Acquired Methemoglobinemia Precipitated By The Use Of Topical Anesthetic Agents: Discussion And Review Of The Literature

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Abstract

There are less than fifty case reports/series describing the rare, but potentially serious side effect of methemoglobinemia following the administration of a topical anesthetic agent. Rapid diagnosis and implementation of treatment is necessary for successful patient outcomes. The focus of this article is to review acquired methemoglobinemia precipitated by the administration of topical anesthetic agents. The causes, diagnosis, treatment, and prognosis of this rare entity are reviewed.

INTRODUCTION ,

The iron in deoxygenated hemoglobin, in order to function as a reversible binder of oxygen, must remain in the ferrous (Fe^{2+}) state after oxygen delivery. The oxidation of ferrous ions in the deoxygenated hemoglobin complex to a ferric (Fe^{3+}) state renders the deoxygenated hemoglobin molecule unable to participate in oxygen delivery in part because of an inability to reversibly bind oxygen. The molecule formed by this oxidative process is referred to as methemoglobin.

In healthy adults, methemoglobin consists of less than three percent of the body's total hemoglobin content. There are multiple reducing pathways that serve to maintain very low amounts of methemoglobin the serum, the two main of which are NADH-diaphorase and NADPH-flavin reductase (alternatively referred to as NADPH-diaphorase). The normal functions of these reducing pathways serve to maintain serum methemoglobin levels under one percent.

The causes of increased serum methemoglobin (i.e., methemoglobinemia) are numerous and can broadly be broken down into two broad categories, congenital and acquired. Each of these broad categories have two major etiologies. Congenital causes may include abnormalities in the structure of hemoglobin or abnormalities in the reducing systems that are responsible for the degradation of formed methemoglobin. Acquired causes are most commonly due to toxins (i.e., pharmacological agents). A transient increase in the level of serum methemoglobin may be due to illness in infants.

The focus of this article is to review acquired methemoglobinemia precipitated by the use of toxins, specifically with the use of topical anesthetic agents. The causes, pathophysiology, diagnosis, treatment, and prognosis of this rare entity will be reviewed.

METHODS

MedLine was searched via PubMed (1966-2005) to identify articles discussing acquired methemoglobinemia precipitated by the use of topical anesthetics. The following broad search terms were utilized: topical, anesthetics, and methemoglobinemia.

PATHOPHYSIOLOGY

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A search of MedLine reveals that less than fifty case reports/series have been published involving the rare side effect of methemoglobinemia following the use of topical anesthetics agents. (A tabulation of the reported cases is listed in the reference section).

A variety of topical anesthetics have been implicated in these cases, most commonly being used as adjuncts for a variety of diagnostic/therapeutic procedures such as echocardiography (transesophageal), endoscopy, and laryngoscopy. Rare cases have been reported with the use of topical, pain relieving ointments with precipitant anesthetics as ingredients. Specific topical anesthetics reported include benzocaine (most commonly), EMLA (composed of lidocaine and prilocaine), lidocaine, cocaine, and cetacaine

(composed of benzocaine, tetracaine, and butamben).

The exact pathophysiology of this entity is not completely understood. In the case of prilocaine induced methemoglobinemia, it is believed that O-toluidine, formed during liver metabolism, is responsible for oxidation of the Fe2+ into the Fe3+ state, and hence the formation of methemoglobin.

DIAGNOSIS ,,

The differential diagnosis of cyanosis, especially in the context on a patient who has recently been administered a topical anesthetic preparation must include methemoglobinemia. The diagnosis of methemoglobinemia is readily made by arterial blood gas analysis. Methemoglobin (631 nm) can be detected by absorption spectrometry.

A serum level of 1.5g/dl (or approximately 10% of total serum hemoglobin) of methemoglobin is adequate to produce the clinical feature of cyanosis. As levels of serum methemoglobin increase, patients may complain of nonspecific symptoms such as fatigue, headache, dyspnea (which may be acute onset and confused with pulmonary embolism), and tachycardia. With increasing levels, consciousness can be impaired and death may result. Patients with anemia are more susceptible to the effects of increased concentrations of methemoglobin.

Several clinical clues can point towards a diagnosis of methemoglobinemia and are listed in Table 1.

Figure 1

Table 1: Methemoglobinemia: Clinical Clues in Diagnosis

Appearance	When an arterial blood gas is drawn, the blood is commonly referred to as having a brown or chocolate color.
Exposure to Air	Upon exposure to air, the color of the blood does not change. If methemoglobin levels are greater than 35%, the observation of a lack of color change when exposed to air (when compared to a control) may be sufficient to make a diagnosis.
Response of Cyanosis	The cyanosis induced by increasing serum methemoglobin is not responsive to increasing FiO_2 concentrations of inspired oxygen.
PaO_2	PaO_2 is normal or even increased.
Metabolic Acidosis	A metabolic acidosis may be present secondary to decreased delivery of oxygen to tissues.
Oxygen Saturation	The oxygenation saturation determined by pulse oximetry and that determined by the arterial blood gas (calculated) differ by more than 5%.

It is important to note that the levels of methemoglobin increase with time; therefore arterial blood gas samples should be tested immediately after drawn to avoid falsely increased readings.

TREATMENT

In the majority of cases, supportive care is all that is required for the successful treatment of methemoglobinemia. This includes withdrawal of the suspected responsible agent. When levels of methemoglobin approach thirty percent of total serum hemoglobin, systemic effects are noted (central nervous system instability, signs of ischemia, cardiovascular effects, etc.), and/or the patient may not be able to tolerate the ischemia due to comorbid medical conditions (such as severe cardiovascular disease), treatment should include additional therapy. Conservatively, this may include 100% oxygen, topical decontamination, and activated charcoal (in cases of ingestion).

In patients who do not have a known history of G6PD deficiency, methylene blue is the pharmacological agent of choice. A functioning G6PD enzyme system, responsible for the formation of NADPH, is necessary for the reduction of methylene blue into the active leukomethylene blue. Leukomethylene blue is responsible for activation of the methemoglobin reducing systems, and hence the reduction in the level of serum methemoglobin.

A dose of 1-2 mg/kg of a 1% methylene blue solution in saline can be given over 3-5 minutes, with responses usually

being seen within 1 hour. Repeat doses can be given for incomplete responses, but it is suggested that a total dose of 7 mg/kg should not be exceeded to avoid side effects. As methylene blue may cause inaccurate pulse oximetry readings, response to therapy should be evaluated by repeat measurements of the amount of methemoglobin in the serum.

Side effects of methylene blue may include non-specific symptoms such as hypertension, tachycardia, and chest pain. It is not uncommon to observe a blue-green color to the urine after administration of methylene blue. It is excreted through the urinary system.

In patients with G6PD deficiency, a variety of therapeutic approaches have been suggested, none of which are as effective. Therapies to consider may include hyperbaric oxygen therapy and exchange transfusion. Other therapies include ascorbic acid and alpha-tocepherol; however, the onset of action of ascorbic acid is too slow for utility in emergency situations.

PROGNOSIS

Quick recognition and administration of appropriate treatment can lead to successful outcomes for patients affected by acquired methemoglobinemia in the setting of topical anesthetic use.

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