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CASE REPORT

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Possible Role of Pseudoephedrine and Other Over-the-Counter Cold Medications in the Deaths of Very Young Children

ABSTRACT: The Philadelphia Medical Examiners Office has reported a series of 15 deaths between February 1999 and June 2005 of infants and toddlers 16 months and younger in which drugs commonly found in over-the-counter (OTC) cold medications were present. A total of 10 different drugs were detected: pseudoephedrine, dextromethorphan, acetaminophen, brompheniramine, carbinoxamine, chlorpheniramine, ethanol, doxylamine and the anticonvulsants, phenobarbital, and phenytoin. The drugs were confirmed and quantified by gas chromatography (GC)-mass spectrometry, with the exception of ethanol, which was analyzed by headspace GC and of phenobarbital and phenytoin that were quantified by GC with a nitrogen phosphorus detector. The most predominant drug was pseudoephedrine, which was found in all of the cases (blood concentration, $n = 14$, range = 0.10–17.0 mg/L, mean = 3.34 mg/L) and was the sole drug detected in three cases. Acetaminophen was detected in blood from each of the five cases with sufficient sample. Other drugs (with frequency of detection) were dextromethorphan (five cases), carbinoxamine (four cases), chlorpheniramine (two cases) and brompheniramine, doxylamine, and ethanol (one case each). In the majority of the cases, toxicity from drugs found in easily available OTC medications was listed either as the direct cause of death or as a contributory factor. The manner of death was determined to be natural in only two of the cases. This postmortem study supports previous evidence that the administration of OTC cold medications to infants may, under some circumstances, be an unsafe practice and in some cases may even be fatal. The treating physicians and the general public need to be made more aware of the dangers of using OTC cold medications to treat very young children so that these types of tragedies might be avoided.

KEYWORDS: forensic science, forensic toxicology, over-the-counter cold medications, pseudoephedrine, infant deaths, pediatric toxicology, postmortem toxicology

The Philadelphia Medical Examiners Office is a metropolitan facility that provides autopsy and toxicology services for Philadelphia County having a population of *c*. 1.5 million. This encompasses the central city of Philadelphia as well as its suburbs and so comprises a diversified demographic area. In each of the 15 cases presented, a young child was given over-the-counter (OTC) cold medication, presumably to treat or prevent symptoms from a cold or other respiratory condition.

We searched our in-house database for cases of young children in which pseudoephedrine and other drugs found in OTC cold medications had been reported. Cases from 1999 to 2002 were stored in the Inquest system database. Cases from 2003 to 2005 were stored in the CME system database.

Materials and Methods

Specimens were taken during autopsies performed between February 1999 and June 2005. When documented at autopsy, the source of blood specimens is included in Table 1. Fluoride-preserved blood was the preferential sample and was taken from the cardiac area. Fluid off tissue was obtained by freezing the tissue and then removing the liquid present after thawing. Two milliliters of blood, two grams of homogenized tissue, or 2 mL of fluid taken off tissue-containing pseudoephedrine, doxylamine, carbinoxamine, dextromethorphan, chlorpheniramine, and/or brompheniramine are extracted by solid-phase extraction using CSDAU303 columns and a modified procedure from United Chemical Technologies Inc. (UCT) for basic drugs (1). Eluates are derivatized using acetic anhydride, followed by gas chromatography-mass spectrometry (GC-MS) analysis (2). Pseudoephedrine and ephedrine are not separated in this method and results are reported as pseudoephedrine.

Specimens containing acetaminophen are extracted with a liquid–liquid procedure using 1 mL of blood or 1 mL of fluid (in-house SOP for confirmation of acetaminophen by GC-MS). Samples are reconstituted in acetonitrile and derivatized with acetic anhydride before analysis by GC-MS (2).

GC-MS analysis is performed with an HP 5890 GC with a 7673 autosampler and a 5971 MS or HP 6890 GC with a 7693 autosampler and 5973 MS. Chromatography is accomplished with an HP-5MS capillary column (Agilent Technologies).

Ethanol analysis is performed by headspace GC (G. Machato, personal communication). One milliliter of sample and 1 mL of internal standard (400 mg% *n*-propanol) are mixed in a 20 mL headspace GC vial. The equipment used is an HP 7694 headspace sampler coupled to an HP 5890 GC with a flame ionization detector, RTX-1 column, and an oven temperature at 40°C.

Two milliliters of blood specimens containing phenobarbital or phenytoin is extracted using a liquid–liquid procedure. Analysis is

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performed using an HP 5890 GC with an nitrogen phosphorous detector (GC-NPD; in-house procedure for confirmation of phenobarbital and phenytoin by GC-NPD).

