

Poison Control Center Management of Benzocaine Exposures

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BACKGROUND

Benzocaine is a topical anesthetic frequently used in healthcare facilities and in over-the-counter medications in concentrations up to 20%.¹ Benzocaine may induce methemoglobinemia, a condition that impairs the blood's ability to carry oxygen.² The optimal management of exposure to benzocaine remains unclear because serious toxicity is uncommon and may not be dose-related.^{1,3} In 2000, it was estimated that more than one million exposures to benzocaine, both therapeutic and unintentional, occur yearly in the US; yet fewer than 100 cases of benzocaine-induced methemoglobinemia have been reported in the medical literature over the last 50 years.^{1,4} Considerable under-reporting of cases probably exists, as patients with mild methemoglobinemia may have minimal symptoms or remain asymptomatic. Severe cases requiring treatment are evidently quite unusual.

Poison Control Centers (PCCs) are often consulted after exposure to benzocaine and make recommendations for home observation or for evaluation in a healthcare facility (HCF). The

experience of one of the investigators (JS) is that many PCCs recommend HCF observation for several hours following benzocaine ingestion to detect delayed development of methemoglobinemia. If benzocaine-induced methemoglobinemia truly is rare, then such conservative recommendations may be unwarranted in the majority of cases. In addition, patients may be subjected to unnecessary expenditures of time and money, as well as the potential risks of diagnostic medical interventions.

We sought to determine if a consensus exists among PCC recommendations for managing benzocaine exposures. We presented two hypothetical cases of pediatric benzocaine exposure to PCCs in the United States and Canada to find out what their recommendations would be in relation to several factors, including: the need for observation, where and for how long such observation should occur, the need for gastrointestinal decontamination, the methods of evaluating for methemoglobinemia, and the indications for treatment with methylene blue.

METHODS

A single investigator (SR) conducted a telephone survey of PCCs in the United States and Canada in February 2001. The list of PCCs was obtained from the American Association of Poison Control Centers (AAPCC) website (www.aapcc.org). Although Canadian PCCs are not members of the AAPCC, their contact information was obtained from the same website and their customary practices are similar to PCCs in the United States. Persons answering the general poison information line of each PCC were asked if they wished to voluntarily participate in the survey, and were given the option of having the investigator call back at a more convenient time or to have another PCC staff member voluntarily complete the survey instead. Participants were also informed that their responses would be recorded in an anonymous fashion. We chose to have the first available volunteer complete the survey whenever possible, rather than a PCC manager or medical director, as we felt this would better represent the actual recommendations received by members of the public with similar inquiries. The survey instrument (see

Table 1) consisted of management questions related to two hypothetical pediatric benzocaine exposures and asked whether that PCC had a written policy or protocol for management of benzocaine exposures. Descriptive statistics were used for reporting the results.

RESULTS

Sixty-two out of a total of 76 PCCs completed the survey, for a response rate of 82%. Results are presented in Table 2.

DISCUSSION

Survey respondents generally used the same reference, Poisindex[®], as their primary source of information in

managing benzocaine exposures, yet PCC recommendations varied considerably. Poisindex[®] states that the threshold toxic dose for benzocaine is 22-40 mg/kg.⁵ Many PCCs appeared to interpret this information conservatively, resulting in the median recommended threshold dose warranting observation or any interventions occurring at the low end of this range.

Almost 15% of PCCs did not give dose-dependent recommendations, and appeared to believe that significant methemoglobinemia is idiosyncratic or related to altered drug metabolism. Sub-clinical methemoglobinemia regularly occurs with therapeutic benzocaine use, while significant methemoglobinemia warranting treatment is rather uncommon.³ If benzocaine-induced methemoglobinemia were dose-

Table 1. Survey instrument for PCC benzocaine management

Scenario 1:

A mother finds her 2-year-old toddler eating the contents of a 10 mL tube of teething gel containing 10% benzocaine. The child is initially crying, but is easily consoled, and otherwise appears normal and is asymptomatic 10 minutes after exposure.

- 1) Do your recommendations depend on the estimated ingested dose?
 - a. (If Yes) What is your threshold dose for changing your recommendations?
- 2) Would you recommend any gastrointestinal decontamination for this child?
 - a. (If Yes) What type?
- 3) Does this patient require a period of observation?
 - a. For how long?
 - b. Should observation occur at home or in a healthcare facility?
 - c. (If Home) What could happen that would make you then recommend transfer to a healthcare facility?
 - d. (If HCF) What would you recommend occur at the healthcare facility?

Scenario 2:

Another 2-year-old ingested an over-the-counter product with 20% benzocaine 1 hour ago. He is reportedly asymptomatic, but the mother thinks his color is "a little funny".

