

Reported Adverse Event Cases of Methemoglobinemia Associated With Benzocaine Products

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Background: Methemoglobinemia (MHb) is characterized by abnormal levels of oxidized hemoglobin that cannot bind and transport oxygen. When induced by benzocaine anesthetic spray and other chemicals, it can result in cyanosis and life-threatening complications.

Methods: From 818439 adverse event reports received by the US Food and Drug Administration from November 1997 through March 2002, we extracted every report for use of a benzocaine product. We classified each case by product type (eg, spray, gel, or solution), by whether MHb was involved, and by the dose given.

Results: Among 198 reported adverse events of all types associated with benzocaine, 132 cases (66.7%) involved definite or probable MHb. The MHb cases included 107 serious adverse events (81.1%) and 2 deaths (1.5%). In

123 cases (93.2%), the product was a spray; in 2 cases (1.5%), a benzocaine-containing lozenge; and 1 case, a gel. In the 69 cases that specified a dose, 37 (53.6%) indicated that a single spray was applied (approximately the recommended amount).

Conclusions: Health professionals involved in endoscopy, intubation, bronchoscopy, or similar invasive procedures using benzocaine-containing sprays should know that (1) administration may cause MHb with potentially serious consequences, (2) identifying the reaction to benzocaine usually requires coximetry (although it can be implied by symptoms), and (3) treatment involves immediate intravenous administration of 1 to 2 mg/kg of methylene blue.

Arch Intern Med. 2004;164:1192-1196

METHEMOGLOBIN IS THE ferric (Fe⁺⁺⁺), or oxidized, form of hemoglobin. While in this oxidized state, hemoglobin cannot perform its most basic function of binding and transporting oxygen.¹ Normally accounting for about 1% of all circulating hemoglobin, methemoglobin is then reduced back to hemoglobin, mainly by the activity of the cytochrome-*b*₅-methemoglobinemia (MHb) reductase system.² Methemoglobinemia is defined as an abnormal elevation of methemoglobin levels and has 3 different etiologic categories³: (1) an autosomal dominant trait that causes production of abnormal hemoglobin, usually presenting as cyanosis at birth; (2) an autosomal recessive trait resulting in decreased activity of methemoglobin reductase, typically resulting in subclinical MHb; and (3) introduction of an external oxidizing agent,⁴ which overwhelms the reducing capacity of red blood cells (the most common cause of MHb). Some external oxi-

dizing chemicals are not meant for human consumption, such as naphthalene and paraquat. Other agents, however, are medicinal compounds. In particular, benzocaine, a commonly used local anesthetic, has been associated with cases of life-threatening MHb.

Benzocaine is available as prescription only or over the counter in a wide variety of products, such as gels for toothache, solutions for otitis, and suppositories for relief of hemorrhoidal symptoms.⁵ Recently reported cases of benzocaine-induced MHb have occurred in the hospital setting in connection with intubation, endoscopic, or bronchoscope procedures. Prior to these procedures, a spray dosage form is used to anesthetize the patient's oropharynx to suppress the gag reflex, theoretically making the procedure less complicated for the physician and more easily tolerated by the patient.

Methemoglobinemia presents a potential challenge to the physician in terms of clinical diagnosis because despite increasing methemoglobin levels, arterial

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blood gas or pulse oximetry readings can be near normal.⁴ Unless a physician is acutely aware of this, valuable time can be wasted before a direct measure of methemoglobin is obtained through cooximetry. The progression of symptoms correlates well with methemoglobin levels. As the methemoglobin level rises above 10% of total hemoglobin, cyanosis is usually present. This is followed by anxiety, fatigue, and tachycardia at levels between 20% and 50%. Finally, with methemoglobin concentrations of more than 50% to 70%, coma and death may occur.⁶ Treatment of severe MHB, when the patient is either symptomatic or has a methemoglobin level above 30%, involves intravenous administration of 1 to 2 mg/kg of methylene blue, which increases the reduction capacity of the protective enzyme systems for hemoglobin.⁷

Several case reports mention an estimated incidence of benzocaine-induced MHB of 1 case per 7000 exposures.⁸⁻¹¹ When traced to the source, this cited figure was the result of a case report extracted from records of 7000 bronchoscopies at 1 institution.¹² Another case report identified 4 cases occurring in 19 months in a 296-bed hospital.¹³ Obviously, the case reports are not designed to look at overall incidence and should not be used as a risk assessment, and systematic incidence studies were not found.

