"Endoscopy Blues"

To the Editor:

A 3-year-old boy with repeated episodes of hematemesis 3 weeks after tonsillectomy underwent diagnostic upper gastrointestinal endoscopy under intravenous sedation. His oropharynx was sprayed twice before endoscopy with topical 20% benzocaine anesthetic spray (Hurricaine, Beutlich Pharmaceuticals, Waukegan, IL). No source of bleeding was identified. He experienced marked cyanosis and became increasingly agitated immediately after completion of this otherwise unremarkable procedure. He did not respond to maximum supplemental oxygen with 100% O_2 by a nonrebreathing mask and had increased respiratory effort. His pulse oximetry dropped to 85%, but simultaneous arterial blood gas analysis showed marked hypoxemia (PO_2 29%), hypocapnia (PCO_2 12), and a compensated metabolic acidosis (pH 7.31). Acquired methemoglobinemia was suspected, and a markedly elevated methemoglobin level (39%) confirmed the diagnosis. Intravenous methylene blue administered at 1 mg/kg promptly cleared his central cyanosis and improved the arterial blood gases.

Methemoglobinemia is an increased blood concentration of methemoglobin, 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. This can cause serious tissue hypoxia from functional anemia and cyanosis, or even death, when the amount of reduced hemoglobin exceeds 5 g/dL. Methemoglobinemia can be seen in the congenital form or, more commonly, the acquired form. The congenital form arises from defects in the cytochrome b5 reductase, usually autosomal recessive, and is often associated with cyanosis from birth.[1] The acquired form may develop after exposure to some drugs and chemicals (eg, dapsone, nitrate, benzocaine, chloroquine), certain foods or food additives (eg, nitrites), or after serious illness and severe dehydration.[2]

Severe acquired methemoglobinemia was a complication of upper gastrointestinal endoscopy in this previously well toddler. The only drug he received with known association with acquired methemoglobinemia was benzocaine spray. His recent tonsillectomy may have increased systemic absorption, resulting in severe methemoglobinemia. His oxygen saturation (SO_2) was measured by two techniques: pulse oximetry, a noninvasive spectrophotometric method to determine relative arterial oxygen saturation (SaO_2), which appeared mildly decreased despite his clinical deterioration; and blood gas analysis, estimating O_2 saturation from empirical equations using pH and PO_2 values. In most patients, the results from the two methods will be virtually identical, but in conditions such as methemoglobinemia, it is crucial that the distinctions and limitations of these methods be understood.[3] SO_2 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%, overestimating the actual O_2 saturation.[3]

Severe methemoglobinemia complicating the use of local anesthetics has been reported as a rare complication, with cyanosis, hypoxemia, and even fatalities after topical exposure to benzocaine spray during direct laryngoscopy,[4] flexible bronchoscopy,[5] and upper gastrointestinal endoscopy[6]; use of lidocaine jelly in transesophageal echocardiogram[7]; use of over-the-counter topical anesthetic teething preparations,[8] and topical treatment with 0.5% silver nitrate solution for burn injuries or necrotizing fasciitis.[9] There are reports of newborns experiencing severe methemoglobinemia after the topical use of lignocaine/prilocaine cream (EMLA, Astra Pharmaceuticals, North Ryde, NSW, Australia) for pain relief after circumcision.[10] Topically administered medications are often presumed to have minimal systemic absorption. Potential risk factors in some reported cases may 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.

Methemoglobinemia should always be suspected in the endoscopy suite in patients with central cyanosis who do not respond to the administration of supplemental oxygen or assisted ventilation. Prompt recognition and treatment may prevent potential 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. 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. The rationale for the routine use of topical anesthetic spray for sedating children for upper gastrointestinal endoscopy may need to be questioned. By bringing this rare but serious complication to the attention of endoscopists, it is hoped that the result will be improved recognition and prompt treatment.

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Treatment of Type II Cryoglobulinemia Associated With Hepatitis C With Rituximab

To the Editor:

Cryoglobulinemia is a severe and common extrahepatic manifestation of hepatitis C virus (HCV) infection.[1,2] Treatment options to date have consisted of antiviral therapies or cytotoxic immunosuppressive agents.[3–5] Recently, rituximab, a human-mouse chimeric monoclonal antibody to the B cell marker CD20, has been used for treatment of HCV-related cryoglobulinemia in European patients.[6–9] We hereby report a United States experience with 3 cases.

A 63-year-old woman with cryoglobulinemia-associated nephropathy, retinopathy, and neuropathy was intolerant of interferon therapy (suicidal ideation). Because of accelerated hypertension, increased neuropathy, and new visual symptoms, she was given rituximab 375 mg/m^2 for 4 weeks. Immediately after treatment, she experienced significant improvement in peripheral neuropathy and visual symptoms, with improved vision in her left eye as well as resolution of a scotoma in her right eye. Her foot numbness and paresthesias resolved. The cryocrit fell from 4% before treatment to less than 1%. For more than 1 year after treatment, her cryocrit has remained below 1%, and she has remained in clinical remission.

A 51-year-old man with severe neuropathy for more than 6 years did not experience sustained improvement with interferon or cytotoxics. He received 375 mg/m^2 rituximab for 4 weeks and had significant clinical improvement within 2 weeks. From a pretreatment cryocrit of 16%, the patient's cryocrit remained less than 2% for 12 months after therapy. He reported increased functionality as well as decreased pain at the 18-month follow-up visit.

A 55-year-old woman with neuropathy was intolerant to interferon and unimproved after treatment with gabapentin. Because of worsening neuropathy, making it difficult for her to ambulate and limiting the use of her hands, she was given 375 mg/m^2 rituximab for 4 weeks. Shortly after completing her rituximab treatment, she underwent liver transplantation. At the 6-month follow-up visit, she experienced improved ambulation and resolution of pain in her lower extremities, and she had tapered off her dose of gabapentin. Her serial cryocrits remained persistently less than 1% for more than 6 months of follow-up.

To our knowledge, we report the first cases in the United States of the efficacy of rituximab in 3 patients with severe HCV-related type II mixed cryoglobulinemia. In all cases, rituximab was shown to be an effective alternative to interferon in patients with symptoms of cryoglobulinemia who were previously intolerant or resistant to interferon therapy. In addition, all these patients had previously tried other therapies, including corticosteroids, cyclophosphamide, gabapentin, and plasma exchange, with only variable improvement. All had considerable sustained decreased cryocrit values, despite no obvious changes in HCV RNA levels. Importantly, all patients tolerated rituximab well. Rituximab represents an important alternative to interferon in the management of HCV-related type II cryoglobulinemia, but its safety should be established in clinical trials.

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