Acute cyanosis and methemoglobinemia developed following topical application and partial ingestion of benzocaine for esophagogastroduodenoscopy. A diagnosis of acute toxic methemoglobinemia should be considered when cyanosis, with or without neurologic symptoms, occurs following the use of local anesthetics in the absence of cardiopulmonary disease. Laboratory tests should include oxygen saturation and methemoglobin concentration. Management includes supplemental oxygen administration and intravenous methylene blue.

INDEX TERMS: CYANOSIS; BENZOCAINE; METHEMOGLOBIN

THE ACUTE ONSET of cyanosis is alarming, even if the etiology is suspected. Cyanosis is usually secondary to hypoxemia caused by tension pneumothorax, pulmonary embolism, obstruction of the upper or lower airways, or collapse of the cardiovascular system. The differential diagnosis should also include methemoglobinemia, which can be caused by several drugs used during surgery and anesthesia. These include local anesthetic agents such as prilocaine. Methemoglobinemia also is a rare complication following the use of benzocaine. The diagnosis is easily made and treatment with methylene blue is effective if it is begun early.

Most reports concerning benzocaine-induced methemoglobinemia are single, isolated cases that involve children. We describe here an episode of acute methemoglobinemia following topical anesthesia with benzocaine 20% (Hurricane) prior to esophagogastroduodenoscopy in an adult.

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the next 20 minutes. The patient was awake and in stable condition when she was transferred to the recovery unit.

Approximately 55 minutes after endoscopy the patient became cyanotic. Arterial pressure and heart rate remained unchanged. She was not tachypneic. Nasal oxygen was administered. Arterial blood gas measurement showed: pH, 7.36; PaCO₂ 30 mmHg; PaO₂ 340 mmHg. Total hemoglobin was 14.6 gm/dL, with an oxygen saturation of 33%. Methemoglobin concentration was 67%. Oxygen content was 7.5 vol%.

Methylene blue, 120 mg, and ascorbic acid, 500 mg, were administered intravenously. The methemoglobin level fell to 4.5% after 2 hours. Except for a brief, slight headache, the patient was asymptomatic. An additional dose of methylene blue, 120 mg, was repeated during the evening. The methemoglobin level on the following morning was 2%. The patient recovered uneventfully and was discharged from the hospital on the second postoperative day.

**DISCUSSION**

The ideal topical anesthetic for endoscopy has a rapid onset and short duration of action, and is not absorbed systemically. Most available topical anesthetics, such as lidocaine, tetracaine, and cocaine, are absorbed through mucous membranes. Because of its onset in 30 seconds, 5-to 15-minute duration of action, and virtual absence of systemic absorption, benzocaine is an obvious choice for this procedure and has been widely and safely used.

Two types of adverse reactions to benzocaine have been noted. They result either from allergic sensitization or methemoglobinemia. Allergic sensitization is common, and it has been long recognized that benzocaine can cause methemoglobinemia. Most reported cases have involved infants or children, and these reports have often cited a break in the integrity of the skin or membrane through which the benzocaine entered the circulation. There was no known inflammatory or ulcerative process in our patient to facilitate the absorption of benzocaine, but endoscopic abrasion of the esophageal mucosa may have been a contributory factor.

Although our patient received other drugs in addition to benzocaine, none are known to produce methemoglobinemia. From the amount of benzocaine solution administered (two vials, 30 mL each), and the concentration of benzocaine in the preparation (20%), the total dose to this patient can be calculated as about 12 g. It is unlikely that more than one-half of this total was swallowed, which in this patient still amounts to a dose of 120 mg/kg. The dose-response relationship for benzocaine toxicity has been estimated from published reports involving infants. As little as 15 mg to 25 mg per kilogram of body weight of benzocaine has been associated with methemoglobinemia and cyanosis. Administration of 100 mg/kg of benzocaine to rats produces 40% to 50% methemoglobinemia within 20 minutes. Recognition of this dose-response should discourage overzealous use.