Although underlying cardiac or respiratory conditions may exacerbate the symptoms of MHB,³ there are no clearly defined risk factors for the development of this blood disorder. This may be due to a relative paucity of adverse event information regarding benzocaine, which could be due to the perception that benzocaine, with its short half-life and minimal systemic absorption,¹⁴ is a relatively benign product. An obvious risk factor would be patients with a hereditary lack of methemoglobin reductase mentioned previously. In addition, one review of case reports suggested an age-related risk, noting that most cases were in infants or the elderly.⁶ Another author suggests that factors include breaks in the mucosal barrier, concomitant use of other oxidative agents, and, in particular, an excessive dose of benzocaine.¹⁰

The listed dose of benzocaine spray in one package insert is 0.5 seconds, repeat if necessary,¹⁵ with no maximum dose specified. Another product insert states a dose of 1 second or less, not to exceed a spray of 2 seconds.¹⁶ In one study, a 2-second spray to mucosal tissues resulted in a statistically significant but clinically unimportant increase in methemoglobin levels.¹⁷ An efficacy study of the use of 20% benzocaine spray prior to endoscopy neither stated the specific dose nor found a statistically significant benefit from the patient or physician perspective.¹⁸ Complicating the dose issue further is the variability of active ingredient delivered per spray. In studying the volume expelled from canisters of Hurricaine spray (20% benzocaine; Beutlich Pharmaceuticals, Waukegan, Ill), it was determined that the dose delivered is a function of residual volume and spatial orientation of the device (upright, inverted, or horizontal).¹⁹ This, along with the infeasibility of accurately spraying for 1 second in a clinical setting, compelled the authors to conclude that there is no correlation between the dose of benzocaine and the duration or number of sprays administered to the patient.¹⁹ These fac-

tors made it difficult to assess dose as a risk factor in the published literature.

These uncertainties and continuing reports of individual cases²⁰ led to this first systematic study of all cases of MHB associated with benzocaine in the US Food and Drug Administration's (FDA's) current system for reporting adverse events.

METHODS

FDA ADVERSE EVENT REPORTING SYSTEM

The data for this study come from the FDA's Adverse Event Reporting System (AERS), one of the agency's primary tools for the postmarket surveillance of approved drugs.²¹ Health professionals and consumers can report drug adverse events directly to the FDA under MedWatch, the agency's safety information and adverse event reporting program, or to the manufacturer, which is required to report to the agency adverse events. The FDA publishes for research use quarterly abstracts from AERS after deleting personal identifiers and the text of the report narratives.²² The data abstracts from AERS contain the linked files with patient and report information, event outcomes (such as death or hospitalization), and medical terms that characterize the adverse event that occurred. In the fiscal year 2001, the FDA received 281 090 adverse event reports from all sources.²¹

IDENTIFICATION OF PRODUCTS

To identify products containing benzocaine, we screened the FDA *National Drug Code Directory*²³ for a listing of all products containing this ingredient, regardless of route of administration. In addition we added an additional over-the-counter product, Hurricaine spray, which was listed in the adverse event database but not in the *National Drug Code Directory*.

From all reports entered in AERS from November 1997 through March 2002, we extracted all those identifying benzocaine, benzocaine product, or combination. Because drug names are not standardized, we searched for all common spelling variants on benzocaine, Hurricaine spray (a brand name), Cetacaine (a brand name of a combination product that includes benzocaine, tetracaine hydrochloride, and butyl aminobenzoate [Cetylite Industries Inc, Pennsauken, NJ]), and close variants of 38 other product names.