- 1) Does abnormal coloration require the patient to be evaluated in a healthcare facility?
 - a. (If Yes) What should be done?
- 2) Does normal pulse oximetry effectively rule out methemoglobinemia?
- 3) What would the methemoglobin level have to be for you to recommend treatment in this asymptomatic child?
- 4) Is it possible to be cyanotic and have methemoglobinemia, but NOT need treatment?

Other Questions:

- 1) Does your Poison Control Center have a written policy or protocol regarding the management of benzocaine exposures?
 - a. (If Yes) Would you be willing to FAX us a copy of it?
- 2) What is the source of the data upon which your recommendations are based?

Table 2. Summary of PCC survey results regarding benzocaine management (n=62 unless otherwise indicated)

- Most recommendations (53/62=85%) depended on the **Estimated Ingested Dose**; the remaining nine centers commented that benzocaine-induced methemoglobinemia was idiosyncratic and/or related to alterations in cytochrome P450-mediated drug metabolism.
- The **Threshold Dose** for recommending observation or any interventions ranged from 5-40 mg/kg.
 - The median threshold dose for recommending observation was 22 mg/kg.
 - Nine of the centers (15%) recommended a lower threshold for patients \leq 1 yr old.
- **GI Decontamination** of asymptomatic patients was recommended by:
 - 23 PCCs (37%) for patients observed at home
 - 41 PCCs (66%) for non-cyanotic patients evaluated in HCFs
 - 40 PCCs (65%) for cyanotic patients evaluated in HCFs
- The recommended **Observation Period** ranged from 0.5 to 24 hours.
 - Most PCCs gave a range of hours (minimum to maximum number of hours).
 - The mean minimum observation period was 3.1 hours overall (median 2 hours).
 - The mean maximum observation period for HCF patients was 3.4 hours (median 4 hours).
- The most commonly recommended **Signs to Observe** for were:
 - Cyanosis (61=98% of PCCs made this recommendation)
 - Respiratory distress (47=76%)
 - Altered level of consciousness (41=66%)
 - Less commonly recommended signs to observe for include the ability to tolerate oral liquids (8=13%), gastrointestinal symptoms such as nausea or vomiting (8=13%), seizures (7=11%), and lethargy (3=5%). For each of the following one PCC recommended observation: anemia, ataxia, hypotension, tachycardia, Down's Syndrome, headache, and "any change".
- **Pulse Oximetry was recommended by 25 PCCs (40%) for asymptomatic non-cyanotic patients and by 32 PCCs (52%) for asymptomatic cyanotic patients. Of note, eight PCCs (13%) explicitly stated that pulse oximetry may be inaccurate with methemoglobinemia, and two PCCs (3%) stated that normal pulse oximetry rules out methemoglobinemia.**
- **Arterial Blood Gas** sampling was recommended by 29 PCCs (47%) for asymptomatic non-cyanotic patients and by 47 PCCs (76%) for asymptomatic cyanotic patients. Only 1 PCC suggested venous blood gas sampling as an alternative to arterial puncture.
- The recommended minimum **Methemoglobin Level Warranting Treatment** ranged from 10% (generally asymptomatic) to 70% (often lethal) with a mean level of 24% and a median level of 20%. Four PCC respondents (6.5%) did not recognize that a patient could be cyanotic with methemoglobinemia, yet not require treatment.
- Poisindex[®] was the most common data source (55=89%) used by PCCs for managing benzocaine exposures.
- 13 PCCs (21%) had a written protocol for managing benzocaine exposures and nine of these centers identified Poisindex[®] as their primary protocol reference.

dependent, one would expect to see it more frequently in the clinical setting, as the drug is used for several indications and in widely varying doses. It is therefore logical to infer that clinically-significant methemoglobinemia represents an idiosyncratic reaction. However, despite an extensive search of the medical literature, we were not able to locate any published human studies supporting this theory. Some animal data supports the hypothesis that methemoglobinemia is idiosyncratic. Eight sheep treated with 56 to 112 mg benzocaine had methemoglobin levels of $22.6 \pm 1.8\%$ within 20 minutes (responders), while four other sheep did not develop methemoglobinemia (non-responders).⁶