Benzocaine, which has a pKa of approximately 3.5, is almost 100% nonionized throughout the normal human physiologic pH range, including gastrointestinal tract milieu when the pH is equal to or greater than 5.0. This, along with the large quantity of drug ingested by this patient, argues for potential rapid absorption. The lack of immediate onset of symptoms in our patient suggests the influence of other factors. For example, delayed gastric emptying could slow the passage of benzocaine to distal absorptive sites, or serum protein binding of the drug could limit its pharmacologic activity. There is scant information in the literature regarding either possibility.

Methemoglobin is the normal oxidation product of a small amount of hemoglobin present within erythrocytes. As a result of oxidation, some of the hemoglobin iron is converted from the ferrous (Fe²⁺) state to the ferric (Fe³⁺) state. Fe³⁺ cannot bind to and transport elemental oxygen. Normally, the methemoglobin reductase system maintains methemoglobin in equilibrium with deoxygenated hemoglobin. Acquired methemoglobinemia occurs when a parent drug or its metabolites cause the rate of hemoglobin oxidation to exceed the reductive capacity of erythrocytes. In an adult, the agent must be present in an amount that is large enough to overwhelm the reductase system. Infants, who have physiologic deficiency of the enzyme, are at a much higher risk.

Rarely, methemoglobinemia may be an inherited condition caused by a deficiency of the enzyme NADH-reductase. The presence of an abnormal hemoglobin (type M) also may cause the condition. These disorders can be excluded by the absence of a history of chronic cyanosis.

Cyanosis following the use of topical anesthetics is an indication for immediate arterial blood gas measurement. A PaO₂ that is higher than expected for the clinical degree of cyanosis, or arterial blood that is darker than indicated by the measured PaO₂, suggests the possibility of methemoglobinemia. Although 5 g/dL of deoxyhemoglobin must be present to cause cyanosis, only 1.5 to 2.0 g/dL of methemoglobin, which has a dark
brown color, is necessary to produce cyanosis of an equal degree.

In methemoglobinemia, cyanosis results from the decreased oxygen-carrying capacity of the blood and from the leftward shift of the oxygen-hemoglobin dissociation curve, with decreased release of oxygen to the tissues. The diagnosis is confirmed spectrophotometrically. Treatment is indicated when the level is 30% or greater.11

Cardiovascular compensatory mechanisms do not occur until the methemoglobin level is above 40%. Ataxia, prostration, and unconsciousness may occur at levels above 60%, with death supervening at a concentration of about 85%.9 Although our patient had a measured methemoglobin level of 67%, she experienced no cardiovascular, respiratory, or neurologic manifestations, except for a slight headache. This may be explained by her high total hemoglobin level, which allowed an oxygen content of 7.5 volume percent to be circulated. Although very low, this amount of circulating oxygen was apparently sufficient to sustain normal nervous and cardiopulmonary system function while she was at rest.

The primary treatment of toxic methemoglobinemia is the intravenous administration of methylene blue, 1 mg to 2 mg per kilogram of body weight, given over 5 to 10 minutes. Methylene blue functions as an artificial electron carrier and increases the rate of methemoglobin reduction in the red blood cell. It rapidly reduces the methemoglobin level within 30 to 60 minutes. Repeated doses are necessary on occasion. This treatment is relatively ineffective in individuals who have glucose-6-phosphate dehydrogenase insufficiency or hemoglobin M.

Ascorbic acid is also used in treatment. It causes a nonenzymatic reduction of a small amount of methemoglobin. The slow action of ascorbic acid permits prolonged tissue hypoxia, so it cannot be recommended exclusively for treatment of acute toxicity.

Benzocaine is among the most widely used and safest of topical anesthetics.3 Methemoglobinemia is uncommon, but it may occur in patients of any age. Why this nonoxidizing compound should cause this response is unknown. It can be diagnosed easily and treated effectively with methylene blue. Even if methemoglobin levels are high, prognosis is excellent if therapy is begun early.

REFERENCES