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Case Report

Severe methemoglobinemia caused by prilocaine: A rare case report

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Abstract

Hemoglobin is a molecule found in erythrocytes that transports oxygen to tissues. Methemoglobin, a form of hemoglobin that can no longer bind oxygen, is formed when the ferrous iron in normal hemoglobin becomes ferric iron as a result of oxidation due to various kinds of oxidative stress. Methemoglobinemia can be congenital, however, exposure to toxins is more often the cause. Local anesthetics can occasionally cause methemoglobinemia, and the potential effects increase with combined or excessive use. Prilocaine-induced methemoglobinemia has been reported, though it is rare. Presently described is the case of an adult case of methemoglobinemia, which developed following a prilocaine injection for fibromyalgia pain. Methylene blue treatment and adjuvant therapy resulted in recovery. This case report serves as a reminder that that prilocaine can be a cause of adult-acquired methemoglobinemia. Methylene blue treatment and adjuvant therapy consisting of infusions of 100% oxygen and 0.9% sodium chloride administered promptly can prevent potentially severe toxic effects.

Keywords: Cyanosis, methemoglobinemia, prilocaine

Hemoglobin (Hb) is a molecule found in erythrocytes that enables the transport of oxygen to tissues. To maintain this function, the iron in its structure must be in the ferrous (Fe^{++}) form. The ferrous iron in normal Hb can become ferric iron (Fe^{+++}) as a result of oxidation due to various oxidative stresses, resulting in the formation of methemoglobin (metHb). Because MetHb cannot efficiently transport oxygen, the Hb-oxygen dissociation curve is shifted to the left [1]. Various mechanisms in an organism can reduce metHb. The effect of cytochrome b5 methemoglobin reductase, which is dependent on reduced nicotine adenine dinucleotide (NADH), known as NADH-diaphorase, is the primary mechanism to convert metHb to Hb. Other adjuvant mechanisms involve ascorbate and reduced glutathione [2]. Under physiological conditions, metHb does not exceed 2% to 3% of total Hb. Acute conditions of 20% to 30% can be tolerated in individuals without anemia; however, a metHb level of >70% can be fatal [3]. The observation of blue-gray cyanosis unresponsive to oxygen therapy in a clinical setting is important.

Methemoglobinemia may develop due to hereditary or acquired causes, however, acquired methemoglobinemia is more common. Several chemical agents and drugs have been reported as a cause of methemoglobinemia. These include nitrites, nitrates, chlorates, quinines, aminobenzene, nitrobenzenes, nitrotoluenes, phenacetin, chloroquine, dapsone, phenytoin, sulfonamides, and local anesthetics [1]. Prilocaine is often used as a local anesthetic. Prilocaine-induced methemoglobinemia is rare [3]. Presently described is a case of methemoglobinemia in an adult, which developed after prilocaine was administered for fibromyalgia pain, and subsequent recovery with methylene blue and adjuvant therapy.

Case Report

A 32-year-old female patient was admitted to the emergency department with complaints of dyspnea, cyanosis in the lips and hands, dizziness, headache, palpitations, shivering, tinnitus, and paresthesia (Fig. 1). The patient had received

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injections of prilocaine for local pain due to fibromyalgia 10 hours prior to presentation (900-1000 mg prilocaine). The patient presented with central cyanosis and a blood pressure of 135/80 mmHg, a pulse rate of 101/rhythmic per minute, and a respiratory rate of 28 per minute. The other system examinations yielded normal findings: Hb value of 12.8 g/dL, hematocrit value of 36%, mean corpuscular volume of 86 fl, leukocyte count of 7900/mm^3, and a platelet count of 284.000/mm^3. Other routine biochemical examinations revealed no abnormalities. Electrocardiography demonstrated a normal sinus rhythm. An arterial blood gas test indicated a pH of 7.30, a pO_2 of 78 mmol/L, sO_2 of 77%, pCO_2 of 35 mmol/L, HCO_3 of 20 mmol/L, and a metHb value of 45%. Pulse oximetry determined a 77% oxygen saturation level. An infusion of 0.9% sodium chloride (NaCl) (100 mL/hour) was initiated, as well as oxygen with a 10 L/min mask, however, the cyanosis persisted and the patient was monitored in the intensive care unit of the department of internal medicine. To treat the methemoglobinemia, 1.5 mg/kg 1% methylene blue was administered by intravenous bolus for 5 minutes. Following that, a 30 mL 0.9% NaCl push was administered. The patient's complaints resolved within 1 hour of emergence; the cyanosis in her hands and lips as well as her other symptoms regressed. No hypotension or arrhythmia developed during follow-up. A second-hour arterial blood gas test revealed a pH of 7.40, pO_2 of 84 mmol/L, pCO_2 of 34 mmol/L, and an sO_2 level of 98%. The metHb level had regressed to 0.3%. The patient recovered in terms of general medical condition and was discharged with a full recovery (Fig. 2).

The patient provided written, informed consent for the publication of this report and the use of images.

Discussion

Methemoglobinemia generally occurs in adults due to toxic exposure, and pharmaceutical drugs constitute a large portion of these causes. Local anesthetics can occasionally cause methemoglobinemia, particularly in combination [4]. It has been reported that methemoglobinemia may develop as a result of the use of local anesthetic creams, especially in newborns and infants [5]. Methemoglobinemia induced by local anesthetics may also be seen in adults; however, prilocaine-induced cases are rare [3]. Prilocaine at therapeutic doses (1-2 mg/kg) may cause limited methemoglobinemia without cyanosis. The maximum safe dose of prilocaine in a single injection is 8 mg/kg (maximum 600 mg) [6]. In this case, 900-1000 mg prilocaine had been administered, which greatly exceeded the recommended limits.

