

Lack of Methemoglobin Elevations After Topical Applications of Benzocaine Alone or Benzocaine Plus Tetracaine to the Oral Mucosa

Steven Wang, DMD, MD, MPH¹; Helen Giannakopoulos, DDS, MD¹; Jamie Lowstetter, BS¹; Laura Kaye, BS¹; Catherine Lee, BS¹; Stacey Secreto, CCRC¹; Vanessa Ho¹; Matthew C. Hutcheson, MS²; John T. Farrar, MD, PhD³; Ping Wang, PhD³; Geraldine Doyle, PhD⁴; Stephen A. Cooper, DMD, PhD⁵; and Elliot V. Hersh, DMD, MS, PhD¹

¹University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania; ²Tegra Analytics, Doylestown, Pennsylvania; ³University of Pennsylvania Pearlman School of Medicine, Philadelphia, Pennsylvania; ⁴Geraldine Doyle, PhD, LLC, Chatham, New Jersey; and ⁵Stephen A. Cooper DMD, PhD, LLC, Palm Beach Gardens, Florida

ABSTRACT

Purpose: This study evaluated changes in methemoglobin and oxygen saturation concentrations after the administration of recommended doses of 14% benzocaine alone or 14% benzocaine combined with 2% tetracaine.

Methods: American Society of Anesthesiology class 1 and 2 subjects (n = 40) were enrolled in this modified crossover study. Subjects were administered 0.2 mL of 14% benzocaine alone, 0.2 mL of 14% benzocaine plus 2% tetracaine, or 0.4 mL of 14% benzocaine plus 0.2% benzocaine to their cheek mucosa. Venous blood (5 mL) was drawn from the antecubital fossa before and 60 minutes after drug application for methemoglobin analyses. Oxygen saturation was also recorded via pulse oximetry at baseline and every 10 minutes through 60 minutes after drug application.

Findings: Methemoglobin and oxygen saturation levels did not change from baseline after the administration of benzocaine alone or when combined with tetracaine.

Implications: Recommended doses of benzocaine or benzocaine combined with tetracaine when applied to the cheek mucosa do not induce even clinically insignificant elevations in methemoglobin levels. Metered dosing, such as that used in this study, can help avoid this overdose phenomena with these drugs. ClinicalTrials.gov identifier: NCT02908620. (*Clin Ther.* 2017;■:■■■-■■■) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: benzocaine, methemoglobinemia, tetracaine, topical anesthetics.

INTRODUCTION

Drug-induced methemoglobinemia is a potentially life-threatening event that typically involves overdoses of strong oxidizing drugs¹⁻⁶ (Table). These drugs can convert the reduced form of hemoglobin (Fe⁺⁺), which readily carries and releases oxygen to tissues, to methemoglobin (Fe⁺⁺⁺).⁶ Methemoglobin does not readily bind oxygen, and when it does, it does not readily release it to tissues.¹ Healthy adults typically possess methemoglobin levels in the 0% to 2% range.^{1,5} The reduced form of hemoglobin can bind oxygen, transport it, and release it into tissues.

Symptoms and signs vary by the blood levels of the methemoglobin species. Methemoglobin levels >10% produce visible signs of cyanosis in the buccal mucous membranes, lips, nose, cheeks, fingers, and toes.^{1,6-8} In addition, arterial blood takes on a distinctive chocolate brown appearance that fails to change color when exposed to air.^{7,8} At concentrations <20%, methemoglobinemia is generally well tolerated, with a lack of overt respiratory distress.^{9,10,16} At 30% to

Accepted for publication August 30, 2017.

<http://dx.doi.org/10.1016/j.clinthera.2017.08.017>
0149-2918/\$ - see front matter

© 2017 Elsevier HS Journals, Inc. All rights reserved.

Clinical Therapeutics

Table. Some drugs implicated in producing methemoglobinemia.

