pain Reliever Suspension Drops, Children's Pain Reliever, Q-Tussin Cough Formula, one baby bottle containing a small amount of infant formula, and one baby bottle containing a pink-tinted liquid.

An autopsy by the medical examiner revealed pulmonary edema; however, there were no gross abnormalities of any organs including the heart and brain, and no evidence of traumatic injuries. Blood (collection site not specified), gastric contents, and liver specimens were sent for toxicological analysis.

Introduction
Over-the-counter (OTC) cough and cold medications are marketed widely for relief of common cold symptoms and are often overlooked in terms of the risk associated with their administration to infants and young children. Although most OTC medications are harmless when used as directed, many can be associated with significant morbidity and even mortality in both acute overdoses and when administered in correct doses for chronic periods of time (1). The dangers of misusing OTC cough and cold medications are further realized when parents (or other caregivers) fail to perceive OTCs as medications that can have significant side effects. In addition, caregivers are often unaware of the potential hazards that dosing errors may have on infants and young children. This case study reports an infant fatality in which an excess amount of an OTC medication containing brompheniramine, dextromethorphan, and pseudoephedrine was administered to a two-month-old child.

Materials
Brompheniramine was obtained from Schering Corporation (Kenilworth, NJ). Dextromethorphan and d-pseudoephedrine were obtained from Cerilliant Corporation (Round Rock, TX). Phenylethanolamine and cyclizine were purchased from Aldrich Chemical Company (Milwaukee, WI). All standards were used without further purification. Standard stock solutions of these substances were prepared at a concentration of 1.0 mg/mL in methanol. All reagents utilized were analytical grade.

Toxicological analysis
Initial drug screening
The initial screening of the gastric contents and the blood and...
serum specimens in this case was by immunoassay (EMIT, Hitachi 705 Analyzer, Syva® Diagnostic Products; FPIA, Abbott Diagnostics; and ELISA, P-Lab Analyzer, OraSure Technologies, Inc.) for benzodiazepines, barbiturates, opiates, benzoylcegonine, amphetamines, acetaminophen, and salicylates. The gastric contents were further screened by thin-layer chromatography (Toxi-Lab® Ansys Technologies, Inc.). Volatile substances were screened using headspace gas chromatography (GC). Collectively, these initial analyses provided negative results for benzodiazepines, opiates, barbiturates, benzoylcegonine, amphetamines, phenycyclidine, acetaminophen, salicylates, and ethanol.

Qualitative gas chromatographic–nitrogen-phosphorus detection (GC–NPD) blood analysis
The qualitative screening procedure that disclosed the presence of pseudoephedrine, brompheniramine, and dextrimethorphan was a general drug screen for chemically basic drugs adapted from Pierce et al. (2). Briefly, 1 mL of saturated sodium borate buffer (pH 9) and 1 mL of cyclizine internal standard (0.50 mg/mL in deionized water) was added to 1 mL of whole blood and vortex mixed. After addition of 8 mL of n-butyl chloride, the mixture was rotated for 15 min followed by centrifugation at 3000 rpm for 10 min. The upper organic phase was transferred to a clean test tube containing 1.5 mL of hydrochloric acid (HCl, 0.10M). The mixture was vortex mixed for 1 min and centrifuged at 3000 rpm for 5 min. The upper organic phase was aspirated and discarded, and the remaining aqueous acid layer was made alkaline by the addition of 150 μL of sodium hydroxide (NaOH, 1.0M) and 2.0 mL of saturated sodium borate buffer (pH 9). After the addition of 8 mL of n-butyl chloride, the mixture was rotated for 15 min, followed by centrifugation at 3000 rpm for 5 min. The organic phase was transferred to a clean test tube containing 2–3 drops of 1% concentrated HCl in methanol. The extract was evaporated to dryness at 40°C under a stream of nitrogen and stored at -15°C Working standards of each were prepared by serial dilution of the stock standard solutions and comprised four concentrations ranging from 0.10 mg/L to 1.0 mg/L. The extraction procedure for the samples, standards, and blank was a one-step liquid–liquid extraction. No sample preparation was required for the blood and baby bottle contents; however, it was necessary to homogenize the liver specimen by blending 5 g of liver with 20 g of deionized water. For the extraction, 1 mL of sodium phosphate buffer (pH 12, 0.50M) and 1 mL of cyclizine internal standard (0.50 mg/L in deionized water) were added to 1 mL of each of the samples and vortex mixed. After addition of 8 mL of n-butyl chloride, the mixture was rotated for 15 min followed by centrifugation at 3000 rpm for 10 min. The upper organic phase was transferred to a clean test tube containing 2–3 drops of 1% concentrated HCl in methanol. The extract was evaporated to dryness at 40°C under a stream of nitrogen and reconstituted with 50 mL of methanol. Extracts were transferred to autosampler vials for analysis on the GC–NPD.

