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REVIEW ARTICLE

Evaluation and Management of Acquired Methemoglobinemia Associated with Topical Benzocaine Use

Mohammed Taleb · Zubair Ashraf · Shahul Valavoor · Jodi Tinkel

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Abstract Benzocaine is a widely used topical oropharyngeal anesthetic and has been reported to cause methemoglobinemia. We discuss benzocaine-induced methemoglobinemia and review the causes, presentation, and management of this serious complication. Treatment with methylene blue will result in reversal of methemoglobinemia and clinical recovery in most cases but needs to be used at appropriate doses in carefully selected individuals. Physicians who perform procedures involving the application of benzocaine for topical anesthesia need to rapidly identify and treat methemoglobinemia to avoid significant associated morbidity and mortality.

1 Introduction

Benzocaine spray is a local anesthetic commonly used for topical anesthesia before endoscopic procedures. Benzocaine-induced methemoglobinemia is a rare and potentially life-threatening complication [1–8].

The first incidence of benzocaine-induced methemoglobinemia was reported in 1950 [9]. On February 10, 2006, the Food and Drug Administration (FDA) issued a Public Health Advisory warning about the risk of methemoglobinemia associated with topical benzocaine used during medical procedures. Since then, the FDA has received more than 70 new cases of serious adverse events, including three deaths, associated with methemoglobinemia after the use of topical benzocaine, bringing the total reported cases to 319 [10]. The incidence of methemoglobinemia associated with transesophageal echocardiography (TEE) based on a large patient series by the Mayo Clinic is low, about 1 case per 1,499 procedures [11].

In this article, we discuss the mechanism of methemoglobinemia associated with topical benzocaine and review how clinicians can identify individuals at risk for this complication, and rapidly diagnose and treat this rare but potentially fatal complication arising from benzocaine use during a variety of commonly performed procedures.

2 Clinical Diagnosis

Methemoglobinemia occurs in the presence of an elevated circulating fraction of methemoglobin within the red blood cells. Normal hemoglobin contains the iron molecule in the divalent ferrous state, $Fe^{(II)}$. Methemoglobin results from the oxidation of $Fe^{(II)}$ to a trivalent ferric form, $Fe^{(III)}$. Methemoglobin cannot bind and carry oxygen, resulting in functional anemia and hypoxia. Oxygen delivery to tissues is further reduced as the presence of iron in the $Fe^{(III)}$ form increases the oxygen binding affinity for the remaining heme groups [12]. As red blood cells are constantly exposed to oxidizing agents, methemoglobin along with superoxide is continuously formed in erythrocytes at a rate of about 3 % per day from the stable oxygenated hemoglobin complex. It is reduced to deoxyhemoglobin by several mechanisms, including nicotinamide adenine dinucleotide (NADH)-dependent mechanism in the resting state and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent methemoglobin reductase enzyme in the acquired type [13]. Under normal physiologic circumstances, these enzymatic systems work efficiently to maintain the methemoglobin levels at less than 1 %.

M. Taleb · Z. Ashraf · S. Valavoor · J. Tinkel (✉)
Division of Cardiovascular Medicine, Department of Medicine, University of Toledo Medical Center, 3000 Arlington Avenue, Toledo, OH 43614, USA
e-mail: jodi.tinkel@utoledo.edu

Methemoglobinemia can be hereditary or acquired. Hereditary methemoglobinemia commonly stems from a deficiency in either the erythrocyte or the membrane-associated NADH cytochrome b5 methemoglobin reductase enzyme [14] (Fig. 1). Acquired methemoglobinemia results from exposure to various chemicals and drugs that can cause methemoglobinemia. Medications that have been associated with methemoglobinemia include antimalarials (chloroquine, primaquine, dapsone), nitrites or nitrates (inhaled nitric oxide, nitroprusside), sulfonamides, acetaminophen, celebrex, acetanilide, flutamide, metoclopramide, phenacetin, phenytoin, probenecid, chlorates, and topical anesthetics (benzocaine, lidocaine, prilocaine) [13, 15–17]. The mechanism of formation is by direct or, more frequently, by indirect oxidation of $Fe^{(II)}$ to $Fe^{(III)}$ [13].

