Severe Methemoglobinemia Complicating Topical Benzocaine Use During Endoscopy in a Toddler: A Case Report and Review of the Literature

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Severe Methemoglobinemia Complicating Topical Benzocaine Use During Endoscopy in a Toddler: A Case Report and Review of the Literature

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ABSTRACT

Severe methemoglobinemia resulting from the use of topical benzocaine has been reported in adults as a rare complication. Here we report a case of severe acquired methemoglobinemia resulting from topical use of benzocaine spray during diagnostic upper gastrointestinal endoscopy in a 3-year-old boy with repeated episodes of hematemesis 3 weeks posttonsillectomy. He developed marked cyanosis and became increasingly agitated immediately after completion of his unremarkable endoscopic procedure, which was performed under intravenous sedation. He did not respond to maximum supplemental oxygen and had increased respiratory effort. His pulse oximetry dropped to 85%, but simultaneous arterial blood-gas analysis showed marked hypoxemia (Po_2 = 29%) and severe methemoglobinemia (methemoglobin = 39%). His cyanosis and altered mental status promptly resolved after intravenous administration of methylene blue. In patients with methemoglobinemia, pulse oximetry tends to overestimate the actual oxygen saturation and is not entirely reliable. Posttonsillectomy bleeding is a rare but occasionally serious complication that could occur weeks after the surgery, although it more commonly occurs within the first few days. Physicians should remain aware of the possibility of its late onset. This case illustrates the severity of acquired methemoglobinemia that may result from even small doses of topical benzocaine and highlights the fact that prompt treatment of the disorder can be life saving. We question the rationale for routine use of topical anesthetic spray for sedated upper gastrointestinal endoscopy in children. By bringing the attention of pediatricians to this rare but serious complication, we hope that it will result in its improved recognition and possible prevention.

Methemoglobin is an altered state of hemoglobin whereby the ferrous form of iron is oxidized to the ferric state, making the heme moiety incapable of carrying oxygen. Methemoglobinemia is an increased concentration of methemoglobin in the blood that may cause serious tissue hypoxia, from functional anemia and cyanosis when the amount of reduced hemoglobin exceeds 5 g/dL, or even death.

Methemoglobinemia could be seen in the congenital form or, more commonly, the acquired form. The congenital form arises from defects in either the erythrocytic or microsomal forms of the cytochrome b5 reductase, usually autosomal recessive, and could be associated with cyanosis from birth.[1,2] The acquired form may develop after exposure to some drugs and chemicals (Table 1), certain foods or food additives such as silver beets and incorrectly stored homemade purees, significant smoke inhalation, or after serious illness such as gastrointestinal (GI) infections and severe dehydration.[3]

Topical anesthetic drugs are widely used by clinicians during inpatient and outpatient procedures and are available also to the public in a variety of over-the-counter preparations.[4,5] Although generally safe, they have the potential of causing life-threatening methemoglobinemia. This has occurred often in older patients with preexisting comorbidity who are undergoing medical procedures involving local-anesthetic application.[6–15] An extensive review of the English-language literature using the PubMed Medline search engine of the National

Key Words: methemoglobinemia, endoscopy, benzocaine, tonsillectomy
Abbreviations: GI, gastrointestinal; ABG, arterial blood gas; Sao2, arterial oxygen saturation

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TABLE 1 **Drugs and Chemicals Associated With Acquired Methemoglobinemia**

Dapsone
Nitrate
Nitrites
Aniline
Phenazopyridine
Phenol
Methanol
Naphthalene
Benzocaine
Prilocaine
Celecoxib
Metoclopramide
Primaquine
Chloroquine
Cyclophosphamide
Trimethoprim-sulfamethoxazole
Riluzole
Ifosfamide
Acetaminophen
Methylene blue

Library of Medicine database for the last 20 years was used to support our review and conclusions.

Here we report a case of severe acquired methemoglobinemia complicating upper-GI endoscopy in a previously well child. By bringing the attention of endoscopists to this rare but serious complication, we hope that it will result in improved recognition and prompt treatment.

CASE REPORT

A 3-year-old previously healthy white boy was hospitalized for repeated episodes of significant upper-GI bleeding 3 weeks posttonsillectomy. He underwent direct laryngoscopy for evaluation of the tonsillar bed 3 days before his admission, with no visible bleeding source identified. He continued to have hematemesis with a significant drop of his hemoglobin to 4.6 g/dL, which required a blood transfusion. The pediatric GI service was consulted for endoscopic evaluation of a possible GI source of his hematemesis.

The child's preprocedure physical examination in the endoscopy suite was within normal limits. Intravenous sedation with 0.1 mg/kg of midazolam and 1 μg/kg of fentanyl was administered. The child's oropharynx was sprayed once with topical 20% benzocaine anesthetic spray (Hurricaine, Beutlich Pharmaceuticals, Waukegan, IL). The endoscopy procedure was uncomplicated, and no GI source of bleeding was identified. As the procedure was completed and the child was becoming more awake, he started to show progressive cyanosis and increased irritability. Oxygen saturation measured by pulse oximetry dropped from 97% during the procedure to the low 80% range while still on O_2 by nasal prongs and later on 100% O_2 by a nonrebreathing mask. He had good air exchange and increased respiratory effort with hyperventilation. His circulation was good with warm extremities, and normal blood pressure was maintained. However, he became tachycardic (heart rate: 140–170/minute) and tachypneic (respiratory rate: 40–50/minute) as he seemed more cyanotic and became more confused. He became agitated with an otherwise normal neurologic examination. A chest radiograph showed no abnormalities. The child was transferred to the PICU, and arterial blood gas (ABG) was obtained to determine the need for mechanical ventilation support. The blood had a chocolate color, and the ABGs revealed significant hypoxemia (Pao_2 = 29%), hypocapnia (Pco_2 = 12), and compensated metabolic acidosis (pH 7.31). Acquired methemoglobinemia was suspected, and a markedly elevated methemoglobin level (39%) confirmed the diagnosis. The child was given an intravenous methylene blue infusion at a dose of 1 mg/kg, which promptly cleared his central cyanosis, restored normal oxygenation, and improved the ABGs. He was observed in the hospital overnight and was discharged fully recovered, without additional cyanosis or signs of neurologic deficit.

