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Fatal Diphenhydramine Intoxication in Infants*†

ABSTRACT: Diphenhydramine is an antihistamine available in numerous over-the-counter preparations. Often used for its sedative effects in adults, it can cause paradoxical central nervous system stimulation in children, with effects ranging from excitation to seizures and death.

Reports of fatal intoxications in young children are rare. We present five cases of fatal intoxication in infants 6, 8, 9, 12, and 12 weeks old. Postmortem blood diphenhydramine levels in the cases were 1.6, 1.5, 1.6, 1.1 and 1.1 mg/L, respectively. Anatomic findings in each case were normal. In one case the child's father admitted giving the infant diphenhydramine in an attempt to induce the infant to sleep; in another case, a daycare provider admitted putting diphenhydramine in a baby bottle. Two cases remain unsolved; one case remains under investigation.

The postmortem drug levels in these cases are lower than seen in adult fatalities. We review the literature on diphenhydramine toxicity, particularly as it pertains to small children, and discuss the rationale for treating these cases as fatal intoxications.

KEYWORDS: forensic science, diphenhydramine, fatal intoxication, infant

Antihistamines are among the most widely used medications in the world (1). Antihistamines are available worldwide, and most do not require a prescription (2).

Diphenhydramine is an antihistamine, first introduced in 1946 (3–5). It is a member of the ethanolamine class of H_1-blocking antihistamines (6). In addition to being known for its effect as an antihistamine, diphenhydramine is also marketed for its sedating and antiemetic properties. It remains widely utilized for its antihistamine activity (4), despite subsequent development of newer, less sedating antihistamines.

The success of H_1-blocking antihistamines in treating rhinorrhea and sinus congestion has made them ubiquitous remedies for allergic rhinitis and the common cold (7). Diphenhydramine preparations are also marketed as nighttime sleep aids, antitussives, and topical preparations for treatment of insect bites/stings and contact dermatitis (8).

Diphenhydramine is identified in a significant number (4%) of all intoxications, fatal and nonfatal, either alone or combined with other drugs or alcohol (9). It is responsible for a small but significant number of fatal, suicidal drug intoxications in adults and teenagers each year (10).

The toxicity of antihistamines in children has been known for five decades. Nonetheless, reported fatalities in children are exceedingly rare, with case reports in predominantly older medical literature (11–14). Only one of four previous reports in the English literature involved an infant (12). In this paper, we present five cases which we believe represent fatal diphenhydramine intoxications in young infants (12 weeks old or younger). By definition, in our cases the infants could not have ingested the drug themselves, but had to have been given the medication by another person or persons. Nonetheless, in only two of our five cases did any of the caretakers admit to having given the child any medication.

We present a review of the relevant literature, focusing on the effects of diphenhydramine in children and how these effects differ from those in adults.

Case 1

A 6-week-old female infant died in a referring county. Gross autopsy demonstrated a well-nourished appearing girl weighing 3.6 kg, without natural diseases or injuries. Microscopic examination was remarkable only for pulmonary congestion. After toxicologic testing demonstrated a postmortem blood diphenhydramine concentration of 1.6 mg/L, the cause and manner of death were listed by the pathologist as "acute toxic concentration of diphenhydramine" and "undetermined," respectively. No law enforcement follow-up occurred.

Case 2

An 8-week-old female infant, healthy except for a "slight cold," had been in the care of a foster mother for four days. She was found "not breathing" by the foster mother's adult daughter while the foster mother was at church. The infant was taken to the emergency room and pronounced dead shortly thereafter. Gross autopsy demonstrated a 4.5 kg girl without natural diseases or injuries, and microscopic examination was noncontributory. The case was initially signed out as sudden infant death syndrome (SIDS), but the cause and manner of death were amended to "diphenhydramine intoxication" and "accident," respectively, after postmortem toxico-

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logic testing demonstrated a blood diphenhydramine concentration of 1.5 mg/L. The police were unable to determine who administered the drug.