Generic Name	Common Trade Names
Aniline	Various dyes and inks
Benzocaine	Anbesol, Hurracaine
Benzocaine plus tetracaine	Cetacaine
Ciprofloxacin	Cipro
Dapsone	Dapsone UPS
Flutamide	Eulexin
Metoclopramide	Reglan
Nitric oxide	-
Nitrates and nitrites	Nitrostat, Nitro-Dur, Isordil
Phenazopyridine	Urobiotic, Pyridium
Phenelzine	Nardil
Phenobarbital	Various generics
Phenytoin	Dilantin
Prilocaine	Citanest
Quinine	Various generics
Resorcinol	Bensulfoid Cream
Tetracaine	Ponticaine
Trimethoprim/sulfamethoxazole	Bactrim

40%, symptoms include headache, weakness, dyspnea, tachycardia, and dizziness.^{1,10,11} At this stage, oxygen saturation concentrations as measured by pulse oximetry can decrease to <90%, although oxygen saturation decreases lag behind the severity of the methemoglobin state.¹² Methemoglobin concentrations >50% are associated with lethargy, confusion, cardiac arrhythmias, and depression of consciousness followed by seizures.^{1,10,11} Death may occur at concentrations exceeding 70%.^{1,6,10} Intravenous methylene blue, a reducing agent, is the treatment of choice for treating methemoglobin levels >30%.¹⁻¹² Although a few individuals (most often found in the Alaskan Eskimo, Navajo Indian, and Siberian Yakutsk populations) possess a genetic deficiency in the enzyme nicotinamide adenine dinucleotide-dependent methemoglobin reductase (NADH cytochrome b5 reductase),^{1,6} which continuously reduces methemoglobin to reduced hemoglobin, most

cases of methemoglobinemia are drug induced in individuals without this deficiency.

Benzocaine and tetracaine are 2 topically applied local anesthetics of the ester class that have been implicated in producing methemoglobinemia when applied to the oropharyngeal membranes in supratherapeutic quantities.¹⁻¹⁹ Usually, these cases involve application of the drug via unmeasured spray by a medical professional.

Benzocaine, butaben, and tetracaine anesthetic spray* has been on the US marketplace since 1960. It was marketed before the 1962 Kefauver Harris Drug Control Act, which mandated that all drugs be proven tolerable and effective before approval by the US Food and Drug Administration (FDA). It currently possesses Drug Efficacy Study Implementation status, meaning that confirmation of its tolerability and efficacy are still pending. It is indicated for the production of anesthesia of all accessible mucous membranes except the eyes and is used to control pain and gagging, including surgical, endoscopic, and other procedures in the ear, nose, mouth, pharynx, larynx, trachea, bronchi, and esophagus.²⁰ Another frequent use of topical anesthetics is to provide anesthesia for minor soft-tissue dental procedures, such as scaling and root planing (dental cleanings) and minor gingival surgery.²¹ The currently marketed formulation of Cetacaine contains 14% benzocaine, 2% tetracaine, and 2% butaben with a chlorofluorocarbon (CFC) propellant in an unmeasured cannister.²⁰ Package insert dosing instructions state that the cannula should be depressed for ≤1 second, delivering approximately 200 mg of product equal to 28 mg of benzocaine plus 4 mg of tetracaine. In no instance should the product be administered for >2 seconds (400 mg of total product or 56 mg of benzocaine plus 8 mg of tetracaine). In the investigational CTY-5339A formulation, the butaben has been removed as has the CFC propellant because of the FDA ban on CFCs because of their ozone-depleting effects.²² By 2020 all products that contain CFCs, such as asthmatic inhalers, must have this propellant removed.²³ In addition, CTY-5339A is contained in a metered canister, with each application expressing approximately 0.2 mL of drug (28 mg of benzocaine plus 4 mg of tetracaine);

*Trademark: Cetacaine® (Cetylite Industries, Inc, Pennsauken, New Jersey).

thus, clinicians can better control how much drug is administered.

Like other investigational drugs, the FDA is requesting that CTY-5339A undergo rigorous studies of tolerability and efficacy.²⁴ Because methemoglobinemia has been a concern of the FDA's with ester-containing prescription and over-the-counter local anesthetic products,²⁵ this study explored the effects of CTY-5339A that contained both 14% benzocaine and 2% tetracaine and 14% benzocaine alone on methemoglobin and oxygen saturation concentrations in American Society of Anesthesiology class 1 and 2 volunteers.