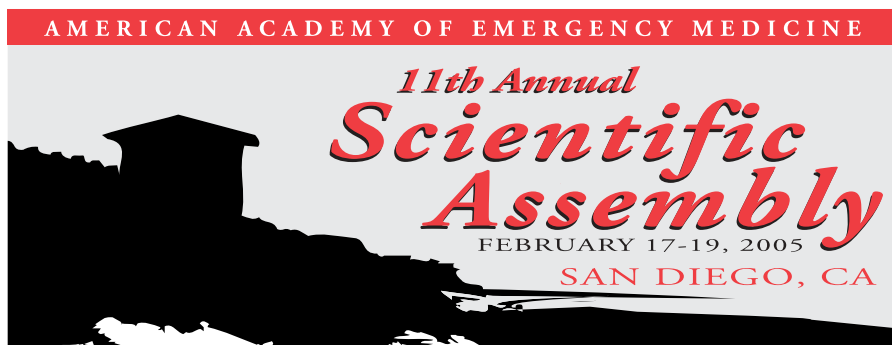
Since most pediatric benzocaine exposures result in little or no toxicity, our results are somewhat concerning. Many PCC recommendations would result in prolonged observation, gastrointestinal decontamination, HCF evaluation, and painful or potentially risky interventions (e.g. arterial blood gas sampling), without good supporting evidence of efficacy or necessity. Some outlying results among the recommendations received are of particular concern, including observation for up to 24 hours and not treating methemoglobinemia until it reaches 70%, a level that is often lethal. Although recommendations generally clustered around those provided by Poisindex[®], there is no firm consensus among American and Canadian PCCs in the management of pediatric benzocaine exposures. The only item on our survey that the great majority (>80%) of respondents agreed upon was that cyanosis was the primary physical sign to observe for among patients exposed to excessive benzocaine doses. Although our results apparently show some general consensus, they should not therefore be taken as the standard of care, as they have not been subject to any validation.

Research to determine the etiology and toxicokinetics of benzocaine-induced methemoglobinemia could be used to establish evidence-based recommendations for managing such exposures in the future. One potential method of investigation would be to administer benzocaine to subjects pre-treated with different cytochrome P450—or other metabolic enzyme—inhibitors. In vitro or animal studies may be necessary, since, as with all toxicologic research, volunteer human studies may be difficult or impossible to conduct in a safe and ethical manner.

Our study is limited by several factors. First, our survey does not necessarily reflect the responses that would be obtained in cases of actual benzocaine exposures. We attempted to mitigate this factor by obtaining responses from the first available person at each PCC whose normal duties would be to answer such queries from the public. Of note, some of the PCCs who opted not to respond to the survey stated that it is their policy not to answer questions relating to hypothetical toxic exposures. The effects of such non-responders are unclear; but given our 82% response rate, it is unlikely to alter the results to a great degree. Secondly, no attempt was made to detect any correlation between the PCC management recommendations and the PCC geographic location, primary specialty (e.g. pharmacist, nurse, physician, other) or amount of training of the respondent. We felt that the number of potential respondents was so low (maximum 76), that such sub-group analysis was unlikely to show any statistical or clinical significance.

Similarly varied results in PCC management recommendations have been reported previously regarding enteric-coated aspirin ingestions.⁷ The lack of clear consensus recommendations in both of these

surveys may stem from several causes. For one thing, clinical toxicology relies heavily on anecdotal case experience. It would not be ethical to conduct controlled, prospective human studies that produce significant toxicity among the subjects. Since case experience will vary widely



between practitioners, it is not surprising that their recommendations will also vary. We additionally suggest that the very nature of a telephone survey to determine PCC recommendations could artificially highlight any differences, when, in fact, clinical practice is more consistent.

CONCLUSION

Considerable variation exists among the recommendations given by PCCs in the United States and Canada regarding the management of pediatric benzocaine exposures. The general consensus among our survey respondents was that: 1) the need for observation or any interventions is related to the estimated ingested dose, 2) patients evaluated in a healthcare facility should receive some kind of gastrointestinal decontamination, 3) patients should be observed for several hours (between 2 to 4 hours), 4) the primary signs to observe for are cyanosis, respiratory distress, and altered level of consciousness, 5) arterial blood gas sampling should be obtained on cyanotic patients, even if asymptomatic, and 6) antidotal treatment with methylene blue should be given for methemoglobin levels at or above 20%.

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CaJEM PRO/CON

This is a forum for the discussion of controversial topics in emergency medicine. Views expressed in this series are those of the discussants and may not reflect those of the editors. We asked, "should the United States adopt a universal health care coverage system?"

Why the US Should Adopt a Universal Health Care Coverage Program

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There has been increasing interest in the development of universal health care coverage in the United States.¹⁻³ The most prominent of these calls has come from a recent Institute of Medicine (IOM) report calling for universal health care coverage in the United States by 2010.⁴ There are several key points made in this report that are clearly worth consideration. Over a series of five reports, the IOM Committee on Consequences of Uninsurance made the following conclusions:⁴

- The number of uninsured individuals under age 65 is large, growing, and has persisted even during periods of strong economic growth.
- Uninsured children and adults do not receive the care they need; they suffer from poorer health and development, and are more likely to die early than are those with coverage.
- Even one uninsured person in a family can put the financial stability and health of the whole family at risk.
- A community's high uninsured rate can adversely affect the overall health status of the community, its health care institutions and providers, and the access of its residents to certain services.
- The estimated value across the population in healthy years of life gained by providing health insurance