Case 3

A healthy 12-week-old male infant was at a daycare provider's residence when he was found unresponsive after 15 min in a reclining bouncer. He was noted to be cool and asystolic in the emergency room before death was pronounced. Gross autopsy demonstrated a 7.2 kg boy without natural diseases or injuries. Scene investigation, radiographs, postmortem cultures, vitreous electrolytes, microscopic examination, and metabolic screen were all negative or noncontributory. After toxicologic testing demonstrated a postmortem blood diphenhydramine concentration of 1.1 mg/L, the cause and manner of death were certified as "diphenhydramine intoxication" and "homicide," respectively. All parties denied ever giving the child medication, and the daycare provider retained counsel and initially refused a search of her home. The case remains under active investigation.

Case 4

A healthy 9-week-old male infant was found unresponsive about 25 min after his mother laid him down. He was taken to the hospital by car where he was pronounced dead. Gross autopsy demonstrated a 5.4 kg boy without natural diseases or injuries. Radiographs, postmortem cultures, and microscopic examination were negative or noncontributory. The parents initially denied any medication use. After toxicologic testing demonstrated a postmortem blood diphenhydramine concentration of 1.6 mg/L, the father subsequently admitted to giving the child 2½ sleeping pills, each of which contained 25 mg of diphenhydramine. The father had wanted the child to stop crying and sleep. The cause and manner of death were certified as "acute diphenhydramine intoxication" and "homicide," respectively.

Case 5

A healthy 12-week-old female infant was found unresponsive at a daycare facility by the daycare center owner. The child was transported to a hospital, but died despite resuscitative efforts.

The daycare center owner initially reported to police that she had fed the baby with the mother's bottled breast milk, then put the baby down in her playpen. Approximately 10 min later the child was found not breathing, and both her nose and mouth contained "formula."

Autopsy demonstrated a 7.3 kg, normally developed infant free of injuries. Cultures, microscopic examination, and metabolic screening were all negative, and full body radiographs were unremarkable.

Though initially pended and believed to be SIDS, the cause of death was certified as "diphenhydramine intoxication" based on a postmortem blood diphenhydramine concentration of 1.1 mg/L. Trace quantities of desmethyldiphenhydramine were also detected. The manner of death was certified as "homicide."

The daycare center owner admitted to giving the child diphenhydramine. The bottle prepared by—and used by—the daycare provider to feed the child tested positive for diphenhydramine, despite having been cleaned and dried prior to its being seized by police. When presented to a grand jury, an indictment was returned for manslaughter and aggravated child abuse for administering diphenhydramine "without lawful justification."

Results

Toxicologic testing—including drug screening and screening for blood volatiles—was performed in each case. Postmortem diphenhydramine blood concentrations were measured in each case. The results are provided in Table 1. Except for desmethyldiphenhydramine as noted in Case 5, no other drugs, volatiles, or other substances were detected in any case.

Discussion

Diphenhydramine blocks the H_1 receptor (7,15). Stimulation of H_1 receptors, which are found throughout the body, causes vasodilation and contraction of smooth muscles (3,6,8,16). Diphenhydramine does not affect H_2 receptors, which when stimulated effect secretion of hydrochloric acid in the stomach (6,8,16). Even at recommended doses, some users of diphenhydramine may experience somnolence, diminished alertness, and slowed reaction time (1).

Diphenhydramine reaches maximum blood concentration in about 2 h (16), with a duration of action of 4 to 6 h (2). Pharmacologic effects may be seen within 15–30 min of ingestion (8,17). It is readily and completely absorbed from the gastrointestinal tract, and rapidly leaves the bloodstream to localize in various tissues (18). A single 50 mg oral dose of diphenhydramine in healthy young adults produced average peak blood levels of 0.066 mg/L (19), and a single 100 mg oral dose of diphenhydramine in young adults produced peak plasma levels of 0.081 to 0.159 mg/L (20). The effective blood diphenhydramine concentration for antihistaminic effect is 0.025 mg/L and for drowsiness is 0.030–0.040 mg/L; mental impairment begins at $>$0.060 mg/L (16).