Because the AERS files may contain both the initial report and any follow-up reports about the same adverse event, we also identified the last or latest report for each unique adverse event that the FDA identified by a case number. This step prevents counting the same adverse event more than once. In the present report, a "case" is defined as a unique adverse event, with the data coming from the most recent report.

HEALTH OUTCOMES

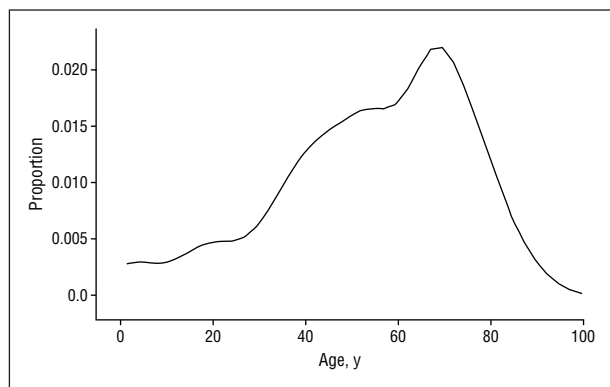
The FDA AERS report form permits the individual observing the adverse event to select 1 or more of these health outcomes: death, congenital anomaly, disability, hospitalization, life threatening, required intervention to prevent harm, and "other." In addition, some AERS reports do not state an event outcome. For this study, the outcomes were divided into 1 of 4 mutually exclusive categories: (1) death, (2) disability/birth defect, (3) serious, and (4) other. When an event was included in more than 1 category, it was placed in the most severe event category in the priority order listed above. The category "other" is ambiguous and may contain "other serious" events, events

Table 1. Reports and Cases of Benzocaine Products*

Reports	MHb: Definite or Probable	Other Adverse Events	Total
Total reports	136 (100)	82 (100)	218
Unique cases	132 (97.0)	66 (80.0)	198
Previous reports	4 (3.0)	16 (20.0)	20
Report type (cases)	132 (100.0)	66 (100)	198
Direct to FDA	119 (90.2)	25 (37.9)	144
Manufacturer			
Expedited	12 (9.1)	19 (28.8)	31
Periodic	1 (0.8)	22 (33.3)	23
Product type (cases)	132 (100)	66 (100)	198
Spray	123 (93.2)	28 (42.4)	151
Solution	0	10 (15.2)	10
Gel	1 (0.8)	3 (4.5)	4
Lozenge	2 (1.5)	3 (4.5)	5
Suppository	0	4 (6.1)	4
Unknown	6 (4.5)	18 (27.3)	24

Abbreviations: FDA, Food and Drug Administration; MHb, methemoglobinemia.

*Data are number (percentage) of cases unless otherwise specified.



Age distribution of methemoglobinemia cases. Mean age of the benzocaine-treated patients was 54 years (75% from age 42-69 years) and 49% were female.

that are “other than serious,” or events in which no outcome was reported.

In the published FDA quarterly abstracts from AERS, the narrative text describing the adverse event has been deleted to protect privacy. Instead, each report contains a list of medical terms selected from a standardized dictionary called MedDRA (Medical Dictionary for Regulatory Affairs).²⁴ The MedDRA dictionary contains sufficient terms capable of capturing MHb. The dictionary terms *methemoglobinemia*, *methemoglobinemia NOS* [not otherwise stated], and *methemoglobinuria present* were used to define a case of definite MHb. We classified a case as “probable MHb” if it contained 1 of the following reaction terms describing distinctive signs or symptoms (but not the term *MHb* itself): *cyanosis NOS*, *oxygen saturation decreased*, *PO₂ decreased*, *oxygen saturation abnormal*, and *blood gases NOS abnormal*.

The FDA MedWatch reporting form allows 3 different choices for listing a specific drug. The block “suspect medications” contains 2 numbered lines that are identified in the quarterly abstracts as “primary suspect” and “secondary suspect” drug. In addition, a separate block allows the respondent to list “concomitant medical products.” In the present study, we included all mentions of a benzocaine product, regardless of suspect status.