Results

Table 1 summarizes the toxicology results according to age and gender of the 15 deceased children. The group was comprised of 12 males and three females ranging in age from 1 to 16 months. Eight of the 15 young children were born prematurely.

Pseudoephedrine was the predominant drug detected and was present in the blood or in the tissue of all of the cases. It was the only drug detected in three of the 15 cases. Pseudoephedrine blood concentration range ($n = 14$) was 0.10–17.0 mg/L with a mean of 3.34 mg/L and a median of 0.98 mg/L. The medications administered to the infants are listed in Table 1. Documentation is incomplete with listings in only four cases (cases 3, 8, 10, and 14). Even there, as many of the OTC medications have very similar names, the exact ingredients are not certain. However, OTC cold medications are known to contain pseudoephedrine and not ephedrine and so no attempt was made to separate them in the analyses of the cases.

Acetaminophen was present in the blood from each of the five cases that had sufficient volume to analyze. In four of the five cases, blood concentrations were within the therapeutic range (< 20 mg/L). In one instance, case 15, the acetaminophen clearly exceeded therapeutic levels.

Other commonly found constituents of OTC cold medications were also detected. Dextromethorphan was present in the blood in five of the cases. Carbinoxamine was present in low amounts in four of the cases; chlorpheniramine in two cases; and brompheniramine, doxylamine, and ethanol in one case each.

Case histories indicate that phenytoin was administered at the emergency room in an attempt to control seizures in case 2 and that phenobarbital had previously been prescribed in case 14.

Discussion

In eight of the 15 cases, (cases 3, 4, 9, 10, 11, 12, 14, and 15), drug involvement was determined to be either the cause of death or a contributing factor with pseudoephederine as the predominant drug. The cause of death for cases 1 was listed as undetermined and case 2 as pneumonia. However, both cases had extremely high pseudoephedrine blood concentrations: 17.0 and 9.6 mg/L, respectively. So it is probable that pseudoephedrine intoxication played a significant role in these infant deaths as well.

In cases 5, 6, and 7, the extent of drug involvement was unclear. The cause of death was listed as sudden unexplained infant death (SUID) or undetermined but contribution from drugs cannot be totally ruled out. In case 5, only liver tissue was available for testing, thus complicating the interpretation of the drug level.

Only in cases 8 and 13 was it determined that drugs were neither the cause of death nor a contributing factor, and that the manner of death was natural. In case 8, cosleeping with an adult was listed as a significant condition and in case 13 the cause of death was myocarditis.

It is apparent from these 15 cases that there is inconsistency in correlating the cause of death with pseudoephedrine concentrations. For example, cases 1 and 2 had the highest pseudoephedrine blood concentrations. In case 1, pseudoehedrine was not listed as the cause of death but was referred to in the final autopsy diagnosis as part of an amended toxicology report. In case 2, no mention was actually made of pseudoephedrine involvement. Both of these cases were from 1999 and were received *c*. 3 weeks apart. At that time, it was the policy of the laboratory to report pseudoephedrine only as present without quantifying. At the request of the medical examiner, the pseudoephedrine concentration was later determined for both. However, in case 2, an amended toxicology report was never generated and so the pseudoephedrine blood concentration was never noted as part of the autopsy report. In contrast, for cases received more than 2 years later, pseudoephedrine toxicity was ruled as the cause of death for cases 3 and 9 even though the concentrations were much lower than in the first two cases. It would appear that the medical examiners were becoming more aware of the possibility of pseudoephedrine toxicity. This is important because a significant number of the infant deaths are unexplained and, as can be seen in Table 1, oftentimes are listed as SUIDs. The possible involvement of pseudoephedrine should not be ignored in these types of sudden and unexplained deaths as the potential for pseudoephedrine and other sympathomimetic amines to cause palpitations, tachycardia, and cardiac arrhythmias has been documented (3).

The effect of postmortem distribution of pseudoephedrine has not been extensively studied but needs to be considered. In our study, all blood specimens collected were cardiac. As was the normal protocol, femoral blood was not provided for analysis. One study of over 300 adult postmortem cases found a mean heart/femoral blood ratio of 1.5 and a range of 0.9–2.2 (4). However, as there is no established therapeutic range for pseudephedrine in infants, redistribution data probably would be of limited value in further accessing the contribution of the drug to cause of death in our study.