In the only study specifically addressing the pharmacokinetics and pharmacodynamics of diphenhydramine in children, Simons et al. administered 1.25 mg/kg oral diphenhydramine to elderly adults (mean age 69.4 $\pm$ 4.3 years), young adults (mean age 31.5 $\pm$ 10.4 years), and children (mean age 8.9 $\pm$ 1.7 years and mean weight 31.6 $\pm$ 6.8 kg). Mean peak blood diphenhydramine levels were 0.188, 0.133, and 0.082 mg/L, respectively, achieved in 1.7, 1.7, and 1.3 h, respectively. Mean serum elimination half-life values were 13.5, 9.2, and 5.4 h, respectively. While 12 of the 14 adults experienced sedation, none of the seven children did. Sedation in adults correlated with peak serum diphenhydramine concentrations (15).

In adults, impaired consciousness is the most common symptom of diphenhydramine overdose, followed by psychotic behavior and anxiety. Other symptoms include hallucinations, mydriasis, and tachycardia; rare symptoms include diplopia, respiratory insufficiency, and seizures. In a series of 29 diphenhydramine monoin-

TABLE 1—*Toxicological testing results.*

Case	Age (weeks)	Weight (kg)	Blood Diphenhydramine (mg/L)	Other Results (mg/kg or mg/L)
1	6	3.6	1.6	
2	8	4.5	1.5*	brain 1.7 liver 7.3
3	12	7.2	1.1	spleen 1.8 liver 5.5 kidney 3.6
4	9	5.4	1.6	urine 9.0 vitreous 0.7
5	12	7.3	1.1	

*Heart blood 1.5 mg/L, inferior vena cava blood 1.3 mg/L.

toxications in adults, only one of which was fatal, no correlation was found between plasma levels and extent or frequency of symptoms (9).

Acute poisoning often mimics anticholinergic poisoning (18), with hallucinations, excitment, ataxia, convulsions, flushed face, sinus tachycardia, urinary retention, dry mouth, fever, and prolonged QT interval (2). Central excitation can be striking in children, and not uncommonly results in convulsions, especially in infants (16). Such convulsions are often tonic-clonic, and can be exceedingly refractory to treatment (18).

The anticholinergic, stimulatory effects of diphenhydramine are not as appreciated as its sedating effect, but are responsible for many of its untoward consequences. Children are more susceptible than adults to the stimulatory effects of antihistamines (18).

Fatal diphenhydramine intoxication in any age group is rare: of 873 reported poisoning fatalities reported to U.S. poison control centers in 1999, only 28 involved antihistamines, two of which were monointoxication with diphenhydramine. None of 24 intoxication or poisoning deaths in children under 6 years old involved diphenhydramine (10). Similarly, despite greater than 11 000 pediatric (<6 years old) exposures to diphenhydramine reported to poison control centers in 1998, there were no deaths (21). No child deaths attributed to diphenhydramine toxicity were found in the National Association of Medical Examiners Pediatric Toxicology (PedTox) registry (22).

Nonetheless, the toxicity of antihistamines in children has been known for five decades. Davis and Hunt, in 1949, reported a case of a 2-year-old that ingested 474 mg of Benadryl. The child died with convulsions, coma, and hyperpyrexia 13 h later; an unknown amount of the ingested Benadryl had been removed by gastric lavage during supportive care (11).

Wyngaarden and Seevers, in 1951, reported fatal child diphenhydramine intoxications that included an infant and the previously reported case of Davis and Hunt. The former ingested an unknown amount and died 2 h later in convulsions. Also described were five cases of nonfatal diphenhydramine intoxication in children ranging from 1½ to 4 years old. These children ingested 150–250 to 700–800 mg diphenhydramine; three had convulsions, 1 had "excitation," and 1 had "epileptiform movements." The authors noted the "remarkable susceptibility of children to the convulsant action of antihistaminic agents," commenting that "the mortality rate in infants in whom convulsions develop is very high" and "the ability to withstand large overdoses appears to increase with age" (12).