ROUTES OF ADMINISTRATION

Based on the routes of administration for the products listed in the *National Drug Code Directory*, we identified the following product categories: 20% benzocaine spray, 12% benzocaine spray, spray with unknown concentration, solution, lozenge, gel, and not stated. We included both products containing only benzocaine and combination products. Information to determine the product categories came from 3 different fields in the AERS database. The category could sometimes be deduced in the drug name field (eg, “Hurricane spray,” and “20% benzocaine”). In other reports it was listed under route of administration (eg, lozenge or gel). Finally, in some reports the product category information was in the field coded as “dose” (eg, “1 spray,” or “1 spray ×3”). In the original report and electronic form, this information is provided in a combined block entitled “Dose, frequency, and route used.” For the product category of sprays, we further grouped the dose entries as follows: 1 spray, 2 sprays, 3 sprays, or 4 or more sprays.

STATISTICAL ANALYSIS

The AERS data were stored in a Microsoft Access (Microsoft Inc, Redmond, Wash) database and analyzed with the SPlus version 6.1 (Insightful Corporation, Seattle, Wash) statistical software package. For most analytical purposes, the data were considered a population and did not require statistical tests of significance. However, to test whether the proportion of reports the FDA received directly rather than from a manufacturer could have occurred by chance, we calculated a χ^2 statistic using all reports in AERS as the expected values and the benzocaine reports as the observed values, using the χ^2 distribution to calculate the *P* value. The age distribution was estimated from the data using a density function and an assumption of normal distribution.

RESULTS

From 818 439 reports in the FDA AERS database from November 1997 through March 2002, we identified 218 adverse event reports in which benzocaine was an ingredient (**Table 1**), 198 of which described unique adverse events. The adverse event cases described 132 (66.7%) defi-

Table 2. Outcome of Adverse Event (Cases)*

Outcome	MHb: Definite or Probable	Other Event	Total
Mutually exclusive outcome groups			
Total cases	132 (100)	66 (1.0)	198
Death	2 (1.5)	5 (7.6)	7
Disability	0	4 (6.1)	4
Serious	107 (81.1)	25 (37.9)	132
Other	23 (17.4)	32 (48.5)	55
FDA (multiple outcomes allowed)†			
Total outcomes	172 (100)	72 (100)	244
Death	2 (1.2)	5 (5.6)	7
Disability	0	4 (5.6)	4
Life threatening	55 (32.0)	8 (11.3)	63
Hospitalized	46 (26.7)	22 (31.0)	68
Required intervention	50 (29.1)	8 (11.3)	58
Other	19 (11.0)	25 (35.2)	44

Abbreviations: FDA, Food and Drug Administration; MHb, methemoglobinemia.

*Data are number (percentage) of cases unless otherwise specified.

†Does not add to total of cases because of multiple outcomes for each case.

nite or probable episodes of MHb and 66 (33.3%) other types of adverse events. Among the 132 cases associated with MHb, 99 cases (75%) were identified as definite MHb and 33 cases (25%) as probable. The mean patient age was 54 years, and the cases were divided evenly between male and female patients (**Figure**).

DIRECT REPORTING

The MHb cases were unusual because 119 (90.2%) were reported directly to the FDA and 13 (9.9%) from manufacturers. In the overall AERS database for all drugs, manufacturers are the source for 91% of reported cases, and direct reports account for 9% of the total. Among the manufacturers, only 3 reports of MHb were submitted by the manufacturer of Cetacaine and none by the manufacturer of Hurracaine spray. Statistically significant differences were found between the number of direct reports to the FDA for benzocaine and for all other types of adverse events ($\chi^2=44.93$; $P<.001$).

PRODUCT TYPE

Although benzocaine is sold for at least 5 different routes of administration, the spray product accounted for 123 cases (93.2%) of MHb. The spray products are intended for use on the mucosal tissues—typically in connection with intubation bronchoscopy or endoscopy. In addition, 100% of cases in which tissue type was indicated, mucosal tissue was specified. Although 4 or more adverse events were found for all product types, no MHb cases were reported for the solution (typically used for earaches), and just 1 for the gel (typically used for dental problems).