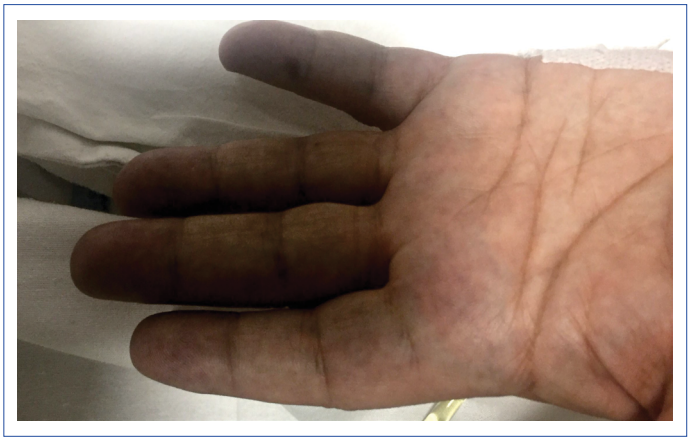

Figure 1. Visible cyanosis in the fingers before treatment.

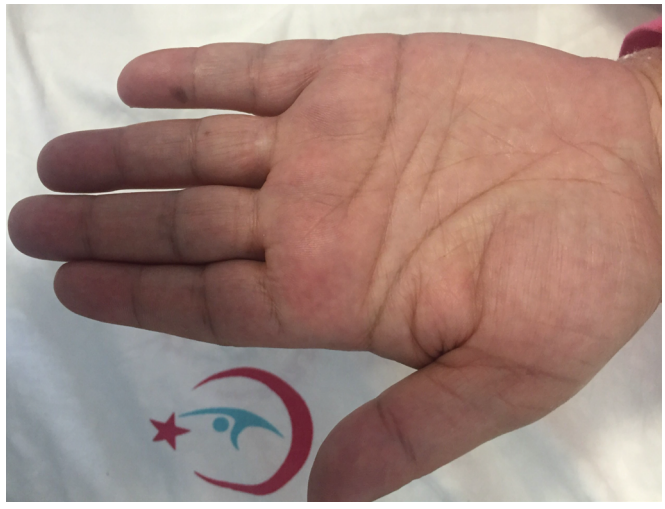

Figure 2. Regression of cyanosis after treatment.

The effects of local anesthetic methemoglobinemia can include seizures, respiratory failure, myocardial infarction, shock, coma, hypoxic encephalopathy, and death. In a retrospective study of methemoglobinemia cases, it was reported that most patients with a metHb value of >8% were symptomatic [6]. The biological half-life of prilocaine is 55 minutes; methemoglobinemia can develop within 20-60 minutes [7]. Methemoglobinemia should be taken into consideration in the differential diagnosis of patients who present with cyanosis and normal circulatory and respiratory system findings. Under physiological conditions, metHb typically represents <1% of Hb and does not exceed 2% to 3%. Disturbance of the balance between oxidation and reduction may raise concentrations above normal levels [8]. Exposure to oxidant agents may cause methemoglobinemia, even in healthy individuals. Ordinarily, the metHb concentration is maintained due to the effect of cytochrome b5 methemoglobin reductase, which is found in red blood cells. In some circumstances, the compensation mechanism does not work properly and as a result of an increased metHb level and reduced delivery of oxygen, the oxyhemoglobin dissociation curve shifts to the left [8, 9].

Mild cases may be asymptomatic, but severe cases can lead to cyanosis, tachypnea, tachycardia, hypotension, confusion, and even death. Cyanosis may be present at varying levels and disparate presentation. A blood metHb level of >10% often results in evident peripheral cyanosis, and tissue hypoxia and generalized cyanosis are seen at a metHb level of 35%.

A metHb level approaching 70% may lead to a coma, and if not treated, potential death [9, 10]. In our case, a metHb level of 45% was observed following an injection of prilocaine to relieve fibromyalgia pain. The patient had dyspnea, cyanosis of the lips and hands, dizziness, headache, and palpitations. The metHb level and clinical findings were consistent with the findings in the literature.

The first precaution to take after development of methemoglobinemia following exposure to a chemical agent or drug is to prevent further exposure to the agent. Although a metHb level of 20% can be tolerated, clinical symptoms may appear and worsen as the level increases [11]. Methylene blue, ascorbic acid, and riboflavin have been advised as treatment alternatives. The risk of death is greater in patients with a metHb level ≥70. In these cases, hyperbaric oxygen therapy is advised [1]. However, methylene blue is the first treatment suggestion in all circumstances. A slow intravenous dose of 1-2 mg/kg can quickly activate the NADPH-metHb reductase enzyme system [1]. Response to treatment should be evaluated quantitatively based on the decrease in metHb in 1-2 hours as well as clinical findings. The conversion of metHb into hemoglobin upon methylene blue administration generally starts in 15-60 minutes [10]. It should also be kept in mind that methylene blue can also be a rare cause of methemoglobinemia [12]. In this case, we administered 1.5 mg/kg of 1% methylene blue solution to the patient intravenously using a 5-minute infusion. Concomitantly, we administered 100% oxygen and 0.9% NaCl treatment. A rapid decrease in the metHb level was observed in 1 hour.

Conclusion

Methemoglobinemia should be considered in patients with inconsistent oxygen saturation and pO_2 values and cyanosis following minimally invasive interventions. Prilocaine, a local anesthetic, is a very rare cause of adult-acquired cases of methemoglobinemia. Prompt adjuvant therapy with infusions of 100% oxygen and 0.9% NaCl as well as methylene blue can prevent toxic effects and result in full recovery.

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