Benzocaine exposure represents the vast majority of cases of methemoglobinemia related to a local anesthetic, accounting for 66 % of the total in a recent case series compared with lidocaine (5 %) and prilocaine (28 %) [17]. A prospective study of benzocaine use in a series of healthy volunteers and patients undergoing upper endoscopy showed that even a 2 s spray of 20 % benzocaine can induce a statistically significant increase in methemoglobin levels. The degree of elevation varied among subjects, although none were clinically significant [18]. In a large series of subjects undergoing TEE who developed methemoglobinemia, none were outpatients [19]. The incidence in this series of over 4,000 subjects was 0.115 % but increased to 0.345 % upon re-exposure.

Several predisposing factors for the development of methemoglobinemia have been identified, but those most commonly associated with the development of clinically significant methemoglobinemia include extremes of age including both the very young and those >65 years of age, sepsis, chronic pulmonary disorders, excessive or repetitive doses of one of the offending agents, concomitant therapy with other agents known to cause this disorder, a break in the mucosal barrier as seen in recent oropharyngeal instrumentation or surgery, and partial, severe or functional deficiency of the methemoglobin reductase enzyme [19, 20]. The manufacturer recommended dose of topical benzocaine is a single 0.5–1 s spray. Using metered dose packaging has been suggested to prevent excess exposure. However, more than 50 % of cases of benzocaine-induced methemoglobinemia reported using only the recommended dose, implying that other factors including patient-specific characteristics may contribute more strongly than dose [17, 21].

The onset of benzocaine-induced methemoglobinemia is usually within 20–60 min of drug administration. Prilocaine-induced methemoglobinemia occurs from 1 to 3 h after exposure [22, 23]. The half-life of methemoglobin is 55 min [24]. Normally, 5 g/dL of deoxyhemoglobin is required to produce noticeable cyanosis as compared with methemoglobin, which produces cyanosis at 1.5 g/dL. The signs and symptoms of methemoglobinemia are similar to those of hypoxemia. Methemoglobin levels below 30 % in a healthy person usually produce no or minimal symptoms like fatigue, lightheadedness, and headache [17, 25]. Levels from 30 to 50 % can produce weakness, headache, tachycardia, and shortness of breath. Levels between 50 and 70 % cause severe symptoms like stupor, bradycardia, respiratory depression, convulsions, arrhythmias, lactic acidosis, and potentially death (Table 1).

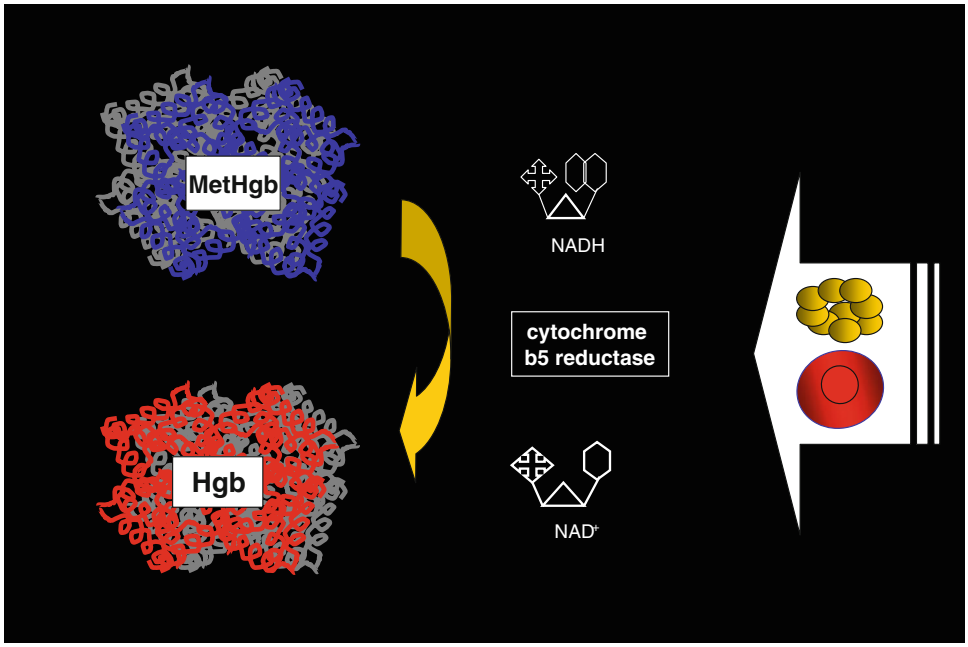

Fig. 1 $MetHgb/Fe^{(III)}$ is reduced to $Hgb/Fe^{(II)}$ in vivo predominantly by NADH cytochrome b5 reductase. This enzyme is available from two sources, a soluble erythrocyte form and a membrane associated form involved in lipid metabolism. *Hgb* hemoglobin, *MetHgb* methemoglobin, *NADH* nicotinamide adenine dinucleotide