METHODS

American Society of Anesthesiology Class 1 and 2 subjects ($n = 40$) of both sexes without contraindications to topical anesthetics and hematologic and blood chemistry values at screening that did not place them at undue risk in the opinion of the principal investigator (E.V.H.) could enroll in the study. The protocol and informed consent document were approved by the University of Pennsylvania Institutional Review Board. Subjects had to read and sign the informed consent document as witnessed by the research coordinator or the principal investigator (E.V.H.) before any research-related procedures (including screening procedures) were commenced. A negative urine pregnancy test result was required of all child-bearing females at screening and at both dosing visits before the administration of study drug. Initial dosing with the study drug had to take place within 30 days of the screening visit.

The study drug was administered in a randomized, double- and single- blinded crossover manner through metered canisters to the left or right cheek mucosa. The treatment assignments consisted of 4 groups: (1) one 0.2-mL spray of CTY-5339A (28 mg of benzocaine plus 4 mg of tetracaine), (2) one 0.2-mL spray of 14% benzocaine alone (28 mg of benzocaine), (3) two 0.2-mL sprays of CTY-5339A (56 mg of benzocaine plus 8 mg of tetracaine), and (4) one spray of 14% benzocaine (28 mg of benzocaine) followed by 0.2 mL of a placebo spray. The placebo (vehicle) spray consisted of 14.4% dehydrated alcohol, 35.5% polyethylene glycol 300, 20.2% propylene glycol, 21.5% purified water, 6.0% benzyl alcohol, 0.5% benzalkonium chloride solution, 1.4% saccharin sodium, and

0.5% banana flavoring. These same constituents at slightly different concentrations were contained in both active drug formulations. Before drug administration by one of the investigators (SS), the research coordinator (SS) drew an approximate 1-in circle using an indelible marking pencil where the drug was to be administered. If a subject was initially assigned to a 1-spray sequence, he or she received the alternate 1-spray drug 4 to 14 days later on the opposite cheek. The 1-spray sequences were double-blind. Likewise, if a subject was initially assigned to a 2-spray sequence, he or she received the alternate treatment 4 to 14 days later on the opposite cheek. However, in the case of the 2-spray benzocaine/placebo sequence, the placebo spray was administered outside the active dosing circle. Thus, the 2-spray sequences were single-blind administrations where the dosers (S.W., H.G., C.L.) and a research assistant (V. H.) knew the assignments, but the research subjects and other members of the research team did not. Subjects were not allowed to expectorate after dosing, but no instructions were given with regard to swallowing the study drugs.

Immediately before and 60 minutes after drug administration, 5 mL of venous blood was drawn for methemoglobin concentrations into sodium heparin vacutainer tubes and placed into a refrigerator (37°F) before being transported within 72 hours to the Hospital of the University of Pennsylvania Core Lab. Methemoglobin concentration was measured by a multiwavelength oximeter (ABL837, Radiometer America, Brea, California). The fraction of methemoglobin was derived by calculation ($\text{Met-Hb}\% = [\text{Met-Hb}/(\text{O}_2\text{-Hb} + \text{deoxy-Hb} + \text{CO-Hb} + \text{Met-Hb})]$). Per protocol and with agreement from the FDA, if in any individual the methemoglobin level increased to $> 5\%$, it was to be considered a serious adverse event. In addition, oxygen saturation was recorded via an automated pulse oximeter/blood pressure unit (Criticare Systems Inc, Series 596NT3, Waukesha Wisconsin) at baseline and every 10 through 60 minutes. Adverse events as elicited by the subject or observed by the research coordinator or a nondosing investigator were recorded if and when they occurred.