The GC system consisted of a Hewlett-Packard model 5890 series II GC equipped with an NPD and a 7673A autosampler. The column used was a DB-1 (100% dimethylpolysiloxane) megabore column (15 m × 0.53-mm i.d., 1.5-mm film thickness, Agilent Technologies). The column temperature was 200°C for 1 min then ramped to 270°C.

Quantitation was based on the preparation of a calibration curve derived by the addition of known amounts of the analytes of interest. Concentrations were calculated using linear regression. When necessary, the specimens were diluted to bring the observed concentration within the limits of the standard curve. Matrix matched controls were extracted and analyzed with each run.

Quantitative pseudoephedrine analysis
Stock standard solutions of pseudoephedrine for quantitation were prepared in methanol and stored at -15°C. Working standards of each were prepared by serial dilution of the stock standard solution and comprised four concentrations ranging from 0.010 mg/L to 0.50 mg/L. The extraction procedure for the samples, standards, and blank was performed using United Chemical Technology Clean Screen solid-phase extraction columns, which were installed on a Zymark RapidTrace System. No sample preparation was required for the blood and baby bottle contents; however, it was necessary to homogenize the liver specimen by blending 5 g of liver with 20 g of phosphate buffer (pH 6, 50mM). Samples were prepared by diluting 1.0 mL of each with 4.0 mL of sodium phosphate buffer (pH 6, 50mM) and 50 mL of phenylethanolamine internal standard (10 mg/L in methanol). The solid-phase extraction columns were sequentially rinsed with 3 mL of 2% ammonium hydroxide (NH₄OH) in ethyl acetate, 3 mL of methanol, 3 mL of deionized water, and 1 mL phosphate buffer (pH 6, 50mM). Samples (5 mL) were loaded onto the columns at a flow rate of 2.0 mL/min. The cartridges were then washed with 3 mL of deionized water, followed by a wash with 2 mL of 0.10M HCl and 3 mL of methanol. The columns were dried under vacuum for 1 min prior to elution with 3 mL of a 2% NH₄OH in ethyl acetate mixture. Approximately 2–3 drops of 1% concentrated HCl in methanol were added to the eluates before evaporating to dryness at 40°C under a stream of nitrogen. Extracts were derivatized with 50 mL MSTFA (n-methyl-n-trimethylsilyl-trifluoroacetamide, Pierce, Rockford, IL), overlayed with nitrogen,
and left to incubate at 75°C for 20 min. An additional 50 mL of MBTFA (n-methyl-bis-trifluoroacetamide, Pierce) was added to the extracts followed by overlay with nitrogen and incubation for 20 min at 75°C. Extracts were allowed to cool before transferring to autosampler vials for analysis on the GC–MS.

GC–MS analysis was performed using a Hewlett-Packard 6890 series GC system equipped with a 16.5-m × 0.25-mm i.d. × 0.30-mm film thickness capillary column connected to a Hewlett-Packard 5973 mass selective detector. Initial oven temperature was 65°C for 0.50 min followed by a temperature ramp of 15°C/min to 290°C. Data processing was performed with an HP Chemstation in the SIM mode monitoring m/z 73, 179, and 227 for both pseudoephedrine and phenylethanolamine internal standard (see Figure 1 for structure and spectrum of pseudoephedrine).

Quantitation was based on the preparation of a calibration curve derived by the addition of known amounts of pseudoephedrine. Concentrations were calculated using linear regression. When necessary, the specimens were diluted to bring the observed concentration within the limits of the standard curve. Matrix matched controls were extracted and analyzed with each run.

Results and Discussion

The results of the toxicological analysis are presented in Table I. Brompheniramine, dextromethorphan, and pseudoephedrine were qualitatively identified and successfully quantitated in postmortem blood and liver specimens, as well as in the baby bottle containing the pink-tinted fluid. None of the drugs were detected in the baby bottle containing the infant formula. Gastric contents were sent to the toxicology laboratory; however, the quantity was not sufficient for analysis.