Table 1 Stages of methemoglobinemia

% MetHgb	Severity	Symptoms
<2	Normal	None
2–15	Mild	None in healthy individuals[a]
15–30	Mild to moderate	Headache, fatigue, exercise intolerance
30–50	Moderate	Dizziness, syncope, confusion, dyspnea
>50	Severe	Seizures, coma, arrhythmias, acidosis, death

MetHgb methemoglobin

[a] Subjects with concomitant lung disease, sickle cell, or extremes of age may experience symptoms at lower levels

Diagnostic suspicion of methemoglobinemia arises from the history of intake of an offending agent, cyanosis in the absence of signs of respiratory distress, dark chocolate colored blood that does not become red after exposure to atmospheric oxygen, and discrepancy or 'gap' between pulse oximetry and arterial blood gas oxygen saturation (Table 2). Atypical presentation can occur as reported in one subject with pale rather than cyanotic skin discoloration or could occur with varying skin pigmentations, relative anemia, or due to the vasoconstrictive effect that methemoglobinemia can cause [26].

CO-oximetry is the diagnostic test of choice as it most accurately reflects oxygen saturations in the presence of methemoglobin. Oxygen saturation can be measured by three different methods: by pulse oximetry, CO-oximetry, and arterial blood gas (ABG) analysis. In pulse oximetry (SpO_2), which measures the ratio of light absorbance at only two wavelengths, methemoglobin absorbs light at a similar frequency to oxyhemoglobin (660 nm) as well as to deoxyhemoglobin (960 nm) and thus will reflect a decrease in SpO_2 until about 84–85 %. Thereafter, the SpO_2 will often decline no further despite further increases in methemoglobin levels and progressive hypoxia. CO-oximetry can measure peak absorbance at a variety of frequencies, including 630 nm, which accurately reflects methemoglobin levels. ABG analysis measures dissolved oxygen, presuming it to be in equilibrium with oxygen carried by hemoglobin in red cells. It also assumes a normal oxygen dissociation curve and will not accurately reflect the true level of methemoglobin and hypoxia. This effect results in the 'gap' between SpO_2 and ABG measurements. Even in severe cases of methemoglobinemia, ABG analysis of PO_2 levels may be normal [12].

Table 2 Clinical signs of methemoglobinemia

- ✔ Exposure to causative agent within 30–90 min of decompensation
- ✔ Cyanosis and hypoxia refractory to supplemental oxygen
- ✔ Chocolate brown color of blood
- ✔ Falsely normal PaO_2 in arterial blood gas

Once the diagnosis of acquired methemoglobinemia has been established, a review of recent medications and toxic exposures must be undertaken. In the medical setting, benzocaine is a common culprit. Benzocaine is available in spray form, throat lozenges, powder, liquid and gel preparations. The toxic effects of benzocaine can be attributed to its toxic metabolite, an N-hydroxy derivative that has an aniline group incorporated in its structure, common to several other compounds that can induce methemoglobinemia and has oxidizing properties [13]. Differences in absorption and metabolism of benzocaine and the predisposing characteristics of the individual may explain the variability of benzocaine-induced methemoglobinemia. Benzocaine spray is the most common preparation reported to cause methemoglobinemia. However, methemoglobinemia has been reported with a variety of preparations [27]. The spray may have the highest incidence because it is the most commonly used preparation.

Care must be taken to differentiate methemoglobinemia from 'pseudomethemoglobinemia.' Other hemoglobinopathies and in particular sulfhemoglobinemia may present in an identical clinical manner [28]. A failure to respond to methylene blue treatment is an indication to use CO-oximetry that includes sulfhemoglobin and carboxyhemoglobin levels to yield the diagnosis.

3 Clinical Management

When a patient is diagnosed with acquired methemoglobinemia, initial management should be directed toward improving oxygen delivery with supplemental oxygen. Levels of <30 % in healthy individuals without symptoms may require only supportive therapy and removal of the causative agent. Levels >30 % in healthy individuals or in subjects with symptoms or co-morbid cardiac or pulmonary disease require treatment. Levels as low as 10 % have been linked with symptoms and warrant aggressive treatment [17].