Because both benzocaine sequences (1 spray and 1 spray followed by a placebo spray) delivered the same 28-mg dose of benzocaine to the cheek mucosa, for analysis these subjects were grouped into a single stratum. Thus, the treatment groups consisted of 1

Clinical Therapeutics

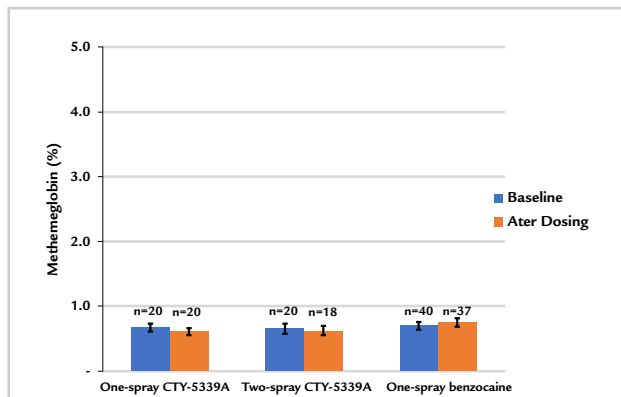


Figure 1. Mean predose and postdose methemoglobin concentrations for the 3 treatment groups. Error bars represent SEM. Reduction in sample size after dosing in 2-spray CTY-5339A and 1-spray benzocaine treatments was attributable to inability to obtain venous access.

spray of CTY-5339A (28 mg of benzocaine plus 4 mg of tetracaine), 2 sprays of CTY-5339A (56 mg of benzocaine plus 8 mg of tetracaine), and 1 spray of 14% benzocaine (28 mg of benzocaine). Methemoglobin concentrations were expressed in percentages and were compared before dosing and at 60 minutes after dosing using a paired *t* test for each treatment group. These data were subsequently expressed as histograms plus the SEMs. Oxygen saturation values were also expressed in percentages, averaged, and plotted via time-action curves. The Wilcoxon signed rank test was not applied to oxygen saturation values because all recorded measurements were 97%, 98%, or 99%.

RESULTS

Figure 1 displays the mean methemoglobin levels immediately before (baseline) and 60 minutes after dosing with study drug. As depicted here, there were no statistically significant or clinically relevant changes in methemoglobin concentrations with both doses of CTY-5339A or 14% benzocaine alone. In addition, oxygen saturation levels remained in a normal range in all subjects (97%–100%) (Figure 2). The only adverse event recorded in this study was a single patient feeling faint during the postdosing blood draw. This event was deemed not to be related to study drug and resolved spontaneously.

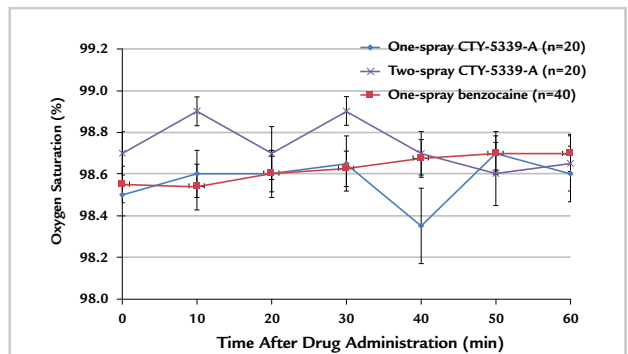


Figure 2. Time-action curves of oxygen saturation concentrations for the 3 treatment groups. Error bars represent SEM.

DISCUSSION

Drug-induced methemoglobinemia has typically been reported from overdoses of strong oxidizing drugs. Of relevance to the present study, the topical application of benzocaine and tetracaine to the oropharyngeal mucosa has been implicated in triggering this phenomenon.^{1–19} Whether the simultaneous administration of both drugs as in CTY-5339A further increases the risk of elevated methemoglobin levels had also not been previously studied. The results of this study indicate that doses of benzocaine alone or benzocaine plus tetracaine administered at recommended doses and also at the maximum recommended dose for benzocaine combined with tetracaine had no effect on predosing methemoglobin or oxygen saturation concentrations (Figures 1 and 2). The study, however, did not explore whether the doses we used provided anesthesia profound enough to complete minor soft-tissue dental procedures, such as biopsies and gingivectomies. These studies are planned as part of the New Drug Application submission for CTY-5339A.