Clinical studies have not demonstrated any benefit of pharmacological treatment in very young children (5). The American Academy of Pediatrics has previously issued a strong policy statement indicating that the use of narcotics including codeine and dextromethorphan as antitussives in children is contraindicated (6). The National Association of Medical Examiners Pediatric Toxicology Registry has reported postmortem concentrations of some drugs including pseudoephedrine and other OTC medications (7,8,9). Despite these warnings and as evidenced in our study and in other publications, the administration and subsequent toxicity of OTC medications in young children still exist. One report documented the cases of three young children, including the fatality of a 9-month-old boy whose pseudoephedrine postmortem blood level was 10.0 mg/L (10). Another, more recent report detailed a series of 10 infant deaths in which a majority of the deaths were related to toxicity from the OTC cold medications either directly or as a contributory factor (11). A third publication documented the fatality of a 2-month-old infant with extremely high levels of pseudoephedrine, brompheniramine, and dextromethorphan (12). Yet an additional report was made summarizing elevated pseudoephedrine concentrations in four pediatric cases (W.A. Dunn, personal communication).

Toxicology results from our cases support recent reports that the administration of OTC cold medication to infants continues to present a serious health hazard. Even though OTC bottles are required to include explicit instructions and warnings regarding dosage and age of the children being treated, our own direct contact with caregivers has found that confusion often exists on their part as to the appropriateness of administering these medications. This may be explained partially by the large number of medications available and by the similarity of the names of many medications (13). In most instances, it is impossible to know whether the caregiver either did not read or did not understand the warnings on the medication labels, or whether an improper dose was

TABLE 1—*Case histories.*

No.	Age/Gender	Drugs	Specimen*	Concentration†	Cause of Death/Manner of Death/Comments	History
1	2/M	Pseudoephedrine Pseudoephedrine Pseudoephedrine Dextromethorphan Dextromethorphan Dextromethorphan Carbinoxamine Carbinoxamine	Blood Liver Brain Blood Liver Brain Blood Liver	17.0 7.4 4.2 1.2 0.080 0.070 Present Present	Undetermined/ undetermined/very high pseudoephedrine levels detected	Full-term infant found unresponsive in baby seat by mother. One week history of cough, congestion, fever, diarrhea, and poor feeding. Evidence of past femur fracture. Infant previously in protective care and returned to mother 2 days before death. Autopsy finding significant for dehydration and microvescular hepatic steatosis
2	3/F	Pseudoephedrine Dextromethorphan Phenytoin	Blood Blood Blood	9.6 0.17 Present	Pneumonia/natural/very high pseudoephedrine concentration detected	Infant born 3 weeks premature. Brought to ER after a 3-day history of cough. Started on Viaxin previous day by pediatrician. At ER, child was found to be febrile with tachycardia and hypotension and phenytoin was given. Parents admitted to giving infant medication prescribed for older sibling. Autopsy significant for hepatic steatosis
3	3/M	Pseudoephedrine Pseudoephedrine Acetaminophen	Blood Liver Blood	1.6 1.1 <20.0	Sudden death associated with pseudoephedrine toxicity/undetermined	Infant born after 8-month gestation found dead in crib. Had cold-like symptoms. Reportedly given OTC Tylenol and Flu for the last 36 h. Autopsy unremarkable
4	5/F	Pseudoephedrine Brompheniramine	Cardiac blood Cardiac blood	6.4 0.34	Congenital heart disease/ undetermined/drug intoxication a contributing factor	Infant born after 32-week gestation found unresponsive at home with small amount of vomit in mouth. Caregivers gave no history of recent illness or medications. Autopsy significant for multiple heart defects: enlarged heart, double outlet left ventricle with subaortic ventricular septal defect and subpulmonic stenosis
5	4/M	Pseudoephedrine	Fluid off liver	0.36	SUID/natural	Full-term infant found unresponsive at home. Was in asystole and apenic upon arrival at hospital. Unable to resuscitate. Autopsy was unremarkable
6	2/M	Pseudoephedrine Dextromethorphan	Fluoridated blood Fluoridated blood	0.23 <0.05	Undetermined/ undetermined	Premature infant born after 27-week gestation found unresponsive in bed at home. Spent over 2 months in hospital after birth with a history of gastric reflux disease and breathing difficulties. Discharged 8 days before death. Current medications consisted of multivitamins and Metoclopramide. Autopsy significant for mild acute anoxic encephalopathy with no evidence of traumatic brain injury
7	4/M	Pseudoephedrine	Fluoridated blood	0.22	SUID/undetermined	Premature infant born after 34 weeks found unresponsive in crib at home. There was admission to giving medication but the symptoms prompting this were not specified. Autopsy was unremarkable
8	2/M	Pseudoephedrine Carbinoxamine	Fluoridated blood Fluoridated blood	0.30 <0.05	SUID/natural/overlie by cosleeping a contributing factor	Full-term infant found unresponsive in the same bed with parents. History of cough, cold, and wheezing 2 weeks before death and was prescribed antibiotics and Tylenol. Carbaxefed DM RF Oral Drops found at scene. Autopsy significant for acute anoxic encephalopathy
9	6/M	Pseudoephedrine Acetaminophen	Fluoridated blood Fluoridated blood	1.6 <10	Pseudoephedrine toxicity/ undetermined	Infant born after 34-week gestation. Spent 10 days in hospital after birth. Found face down with vomit on face. Mother reported infant having high fever in morning and admitted to administering antipyretics, fan therapy, and cool baths. Autopsy significant for adrenal hemorrhage and congenital asplenia
10	1/M	Pseudoephedrine Acetaminophen	Fluoridated blood Cardiac blood	0.34 <10	SUID/undetermined/ acute anoxic encephalomyopath and pseudoephedrine ingestion contributing factors	Full-term infant found unresponsive and face down in bassinet. Mother admitted to giving infant one-half dropper of Tylenol Plus to alleviate wheezing. OTC Concentrated Infant Drops Plus Cold retrieved at scene. Autopsy unremarkable except for anoxic encephalopathy
11	6/M	Pseudoephedrine	Fluoridated blood	0.44	Acute anoxic encephalopathy/ undetermined/ pseudoephederine in blood a contributing factor	Premature infant born after 27 weeks with heart defect that required surgical intervention. Found face down, rigid, apneic, and cold in bassinet by medics. Infant spent the first 3 months in hospital. Treated *c*. 1 month before death for esophageal reflux. Parents admitted to administering medication but symptoms that prompted treatment were not specified. Autopsy significant for acute anoxic encephalopathy
12	16/M	Pseudoephedrine Acetaminophen Chlorpheniramine Dextromethorphan Ethanol Ethanol Ethanol	Fluoridated blood Cardiac blood Fluoridated blood Fluoridated blood Fluoridated blood Fluid off liver Gastric contents	0.96 <10 0.069 0.050 0.034 0.023 1100	Anoxic encephalopathy/ undetermined/drug intoxication a contributing factor	Infant previously had been taken to emergency room with diarrhea, vomiting, and fever, where he was given Pedialyte and breathing treatment and discharged. Upon arrival at home, Medics found family member giving the infant CPR. Autopsy revealed anoxic encephalopathy
13	15/F	Pseudoephedrine	Blood	0.10	Myocarditis/natural	

