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CASE REPORT

Barry K. Logan,[1] *Ph.D., DABFT and Ann Marie Gordon, M.S.*[1]

Death of an Infant Involving Benzocaine

ABSTRACT: This report describes the death of a four-month-old Hispanic male which may be related to benzocaine toxicity. A toxicological evaluation revealed benzocaine at a concentration of 3.48 mg/L, and postmortem methemoglobin of 36% (normal 0.4–1.5). Methemoglobinemia is a complication of benzocaine toxicity. In light of the toxicology findings, the coroner investigated the source of the benzocaine and discovered that the child was treated with Zenith Goldline Allergen Ear Drops containing 0.25% w/v benzocaine and 5.4% w/v antipyrine. There was an admission by a caregiver that on the day prior to the child's death, he had been treated with three times the prescribed dose. Blood benzocaine concentrations in nine other unrelated cases were determined and concentrations ranged from <0.05–5.3 mg/L (mean 1.48 mg/L). Seven of the nine cases were positive for drugs of abuse, and one additional case was described as a known drug user. Methemoglobin in these benzocaine positive cases ranged from 6–69%; however, methemoglobin concentrations in postmortem cases are frequently elevated and should be interpreted with caution. The unknown significance of the benzocaine, and the circumstances of the case raise questions about the ultimate attribution of this death to SIDS.

KEYWORDS: forensic science, toxicology, benzocaine, pediatric toxicology

Benzocaine is a widely used local anesthetic found in many over-the-counter medications including teething gels, vaginal and hemorroidal creams, first aid ointments, throat lozenges and in prescription otic solutions for the temporary relief of ear pain. The benzocaine concentration of these preparations is from 6.3–20%. Benzocaine is a relatively safe local anesthetic but there are two recognized adverse reactions, allergic sensitization and methemoglobinemia, the latter is a rare occurrence (1,2). McKinney et al. (3) have reported a case of methemoglobinemia in a drug user induced by benzocaine adulterated street cocaine. Methemoglobin is hemoglobin with the iron oxidized to the ferric state (rather than the reduced ferrous state) and methemoglobin is incapable of reversibly binding oxygen. Methemoglobinemia occurs when more than 1% of the heme iron is oxidized to the ferric form. Death from methemoglobinemia may result if medical intervention is delayed.

Benzocaine-induced methemoglobinemia is most often attributed to the topical application to the skin, mucous or pulmonary membranes. Benzocaine induced methemoglobinemia is frequently not described on the package inserts or the containers, although some references advise against using these products with children under the age of two years. The Physicians Desk Reference lists a perforated eardrum as a contraindication for the use of the otic solutions. Ingestion of oral benzocaine (as little as 1/4 teaspoon teething gel) and liberal application of benzocaine to denuded diaper rash areas have produced methemoglobinemia (4–6). Infants and the elderly are more susceptible because fetal hemoglobin is more susceptible to oxidation, and both groups have lower levels of reduced NADH-methemoglobin reductase (1,4,7). In a 1994 review, Rodriguez et al. (7) suggested that the incidence of methemoglobinemia may be under-reported due to the lack of knowledge of the condition in the general medical community.

Case History

A four-month-old Hispanic male was found unresponsive in bed, face down on a pillow. Emergency efforts to resuscitate the infant were unsuccessful. The family reported that the child had suffered "flu-like" symptoms and had recently developed a "raspy" cough. A peripheral blood sample could not be obtained due to the low mass if the infant, and a heart blood sample was sent to the Washington State Toxicology Laboratory for analysis. The pathologist determined the cause of death to be SIDS. Following the discovery of the elevated benzocaine concentrations, the coroner made further inquiries of the family regarding the use of products containing benzocaine. A prescription for "Zenith Goldline Allergan Ear Drops," 1.4% w/v benzocaine and 5.4% w/v antipyrine was being used to treat an ear infection. A caregiver admitted to administering three times the prescribed dose to the child on the day prior to his death.

Blood samples were screened by enzyme multiplied immunoassay technique (EMIT) for cocaine metabolite, opiates, PCP, benzodiazepines, amphetamines, and cannabinoids. Liquid-liquid partition extraction for basic drugs, and analysis by gas chromatography with mass spectrometric and nitrogen/phosphorus detection was performed using procedures described elsewhere (8).

The blood from the infant was found to be negative for ethanol and for drugs of abuse by EMIT. The basic drug screen showed the presence of benzocaine at a concentration of 3.48 mg/L and atropine at a concentration of 0.11 mg/L. Atropine was administered during unsuccessful attempts at resuscitation, and is not considered significant in the cause of death. Because of the potential for benzocaine-induced methemoglobinemia, the methemoglobin level was determined by co-oximetry and was found to be 36% (normal 0.4–1.5%).

[1] Washington State Toxicology Laboratory, Forensic Laboratory Services Bureau, Washington State Patrol, 2203 Airport Way S., Seattle, WA 98134.