Aaron, in 1953, reported a 31-month-old child who ingested an unknown quantity of diphenhydramine. Approximately 2 h later he became excitable and began having "fits;" he died approximately 4 h post-ingestion, with repeated convulsions (13).

Goetz et al., in 1990, reported a case of a 15-month-old, 15 kg boy who ingested an unknown amount of diphenhydramine and presented with fever and generalized seizures. Blood diphenhydramine concentration was 10 mg/L. He died seven days after ingestion (14).

Large doses of diphenhydramine are not required to elicit serious toxic effects in children. Reyes-Jacang and Wenzl, reviewing cases of antihistamine toxicity in children, reported a 34-month-old, 11.5 kg child who suffered ataxia, aphasia, and grand mal seizures after ingesting only 50 mg of diphenhydramine (17). Hestand and Teske described a 13-month-old, 10 kg male who ingested 100–150 mg diphenhydramine. He suffered major motor seizures and respiratory arrest with left bundle branch block, but recovered after supportive care (4).

Previous reports of fatal diphenhydramine intoxications have reported a minimum blood concentration of 5 mg/L, with a mean of 16 mg/L (5,23). Toxic diphenhydramine levels in children have been regarded as 0.5 to 1.5 mg/L, with lethality beginning at 5 mg/L (14). Filloux reported a case of a 9-year-old child with a serum diphenhydramine level of 1.4 mg/L (due to topical diphenhydramine administration for varicella)—this child was agitated, disoriented, and suffering visual and auditory hallucinations (24). Two similar cases were reported by Schunk and Svendsen, in which a 4-year-old with a blood diphenhydramine level of 1.5 mg/L presented with nonsensical speech, ataxia, and agitation; and a 5½-year-old with a blood diphenhydramine level of 0.96 mg/L presented with dysmetria and hallucinations (25). Two similar cases were reported by Huston et al., in which a 4-year-old with a blood diphenhydramine level of 2.4 mg/L presented with hallucinations, agitation, and fine tremor; and a 4-year-old with a blood diphenhydramine level of 2 mg/L presented with hallucinations, agitation, ataxia, and fine tremor (26).

Some postmortem redistribution of diphenhydramine occurs: in 32 cases, Dalpe-Scott et al. calculated an average central:peripheral blood ratio of 2.3 (range 0.8–21) (27). More recently, Levine et al. reviewed 44 postmortem cases in adults where diphenhydramine was detected but *not* considered to be the cause of death. Based on the blood and liver concentrations in these cases, they concluded that the "normal" postmortem blood and liver diphenhydramine concentrations may be regarded as <1.0 mg/L and <3.0 mg/kg, respectively. Toxicity may be considered where blood or liver concentrations exceed these levels and postmortem redistribution effects are accounted for (28).

The maximum recommended dosage of diphenhydramine for children 6–12 years old is 12.5–25 mg every 4–6 h, not to exceed 150 mg/24 h (8). For children under six years old, the medication should not be used without consulting a physician (29).

Children in general, and infants in particular, appear to suffer substantially more CNS stimulation (including seizures) than adults with supratherapeutic blood diphenhydramine levels. The ability to tolerate a supratherapeutic dose without untoward central nervous system stimulatory effects appears to increase with age. Based on our cases, as well as the known toxic effects of diphenhydramine in infants and children, we believe the lethal toxic threshold for diphenhydramine in infants is substantially lower than 5.0 mg/L. Given that a 1.25 mg/kg dose produces average blood levels in children of 0.082 mg/L (15), the levels seen in the cases we present are orders of magnitude larger, even when allowing for postmortem redistribution.

None of our cases had any other findings to suggest a cause of death. The argument could be made that these children died of sudden infant death syndrome (SIDS), and the high levels of diphenhydramine seen are coincident and noncontributory. We would find it difficult to accept the assertion that the children in our cases died of SIDS, and coincidentally had a known toxic level of a drug in their blood.

We share the opinion with others that routine, comprehensive toxicologic testing in cases of sudden and unexplained deaths in children (including infants) is warranted to accurately determine cause of death (7). Only thorough investigation is likely to distinguish between intentional and inadvertent overdose.

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