EVENT OUTCOME

The MHb cases resulted in 2 deaths (1.5%), 107 serious events (81.1%), and 23 cases of “other” severity (17.4%) (**Table 2**). Both of the reported deaths were “probable MHb” rather than “definite MHb.” The first death case iden-

tified Cetacaine as the principal suspect drug and reported cyanosis, dyspnea, overdose, and a complication of intubation. The second death case identified midazolam as a principal suspect (Cetacaine was also identified), and the reaction was described as “hypoxia” and “restlessness” leading to death. Although both reports involving death came from health professionals, the absence of a specific diagnosis of MHb suggests that the adverse reaction to benzocaine may not have been recognized and that other factors may have contributed to the fatal outcome.

DOSE OF SPRAY PRODUCTS

In 69 (56.1%) of the MHb cases involving a spray product, some statement was included about the dose administered. The packaging for Cetacaine indicates that it should be sprayed “for one second or less” and “spray in excess of two seconds is contraindicated.” The packaging for Hurracaine spray states, “Spray for one-half second. Repeat if necessary.” The tabulation below gives the reported doses (spray in MHb cases):

No. of Sprays	No. (%) of Spray Cases
Total	132 (100)
1	37 (30.0)
2	18 (14.6)
3	8 (6.5)
≥4	6 (4.8)
Not available	63

The reports for 10 cases contained a specific term indicating medical error: “drug maladministration” (5 cases) and “medication error” (5 cases).

COMMENT

These data show that MHb is the most frequent reported adverse event of topical benzocaine products and that these cases primarily involve the spray product applied to mucosal tissues. These events were serious, occurred across a wide age spectrum, and were potentially

life threatening. Unlike a previous analysis, these data show that the adverse events were not concentrated among the very old and young. That most cases occurred when spray was applied to mucosal tissues is consistent with the chemical and pharmacokinetic properties of benzocaine, which is not water soluble and poorly absorbed through unbroken skin.

Of special concern are the 33 “probable MHb” cases (25% of total), including 2 fatalities that were identified by the distinctive symptoms such as cyanosis or decreased PO₂ but without a specific finding of MHb. Given that the diagnosis may require a cooximetry reading and may not be apparent in routine blood gas evaluations, these cases may have been unrecognized (and therefore untreated) cases of MHb. More detailed case reports in the literature also included instances of delay in recognizing and treating MHb.^{9,10,25}

Because reports to the FDA AERS system are voluntary and spontaneous, these data do not provide reliable information about the incidence of these adverse events. The FDA has estimated that around 10% of serious adverse events are reported, noting that some studies show 1% or less.²⁶ In addition, the small number of reports from the manufacturers of the spray products suggests a lower intensity of postmarket surveillance for over-the-counter products.²⁷ Given the known extent of underreporting, it is reasonable to hypothesize that thousands of MHb cases have occurred since November 1997.

However, the reporting of an adverse event does not in itself establish causality but only that an observer believed a link between the drug and the event might exist. In this instance, however, the inference of causality is stronger given a rare and distinctive adverse event that is chemically plausible and well documented in the scientific literature. In addition, the computer abstracts of the reported cases do not provide sufficient detail to capture the full complexity of the adverse events, including medical history, alternative, and contributing factors.

Our initial hypothesis that most cases would be linked to accidental overdoses of spray applied to mucosal tissues was not supported by the available data. Although we identified 14 cases that may have involved an overdose, in 37 other cases the dose was listed as a single spray of unspecified duration. Correct dose, however, involves much guesswork because of the difficulty of accurately timing a 0.5-second spray, variations in the amount dispensed depending on spray canister position, and amount of remaining contents. We believe that a metered dose and a more prominent package warning about MHb would enhance the safety profile of benzocaine products.

Accepted for publication May 22, 2003.

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