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TABLE 1—*Benzocaine and methemoglobin concentrations in unrelated cases.*

Benzocaine mg/L	MetHb	Cause/Manner of Death	Other Drugs Identified (Blood Unless Otherwise Indicated)
<0.05	66.9%	Head Trauma/Traffic Accident	Blood: methamphetamine amphetamine, diazepam, Urine: cocaine, opiates, amphetamines
0.36	24.4%	Cardiac Arrythmia and Ethanol Intoxication/Accident	ethanol
0.39	42.9%	Alcohol & Methadone Intoxication/Accident	ethanol, methadone diphenhydramine
0.46	69.1%	Gunshot Wounds/Homicide	cocaine and metabolites
1.14	65%	Gunshot Wounds/Homicide	methamphetamine amphetamine
1.49	65.8%	Head Trauma/Homicide	Urine: cocaine metabolites
1.47	15.9%	Dehydration/Natural	cannabinoids
2.73	21.7%	Cardiac Arrythmia and Methamphetamine Intoxication/Accident	methamphetamine amphetamine diphenhydramine dextromethorphan
5.3	37.2%	Skull Fracture and Lacerated Liver/Homicide	none

The death was attributed to SIDS despite the elevated benzocaine concentration.

Discussion

Assessing the significance of the benzocaine concentration in this infant was difficult due to a paucity of reported concentrations in the literature. There is one report of benzocaine urine concentrations in a subject who ingested an overdose of benzocaine adulterated cocaine (3). The urine concentrations in that case were 3.8 mg/L; however, the authors did not indicate the time elapsed from the onset of symptoms to the urine collection. Blood benzocaine concentrations were not reported.

For comparative purposes, benzocaine concentrations were determined in unrelated cases where benzocaine was thought to be an incidental finding. These are reported in Table 1, and ranged from <0.05–5.3 mg/L (mean 1.48 mg/L, median 1.3 mg/L). The case with the highest concentration of benzocaine, 5.3 mg/L, was a victim of homicidal child abuse with skull fractures and lacerated liver. Four of the cases involving drugs of abuse came from the same county in Washington State. Local law enforcement sources in this county related that a group of local drug dealers were known to be cutting cocaine with benzocaine-based horse liniment obtained from a veterinary supplier. Benzocaine adulterated cocaine use has previously been reported resulting in methemoglobinemia (3).

Methemoglobin levels were determined in these cases, and were above the normal antemortem range of 0.4–2.5% in all cases. The significance of these postmortem methemoglobin concentrations is unclear because methemoglobinemia is a frequent postmortem artifact. Reay et al. (9) reported a wide range of methemoglobin concentrations (0.8–57%, mean 13.7%) determined by co-oximetry in postmortem blood from individuals expected to have normal antemortem methemoglobin levels. They concluded that postmortem methemoglobin concentrations were of limited value in assessing antemortem concentrations. For comparative purposes, methemoglobin concentrations were determined in an additional 25 random postmortem cases, all of which were negative (<5%) for carbon monoxide, or for drugs known to cause methemoglobinemia. The range was 2.0 to 67.7% methemoglobin (mean 21.2%, median 14.9%), confirming the observations of Reay et al. (9), and supporting the use of caution in interpreting postmortem methemoglobin results.

Benzocaine is available in many over-the-counter and prescription medications, including ointments, oral gels, sprays and ototic preparations. Package inserts from for benzocaine containing products that we examined have inconsistent warnings of methemoglobinemia as a complication of benzocaine use. Benzocaine (20% spray) was implicated in a study of 138 cases of acquired methemoglobinemia (10), resulting in methemoglobin concentrations of 19.1–60.1% (mean $43.8 \pm 15.1\%$), and the authors note that three one-second sprays with a 20% solution can deliver up to 600mg of benzocaine. No blood benzocaine concentrations were reported. Some package inserts and the Physicians Desk Reference do caution against use of some of these products in children under the age of two. A survey of 198 adverse reaction reports involving benzocaine (11) identified methemoglobinemia in 33% of cases, but noted that this may be under-reported as methemoglobin levels were likely not determined in all cases. None of these cases involved ototic preparations, and only two cases resulted in deaths.

The case reported here is suspicious for benzocaine-induced methemoglobinemia, due to the otherwise unremarkable history, the excessive benzocaine dosing, the significant concentrations of benzocaine relative to other benzocaine cases tested, and the known susceptibility of infants to methemoglobinemia due to the relative ease of oxidation of fetal hemoglobin. On the other hand, while the methemoglobin concentration of 36% is high, it must be interpreted with caution since postmortem methemoglobin can be artifactually elevated, and there are no reference data to assist with the interpretation of the blood benzocaine concentration in infants. SIDS is a diagnosis of exclusion, and is probably not an appropriate finding given the unanswered questions raised by this toxicological finding. In the absence of a reliable antemortem methemoglobin measurement, the cause of death should be considered undetermined.

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Additional information and reprint requests:
Barry K. Logan, Ph.D., DABFT
Washington State Toxicology Laboratory
Forensic Laboratory Services Bureau
Washington State Patrol
2203 Airport Way S, Suite 360
Seattle, WA 98134
E-mail: barry.logan@wsp.wa.gov