Other potential limitations of this study were that the subject population evaluated included generally healthy adults who were not taking other oxidizing drugs that could increase the risk for this sequela. At least one published report suggests that the administration of topical tetracaine to a patient already taking the antibiotic sulfamethoxazole, which is also a strong oxidizing drug and implicated in producing methemoglobinemia, may increase the risk of this event.¹³ In addition, all subjects in this study had

relatively low exposures to benzocaine and tetracaine, with the highest doses of benzocaine and tetracaine combined being 56 and 8 mg, respectively.

Of note, other studies performed at our institution have revealed that topical benzocaine self-administered by subjects to the oral mucous membranes for toothache pain in doses ranging from 40 to 200 mg produced no visible signs (bluish mucous membranes, cyanosis) of methemoglobinemia.²⁶ Likewise, intranasal administration of 3% tetracaine plus oxymetazoline in doses ranging from 12 to 36 mg of tetracaine produced no visible signs of methemoglobinemia and no significant changes in oxygen saturation levels.^{27,28} On the basis of published case reports and case series, it has been reported that the dose of benzocaine typically needed to produce clinically significant methemoglobinemia is approximately 15 mg/kg or at least 1000 mg in a 70-kg (150-lb) adult.^{5,10} It must be stressed, however, that like many drug-induced toxic effects, the dose necessary to produce methemoglobinemia is weight based, a factor that clinicians and parents must take into effect when treating intraoral pain with over-the-counter benzocaine in teething infants.²⁹

Our results indicate that in relatively healthy adults, the intraoral administration of up to 56 mg of benzocaine plus 8 mg of tetracaine contained in 0.4 mL of CTY-5339A produces no changes in methemoglobin concentrations and oxygen saturation levels. Future studies plan to explore the tolerability of higher doses of CTY-5339A and to characterize its effectiveness in anesthetizing the oral mucous membranes by using quantitative sensory threshold analysis.³⁰

ACKNOWLEDGMENTS

The author would like to acknowledge Rosalie Hilton.

FUNDING SOURCES

This study was supported by a grant from Cetylite Industries Inc to Elliot V. Hersh, representing the Trustees of the University of Pennsylvania.

CONFLICTS OF INTEREST

Elliot V. Hersh, representing the Trustees of the University of Pennsylvania, received grant funding from Cetylite Industries Inc for his work in preparing the protocol and performing the research study. Stephen A. Cooper and Geraldine Doyle were paid

consultants of Cetylite Industries Inc for their work in preparing the protocol and monitoring the study. Matthew C. Hutcheson was a paid biostatistical consultant for Cetylite Industries Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. King A, Menke N, Katz K. Toxic hemoglobinopathies in the emergency department. *Emerg Crit Care*. 2013;3:1-17.
2. Hall DL, Moses MX, Weaver JM, et al. Dental anesthesia management of methemoglobinemia-susceptible patients: A case report and review of literature. *Anesth Prog*. 2004;51:24-27.
3. Aepfelbacher FC, Breen P, Manning WJ. Methemoglobinemia and topical pharyngeal anesthesia. *N Engl J Med*. 2003;348:85-86.
4. Nguyen ST, Cabes RE, Bashour CA, et al. Benzocaine-induced methemoglobinemia. *Anesth Analg*. 2000;90:369-371.
5. Ellis FD, Seiler JG, Pahnore MM. Methemoglobinemia: A complication after fiberoptic orotracheal intubation with benzocaine spray: A case report. *J Bone Joint Surg Am*. 1995;77:937-939.
6. Udeh C, Bittikofer J, Sum-Ping STJ. Severe methemoglobinemia on re-exposure to benzocaine. *J Clin Anesth*. 2001;13:128-130.
7. Gupta PM, Lala DS, Arsura EL. Benzocaine-induced methemoglobinemia. *South Med J*. 2000;93:83-86.
8. Guertler AT, Pearce WA. A prospective evaluation of benzocaine-associated methemoglobinemia in human beings. *Ann Emerg Med*. 1994;24:626-630.
9. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother*. 1996;30:1251-1254.
10. Rodriguez LF, Smolik LM, Zbehlik AJ. Benzocaine-induced methemoglobinemia: Report of a severe reaction and review of the literature. *Ann Pharmacother*. 1994;28:643-649.
11. Wilburn-Goo D, Lloyd LM. When patients become cyanotic: Acquired methemoglobinemia. *J Am Dent Assoc*. 1999;130:826-831.
12. Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. *Anesth Analg*. 2009;108:837-845.
13. Whited C, Cohen SM. Nasal tetracaine spray-induced methemoglobinemia. *Otolaryngol Head Neck Surg*. 2012;146:678-679.
14. Lavergne S, Darmon M, Levy V, Azoulay E. Methemoglobinemia and acute hemolysis after tetracaine lozenge use. *J Crit Care*. 2006;21:112-114.

