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

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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 drugs[1–6] (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

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Table. Some drugs implicated in producing methemoglobinemia.

Generic Name	Common Trade Names
Aniline	Various dyes and inks
Benzocaine	Anbesol, Hurricaine
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 unmetered 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 unmetered 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).