TABLE 1— *Continued.*

No.	Age/Gender	Drugs	Specimen*	Concentration†	Cause of Death/Manner of Death/Comments	History
						Infant had been vomiting at daycare center all day. Mother transported infant to hospital and baby treated for dehydration. Baby died at hospital short time later. Autopsy revealed myocarditis
14	4/M	Pseudoephedrine Chlorpheniramine Carbinoxamine Phenobarbital	Cardiac blood Cardiac blood Cardiac blood Cardiac blood	1.0 Trace Trace < 50	Acute anoxic encephalopathy/ undetermined/drug poisoning a contributing factor	Full-term infant found unresponsive after afternoon nap. Previous hospital admission for pneumonia and brain bleed. Current medications included Phenobarbital. CarbaxefedDM RF Oral Drops and BromaxefedDM RF Syrup were found at scene. Autopsy revealed acute anoxic encephalopathy
15	3/M	Pseudoephedrine Pseudoephedrine Acetaminophen Dextromethorphan Dextromethorphan Doxlyamine Doxylamine	Fluoridated blood Gastric contents Fluoridated blood Cardiac blood Gastric contents Fluoridated blood Gastric contents	7.1 120 190 0.39 40 1.0 13	Drug poisoning/ undetermined	Premature infant born after 34 weeks found face down and lifeless when checked in the morning. No history of recent cough, cold, or fever. Parents denied administering any medication. History of Thrush and diaper rash, which was treated with oral and topical Nystatin. Autopsy revealed acute anoxic encephalopathy. Postmortem skeletal survey reveals a left tibial fracture

*Specimen information noted as documented during autopsy. Normal protocol was collection of blood from the cardiac area only.
†Blood concentrations = mg/L, liver and brain concentrations = mg/kg, ethanol blood concentrations = g%, gastric contents = mg/L.
SUID, sudden unexplained infant death.

given intentionally to ensure sedation. Nevertheless, it is disturbing that the case histories presented here and elsewhere would indicate that the caregivers were not heeding the manufacturer's clearly stated warnings.

Further documentation is provided here of deaths of 15 very young children to whom OTC cold medications were administered. Drug levels in blood and other tissues are reported to supplement the relatively small amount of data available in the literature for these types of cases, many in which the cause of death is unexplained. Recently, many states have instituted laws restricting access to OTC pseudoephedrine. Although this is being done primarily to control the availability of the drug as a precursor for synthesis of methamphetamine, hopefully, it will also have the added benefit of reducing access and use by caregivers of infants as well. In any case, additional, strong emphasis needs to be placed on the necessity for the continuing widespread education of both medical personnel and caregivers, warning them of the dangers in the prescribing and administering of OTC medication to infants and young children.

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