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Case Series

Prilocaine Induced Methemoglobinemia: Two Case Reports

Sezin Okdemir*

Department of Emergency Medicine, Bilecik Training and Research Hospital, Bilecik, Turkey

***Corresponding Author:** Sezin Okdemir, Department of Emergency Medicine, Bilecik Training and Research Hospital, Bilecik, Turkey.

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Abstract

Background: Methemoglobinemia is a disease that develops as a result of the oxidation of iron in hemoglobin, causing cyanosis due to inadequate oxygen transport to tissues. Prilocaine is a widely used local anesthetic that causes methemoglobinemia in infants, even in therapeutic doses.

Purpose: Here, I present my experience on the intravenous ascorbic acid treatment of two cases that developed cyanosis after prilocaine-induced toxic methemoglobinemia.

Procedures: A five-month-old infant male and a 36-day-old newborn male were admitted to the Emergency Department after circumcision operations. Blood methemoglobin levels were 31.8% and 45.4%, respectively. The patients were treated intravenously with 300 mg/kg ascorbic acid. Cyanosis had completely resolved within 2h.

Main Findings: In toxic methemoglobinemia, intravenous ascorbic acid could be used when methylene blue is not available.

Principle Conclusions: Local anesthetic agents should be used at the lowest effective dose in infants and risk of methemoglobinemia should considered.

Keywords: *Methemoglobinemia; Prilocaine; Infant; Cyanosis*

Introduction

Methemoglobinemia is a disease that develops as a result of iron (Fe) in hemoglobin oxidizing from Fe^{+2} to Fe^{+3}, which causes cyanosis due to inadequate oxygen transport to tissues. Under normal circumstances, < 1% to 2% of circulating hemoglobin exists as methemoglobin (MetHb), with the accumulation of high concentrations causing methemoglobinemia [1]. There are three common causes of methemoglobinemia namely, hemoglobinopathy, hereditary enzyme deficiency and exposure to drugs [2]. While local anesthetic agents (such as prilocaine, benzocaine, and lidocaine) are generally safe and often used in practice, they sometimes lead to life-threatening toxic methemoglobinemia [3,4]. Mild forms of methemoglobinemia can be asymptomatic; however, more severe cases may exhibit cyanosis, tachypnea, tachycardia, hypotension, confusion and even death [1].

Cases

Case 1

A 5-month-old male patient was admitted to the emergency department (ED) with a complaint of cyanosis. The patient's medical history contained no items of note, except that he had received local anesthetic with 2 mg/kg prilocaine before a circumcision operation 4-h

previously, with a diagnosis of phimosis. On physical examination, the patient was restless with central cyanosis. Oxygen saturation was 88% based on pulse oximetry. Complete blood counts, blood electrolyte levels, renal function tests, and liver function tests were normal. MetHb was 31.8% in venous blood gas analysis. Despite treatment with 5 L/min oxygen with a mask, the patient's symptoms continued. Ascorbic acid was administered intravenously at 300 mg/kg. Two-hours after the treatment, the patient's cyanosis improved. All symptoms completely regressed 24-h after treatment (blood MetHb levels declined to 0.3%) and the patient was discharged.

Case 2

A 36-day-old male patient was admitted the ED with a complaint of cyanosis. The patient had had a circumcision operation 4-h previously, with prilocaine being used as the local anesthetic agent. The medical history showed no other items of note. The patient was restless, would not suckle, and physical examination revealed central cyanosis. Oxygen saturation was 82% based on pulse oximetry. Chest radiograph, complete blood count, renal function tests, and electrolytes were all in the normal range. MetHb was 45.4% in venous blood gas analysis. Despite treatment with 5 L/min oxygen, symptoms continued. The patient was admitted to the intensive care unit and 300 mg/kg ascorbic acid was given intravenously. Two-hours after treatment, the patient's symptoms improved, and oxygen saturation increased to 93%. Twenty-four hours after treatment, the patient as free of symptoms (MetHb of 0.3%) and was discharged.

Discussion

Methemoglobinemia can develop via hereditary or acquired factors [5]. Many drugs and chemical substances induce acquired methemoglobinemia. Under physiological conditions, MetHb constitutes 1% Hb (not exceeding 2 - 3% Hb [4]. Exposure to certain oxidant substances induces methemoglobinemia, even in healthy individuals. However, in healthy individuals, raised MetHb concentrations are lowered to normal levels by the cytochrome b5 reductase enzyme, which is found in red blood cells. During the first months of life, the transient deficiency of cytochrome b5 reductase enzyme activity predisposes newborns and infants to methemoglobinemia [1]. During the first three months of life, cytochrome b5 reductase activity is 50% below that of adults, even with therapeutic doses of prilocaine; consequently, methemoglobinemia can develop [2]. Therefore, many cases of methemoglobinemia have been documented in the published literature, primarily associated with surgical procedures performed on newborns with local anesthesia [7-9]. Cases with methemoglobinemia exhibit varying degrees of cyanosis associated with blood MetHb levels. [6,7]. When blood MetHb levels exceed 10%, peripheral cyanosis becomes apparent. When MetHb is ≥ 35%, tissue hypoxia and diffuse cyanosis arise. When MetHb approaches 70%, patients enter a coma and, if untreated, may die [1,6]. When MetHb is > 20%, spontaneous recovery is usually observed after drug avoidance; however, treatment may be necessary in newborns and infants [10]. Methylene blue, ascorbic acid, and riboflavin represent potential treatment modalities [11]. Methylene blue is contraindicated in patients with glucose 6 phosphate dehydrogenase deficiency, because methylene blue administration aggravates methemoglobinemia, cyanosis, and hemolytic anemia [3,12]. In such cases, ascorbic acid represents a viable antidote [13,14]. Ascorbic acid reduces MetHb via non-enzymatic processes in animal and human erythrocytes in vitro, making it a candidate for treating methemoglobinemia [15]. Ascorbic acid is most commonly used orally in the long-term treatment of patients with hereditary methemoglobinemia [1]. However, methylene blue should be used preferentially for treating methemoglobinemia, if experience using ascorbic acid in toxic methemoglobinemia is limited [16]. Ascorbic acid antidote therapy was selected for the two cases presented here because they were symptomatic and because methylene blue supply was limited in the hospital.

Conclusion

Prilocaine is a local anesthetic that can cause methemoglobinemia, especially in infants, even at therapeutic doses. Thus, toxic methemoglobinemia should be considered in cases developing central cyanosis after the administration of prilocaine.

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