Methylene blue is the most effective and frequently used agent for treatment of severe or symptomatic acquired methemoglobinemia. The recommended dose of methylene blue is 1–2 mg/kg (up to 50 mg) of 1 % solution intravenously over 5 min [29] (Table 3). A dose of 1–2 mg/kg for levels of 30–50 % depending on the severity of the symptoms and a dose of 2 mg/kg for levels >50 % have been suggested [30]. Methylene blue, in low concentrations, is reduced in red blood cells and presumably in tissues, to leucomethylene blue by NADPH methemoglobin reductase [31, 32] (Fig. 2). Leucomethylene blue reduces

$Fe^{(III)}$ back to $Fe^{(II)}$, restoring the oxygen carrying capacity of hemoglobin and improving the release of oxygen [32]. Cyanosis usually resolves within 15–30 min. Marked reduction in methemoglobinemia, usually by 50 %, is seen within 30–60 min. Repeat CO-oximetry has been reported as early as 15 min and re-dosing as early as 30 min after initial methylene blue therapy [25, 33]. This is warranted in subjects who do not show a rapid clinical response. In those who do improve after initial therapy, consider retesting 60 min after dosing and repeat the methylene blue dose if levels remain >30 % [34]. After response to methylene blue, subjects should be monitored for at least 24 h for the possibility of rebound methemoglobinemia [35]. Methylene blue, when given in high doses (>7 mg/kg) or to subjects with reduced methemoglobin reduction activity, can be an oxidizing agent, resulting in increased methemoglobin production and hemolysis [17, 29].

Subjects with hereditary glucose 6-phosphate dehydrogenase (G6PD) deficiency lack part or all of the ability to produce the necessary NADPH to reduce methylene blue to leucomethylene blue, making this antidote potentially ineffective [36]. Many patients with G6PD deficiency have some enzymatic activity, and methylene blue is still the first-line therapy but at a lower initial dose (0.3–1 mg/kg) [37]. In the presence of hemolysis, no further methylene blue should be administered and hyperbaric oxygen, exchange transfusion, or ascorbic acid should be initiated [22, 38–40]. Ascorbic acid (300 mg/kg intravenous or 600 mg by mouth four times daily) acts as a direct reducing agent and can be used in less severe cases or when

Table 3 Treatment of methemoglobinemia

Antidote	Dose	Mechanism
Methylene blue	1–2 mg/kg IV over 5 min	Indirect, reducing agent via NADPH
	Redose 1–2 mg/kg IV if cyanosis or levels >30 % after 60 min	
Ascorbic acid	300 mg/kg IV or 400 mg by mouth q6h	Direct as electron donor
N-acetylcysteine[a]	150 mg/kg IV over 1 h, then 14 mg/kg/h IV for 40 min	Glutathione precursor and electron donor
Exchange transfusion	Replace MetHgb with Hgb	
Hyperbaric oxygen	Increase dissolved oxygen in blood	

Hgb hemoglobin, *IV* intravenous, *MetHgb* methemoglobin, *NADPH* nicotinamide adenine dinucleotide phosphate, *q6h* every 6 hours

[a] N-acetylcysteine not shown effective in healthy volunteers [41]