Postmortem drug concentrations in the blood and liver specimens revealed elevated concentrations of brompheniramine, dextromethorphan, and pseudoephedrine. However, information regarding therapeutic and toxic data on serum and postmortem drug concentrations in infants and children is limited. Therapeutic blood concentrations of brompheniramine (2mg orally every 4 h for 7 days) are reported to be between 0.018 mg/L and 0.022 mg/L (3,4). In a case involving a fatal overdose of brompheniramine and several other drugs, concentrations of brompheniramine were reported to be 0.10 mg/L and 4.5 mg/kg in the blood and liver, respectively (5).

Dextromethorphan (30 mg) given orally every 4 h for 7 days resulted in therapeutic blood concentrations averaging from 0.0024 mg/L to 0.207 mg/L (3,6). Two reported fatalities in adults yielded dextromethorphan concentrations of 3.3–9.5 mg/L in blood and 31–230 mg/kg in the liver (3,7). Nine adults who overdosed on a combination of dextromethorphan and zizeprol exhibited postmortem blood dextromethorphan levels of 1.1–18 mg/L (3,8). Therapeutic blood concentrations of 360 mg of pseudoephedrine administered daily for 14 days averaged between 0.50 mg/L and 0.64 mg/L (3). In one report, a two-year-old child believed to have ingested a large amount of pseudoephedrine tablets had a postmortem blood level of 66.0 mg/L (3).

Another fatal overdose demonstrated a pseudoephedrine concentration of 19.0 mg/L in the blood and 33.0 mg/kg in the liver (3,9). Although there are limitations in interpreting postmortem drug levels in the blood, especially in the context of limited data on infants and young children, the values in this report are elevated and definitely confirm that multiple substances were present in the infant's body at the time of death.

Clearly, OTC cough and cold medications are not administered without risk. In this particular case, it is uncertain which OTC medication containing brompheniramine, dextromethorphan, and pseudoephedrine was administered to the child as none of the medications sent to the Medical Examiner Department contained those three ingredients. However, it is obvious that the caregivers did not follow the dosing guidelines on the medication package. For a 1–3 month-old infant, the recommended dose of an OTC medication containing these drugs is ¼ dropperful (¼ mL) QID containing 0.25 mg brompheniramine, 1 mg of dextromethorphan, and 3.75 mg of pseudo-

![Figure 1. Structure of pseudoephedrine (A); proposed structure for pseudoephedrine derivatized with MSTFA and MBTFA (B); and mass spectrum and fragment ions of pseudoephedrine derivatized with MSTFA and MBTFA (note that m/z 333 is not present)](image)

### Table 1. Toxicology Results

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Brompheniramine</th>
<th>Dextromethorphan</th>
<th>Pseudoephedrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.40 mg/L</td>
<td>0.50 mg/L</td>
<td>14.4 mg/L</td>
</tr>
<tr>
<td>Liver</td>
<td>0.16 mg/kg</td>
<td>0.57 mg/kg</td>
<td>16 mg/kg</td>
</tr>
<tr>
<td>Bottle (white)</td>
<td>ND*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Bottle (pink)</td>
<td>1.4 mg total</td>
<td>9.4 mg total</td>
<td>40 mg total</td>
</tr>
</tbody>
</table>

* ND, not detected.
ephedrine (10). The amount of these drugs remaining in the baby bottle far exceeds the recommended dosage for each of these drugs. Total quantities of brompheniramine, dextromethorphan, and pseudoephedrine remaining in the bottle were 1.4 mg, 9.4 mg, and 40 mg, respectively. The caregivers must have misunderstood the recommended dose, used an incorrect measuring device, or neglected to read the instructions on the medication package. It is also possible that the caregivers intentionally gave the infant a supratherapeutic dose in an effort to cause sedation.

This case underscores the need for educating parents and caregivers that administering OTC medications to infants and young children can be hazardous and that recommended doses must not be exceeded without a physician's authorization. Given the age of the infant, the autopsy results, and the finding of elevated levels of brompheniramine, dextromethorphan, and pseudoephedrine, other diagnosis such as sudden infant death syndrome are unlikely. Instead, the cause of death for this two-month-old infant was listed as multiple drug intoxication (brompheniramine, dextromethorphan, and pseudoephedrine).

References