DISCUSSION

The only drug that this patient received known to be associated with acquired methemoglobinemia was topically administered benzocaine spray to the oropharynx before his endoscopy. The administered dose from a single spray averages 56 mg of benzocaine, which would be ~3 to 5 mg/kg in this patient (Beutlich Pharmaceuticals, verbal communication, 2005). Doses as low as 20 to 40 mg/kg have been associated with methemoglobinemia, but this was obviously a much lower dose than normally expected to be problematic. His recent tonsillectomy and suspected rebleeding from the peritonsillar bed may have increased the systemic absorption of the topical benzocaine, resulting in this severe methemoglobinemia.

Our patient had pulse-oximetry recordings that seemed satisfactory and then mildly decreased despite his clinical deterioration. His oxygen saturation was measured by 2 techniques that are frequently used interchangeably, although the measuring systems are different. Pulse oximetry is a noninvasive, spectrophotometric method to determine relative arterial oxygen saturation (Sao_2). Blood-gas instruments calculate the estimated O_2 saturation from empirical equations using pH and Po_2 values. In most patients, the results from the 2 methods will be virtually identical, but in conditions such as methemoglobinemia, it is crucial that the distinctions and limitations of these methods be understood.[16] Oxygen saturation calculated from pH and Po_2 should be interpreted with caution, because the algorithms used assume normal O_2 affinity, normal 2,3-diphosphoglycerate concentrations, and no dyshemoglobins or hemoglobinopathies. In cases of increased methemoglobin fraction, pulse-oximeter values trend toward 85%, over-

estimating the actual oxygen saturation. When increasing levels of methemoglobin were induced in an animal model, Barker et al[17] showed that pulse-oximeter saturation overestimated the fractional Sao2 by an amount proportional to the concentration of methemoglobin until the latter reached ~35%. At that level, the pulse-oximeter saturation values reached a plateau of 84% to 86% and did not decrease further; thus, it is recommended that pulse-oximetry data be used with caution in patients with methemoglobinemia.

Another method of measuring blood oxygen saturation is co-oximetry. This is a more complex but also more reliable method that measures the concentration of hemoglobin derivatives in the blood from which various quantities such as hemoglobin derivative fractions, total hemoglobin, and saturation are calculated. Co-oximeter reports usually include the dyshemoglobin fractions (carboxyhemoglobin and/or methemoglobin) in addition to the oxyhemoglobin fraction.[16] Therefore, in cases of suspected methemoglobinemia, it is more helpful to check the oxygen saturation by co-oximetry when available.

There are several reports of drug-induced methemoglobinemia with significant cyanosis, hypoxemia, and even fatalities, mainly in adults with compromised cardiovascular status. Exposure to benzocaine spray or lidocaine jelly occurred during endotracheal intubation,[6] flexible bronchoscopy,[7] transesophageal echocardiogram,[8,9] direct laryngoscopy,[10] upper-GI endoscopy,[11,12] topical anesthetic teething preparations,[5] and after topical treatment with 0.5% silver nitrate solution for burn injuries or necrotizing fasciitis.[13]

There are some reports of younger patients, including infants and newborns, who developed severe methemoglobinemia after use of topical lignocaine/prilocaine cream (EMLA; Astra Pharmaceuticals, North Ryde, New South Whales, Australia) for pain relief after circumcision in newborns.[14,15]

Clinicians do not usually expect significant systemic absorption from the use of topical benzocaine spray, but clearly this is not always true. Potential risk factors include greater concentration in topical anesthetic gel or ointment, increased systemic absorption from mucosal surfaces, compromised or abraded skin, the addition of occlusive dressing, or delayed clearance in neonates with immaturity of the methemoglobin-reductase pathway.

Delayed bleeding after tonsillectomy is a rare but occasionally serious complication that could occur several weeks after surgery, although it occurs more commonly within the first few days.[18] Physicians should remain aware of the possibility of late-onset bleeding, as highlighted by this case.

Methemoglobinemia should always be suspected in the endoscopy suite in patients with central cyanosis (in the absence of other identifiable etiology) who do not respond to administration of supplemental oxygen or assisted ventilation. There is often a discrepancy between oxygen saturation measured by pulse oximetry and the arterial fractional Sao2 determined by blood-gas analysis. Prompt recognition and treatment may prevent potentially life-threatening complications. Primary prevention may eliminate the morbidity and mortality associated with this condition; hence, the need to identify some of its risk factors cannot be overemphasized.

Gunaratnam et al[19] argue against the routine use of topical anesthetic spray in sedated adults undergoing upper-GI endoscopy. Recent reports have urged caution when using topical anesthesia during GI endoscopic procedures,[20,21] indicating that liberal use of topical anesthetic spray could result in severe methemoglobinemia. Hence, Armstrong et al[22] strongly recommend that all endoscopists be aware of benzocaine-induced methemoglobinemia. With increasing concerns about systemic toxicity and possible risk of aspiration after its topical use, some gastroenterologists argue that benzocaine spray could become obsolete.[23] Therefore, it may be prudent to avoid the use of topical anesthetic ointment or spray in patients undergoing endoscopic procedures, particularly in those who may have undergone any recent oropharyngeal surgery.

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