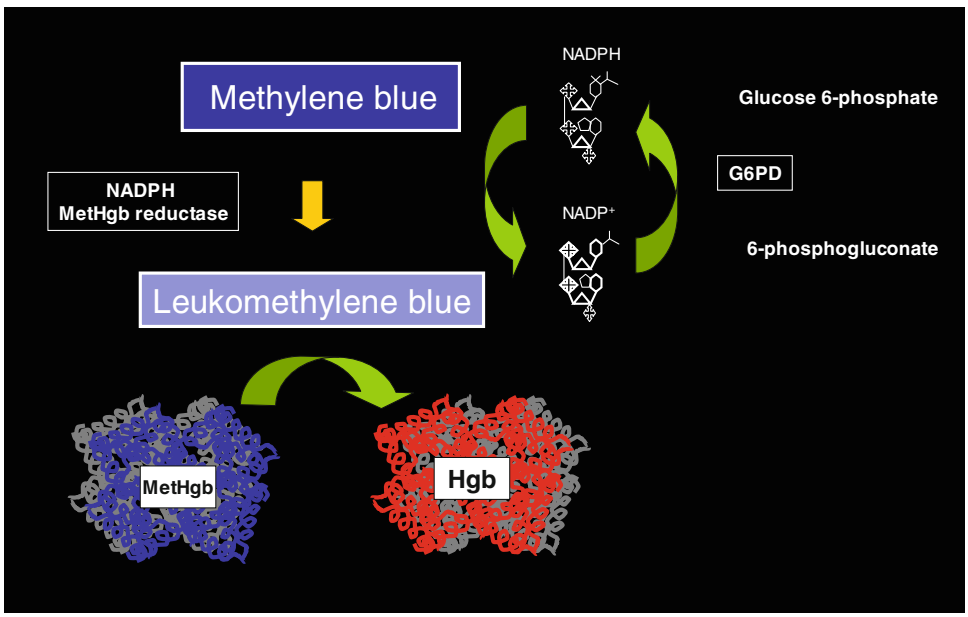

Fig. 2 Treatment of acquired methemoglobinemia with an infusion of methylene blue requires reducing methylene blue to leucomethylene blue using a proton donated from NADPH. The NADPH is produced using G6PD. Leucomethylene blue then reduces MetHgb to Hgb. Individuals with a deficiency of G6PD enzyme and thus reduced levels of available NADPH may not benefit from methylene blue therapy and may develop worsening methemoglobinemia and severe hemolysis due to the further depletion of available NADPH and glutathione. *G6PD* glucose 6-phosphate dehydrogenase, *Hgb* hemoglobin, *MetHgb* methemoglobin, *NADPH* nicotinamide adenine dinucleotide phosphate

methylene blue is ineffective. N-acetylcysteine theoretically would increase glutathione levels and act as a direct reducing agent but has been shown ineffective in vivo to reduce methemoglobin levels in a study of healthy volunteers [41]. It is unclear whether this remedy would work in the setting of acquired methemoglobinemia or for individuals with reduced methemoglobin reductase activity.

Inhibiting the formation of metabolites that oxidize deoxyhemoglobin into methemoglobin has been evaluated in clinical use. Cimetidine, which inhibits the CYP2C19 isoenzyme in the liver, and thus the formation of N-hydroxy metabolites of dapsone, has been shown to reduce methemoglobinemia during dapsone therapy [16]. However, agents like dapsone and benzocaine, which oxidize deoxyhemoglobin indirectly via metabolites, have also been the cause of rebound methemoglobinemia. In the case of dapsone, benzocaine, and other indirect oxidizing agents, the hydroxymetabolite undergoes auto-oxidation to more reactive oxidative species, which are then reduced back to the hydroxymetabolite to extend the half-life of this compound, which results in rebound formation of methemoglobin [13, 16].

4 Discussion

Methemoglobinemia associated with topical benzocaine use is rare, but knowledge of this potential complication can significantly impact patient outcomes for prevention and early recognition and treatment. Strategies to reduce its incidence include limiting benzocaine dosing, avoiding re-exposure, and avoiding its use in subgroups prone to this complication. Indeed, some have questioned whether the use of topical anesthetics should be standard during endoscopic procedures [42, 43]. A recent meta-analysis of five randomized controlled trials supports its use as it improves patient-reported comfort and physician-reported ease of procedure [44]. However, there were wide variations in intravenous sedation between the studies, and no studies have been performed with the use of propofol. The authors conclude that the use of topical anesthetics can be used judiciously in subgroups not having high-risk characteristics when intravenous sedation dosing must be limited. Interestingly, the redox activity of methemoglobinemia has been used advantageously to treat cyanide poisoning. Subjects with critical cyanide poisoning are given inhaled amyl nitrite, which induces methemoglobinemia at levels of 20–25 %. Cyanide rapidly complexes with methemoglobin, thereby releasing cytochrome oxidase to return to the cellular respiratory cycle [45]. The therapeutic to toxic ratio of this antidote is obviously narrow and these subjects need to be closely monitored.

5 Conclusions

Benzocaine and other local anesthetics are widely used in a variety of procedures, including endotracheal intubation, bronchoscopy, upper and lower gastrointestinal tract endoscopy, nasogastric tube placement, and TEE. Physicians may want to consider deferring its use in high-risk subgroups to prevent methemoglobinemia. Benzocaine-induced methemoglobinemia can be fatal. Therefore, physicians using this and other drugs known to cause methemoglobinemia should be able to rapidly recognize and treat this severe, albeit rare, side effect. CO-oximetry will rapidly and accurately yield the diagnosis. The most common antidote, methylene blue, should be readily available in medical institutions where topical anesthetics are frequently used.

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