Clinical Therapeutics

15. Basra SK, Vives MJ, Reilly MC, et al. Methemoglobinemia after fiberoptic intubation in a patient with an unstable cervical fracture: a case report. *J Spinal Disord Tech.* 2006;19:302-304.
16. Lunenfeld E, Kane GC. Methemoglobinemia: sudden dyspnea and oxyhemoglobin desaturation after esophagoduodenoscopy. *Respir Care.* 2004;49:940-942.
17. Byrne MF, Mitchell RM, Gerke H, et al. The need for caution with topical anesthesia during endoscopic procedures, as liberal use may result in methemoglobinemia. *J Clin Gastroenterol.* 2004;38:225-229.
18. Gregory PJ, Matsuda K. Cetacaine spray-induced methemoglobinemia after transesophageal echocardiography. *Ann Pharmacother.* 2000;34:1077.
19. Ferraro L, Zeichner S, Greenblott G, Groeger JS. Cetacaine-induced acute methemoglobinemia. *Anesthesiology.* 1988;69:614-615.
20. Cetacaine® topical anesthetic. <http://www.cetacaine.com/dental/about/prescribing-information>. Accessed July 12, 2017.
21. Meechan JG. Intraoral topical anesthesia. *Periodontol.* 2008;46:56-79.
22. Use of ozone-depleting substance. Federal Register. <https://www.federalregister.gov/documents/2016/10/26/2016-25852/use-of-ozone-depleting-substances>. Accessed July 12, 2017.
23. US Food and Drug Administration. Phase-out of CFC metered-dose inhalers containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil - Questions and answers. <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm208138.htm>. Accessed July 13, 2017.
24. US Food and Drug Administration. CPG Sec. 440.100 Marketed new drugs without approved NDAs and ANDAs. <https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074382.htm>. Accessed July 13, 2017.
25. US Food and Drug Administration. FDA Drug Safety Communication: FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medical procedures. <https://www.fda.gov/Drugs/DrugSafety/ucm250040.htm>. Accessed July 13, 2017.
26. Hersh EV, Ciancio SG, Kuperstein AS, et al. An evaluation of 10 percent and 20 percent benzocaine gels in patients with acute toothaches: Efficacy, tolerability and compliance with label dose administration directions. *J Am Dent Assoc.* 2013;144:517-526.
27. Giannakopoulos H, Levin LM, Chou JC, et al. The cardiovascular effects and pharmacokinetics of intranasal tetracaine plus oxymetazoline: Preliminary findings. *J Am Dent Assoc.* 2012;143:872-880.
28. Hersh EV, Pinto A, Saraghi M, et al. Double-masked, randomized, placebo-controlled study to evaluate the efficacy and tolerability of intranasal K305 (3% tetracaine plus 0.05% oxymetazoline) in anesthetizing maxillary teeth. *J Am Dent Assoc.* 2016;147:278-287.
29. Townes PL, Geertsma MA, White MR. Benzocaine-induced methemoglobinemia. *Am J Dis Child.* 1977;131:697-698.
30. Pigg M, Baad-Hansen L, Svensson P, et al. Reliability of Intraoral quantitative sensory testing. *Pain.* 2010;148:220-226.