Methemoglobinemia Associated with a Prilocaine-Lidocaine Cream

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Introduction

EMLA® (Astra Pharmaceutical West Borough, MA.) cream has been used successfully for the painless separation of preputial adhesions in older boys (aged 2–12 years) who would otherwise have required circumcision.[1] More recently, Benini et al[2] evaluated the efficacy of EMLA cream as an anesthetic agent in 21 newborns undergoing circumcision. Newborns in this study who had an application of EMLA 45–60 minutes prior to circumcision showed less increase in heart rate, less decrease in oxygen saturation, fewer facial actions, and less crying associated with pain than newborns who had received placebo cream. No untoward clinical effects from EMLA cream were noted; however, any changes in methemoglobin levels were not reported in this study.

A 12-week-old male with moderate methemoglobinemia treated with trimethoprim-sulfamethoxazole and a topical mixture of Lidocaine and Prilocaine has been reported.[3] Methemoglobinemia, after application of EMLA cream to term infants, has not been previously reported.

Patient Report

We report a term, appropriate for gestational age, 2-day-old white male, delivered vaginally with APGAR scores of 8 and 9 at 1 and 5 minutes respectively.

After parental consent was obtained, the infant was scheduled for circumcision. Before the procedure, EMLA cream was applied on the outside of the prepuce and was covered with an occlusive gauze dressing. After 60 minutes, the dressing was removed and the newborn was placed in a supine position on a restraint board. It was noted that the infant's lips and skin were becoming cyanotic. Vital signs were normal.

A pulse oximeter showed an oxygen saturation of 91% without oxygen supplementation. After the procedure, the baby appeared pale and continued to have cyanosis. The color did not improve with the administration of 100% supplemental oxygen, but the oxygen saturation increased to 94%.

A blood culture, complete blood count (CBC), and arterial blood gases were obtained from the right radial artery. The results were: pH 7.38; partial pressure of carbon dioxide (Pa_{CO_2}) 36 torr; partial pressure of oxygen, arterial bicarbonate (Pa_{O_2}) 54.9 torr; base excess -3, (HCO_3) 21.0 meq/L; O_2 saturation 93.1%. The CBC results were: white blood cells 23,000/mm^3; hematocrit 56.9%; hemoglobin 19.4 g/dL; bands 9%; segs 53%; eosinophils 2%; atypical lymphocytes 8%. The chest radiograph revealed normal heart size and pulmonary vascular markings. The echocardiogram demonstrated normal structure and pressures as estimated by Doppler.

After we reviewed all the results and found no cause for the cyanosis, the possibility of methemoglobinemia secondary to EMLA cream was considered. The methemoglobin level was found to be 16%. This was measured by ABL 520 Radiometer, Cleveland, Ohio, USA.

The infant was given 100% oxygen until the next day, when the oxygen was gradually weaned off. After discontinuation of oxygen therapy, the patient remained acyanotic. A follow-up methemoglobin determination showed a level of <2.1%.

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Discussion

Methemoglobin is a form of hemoglobin in which the heme iron has been oxidized by one electron from Fe^{2+} to Fe^{3+}. This is accomplished by transfer of an electron with an enzyme NADH cytochrome b5 reductase.

In the normal red cell, the methemoglobin amounts to less than 1% of the total hemoglobin in the cell. In certain diseases, methemoglobin accumulates in the red cell. This condition is known as methemoglobinemia. There are three categories of disease in which methemoglobinemia occurs: hemoglobin M, methemoglobin reductase deficiency, and ingestion of oxidizing agents.[4]

Our patient was exposed to an oxidizing agent, that is, prilocaine in the EMLA cream. Prilocaine has been associated with methemoglobinemia. Two of its metabolites, 4 hydroxy-2 methylaniline and 2 methylaniline (o-toluidine) have been implicated in this condition.[5] All newborn infants have a lower activity of NADH cytochrome b5 reductase, and are therefore more susceptible to oxidative stores and thus more readily develop methemoglobinemia. Engberg et al[6] concluded in their study that EMLA cream can safely be used with regard to plasma concentrations of local anesthetics, methemoglobinemia formation, and local skin reactions in infants older than 3 months if the following conditions are met:

- They are without medication with a met-hb inducing agent.
- The total amount of cream applied is 2 g or less.
- The cream is applied on a total area of 16 cm^2 or less.
- The application time does not exceed 4 hours.

The hallmark of methemoglobinemia is a brownish cyanosis that is not reversed by breathing 100% oxygen. Cyanosis develops at a methemoglobin level of 5%. A level of 20–30% is often well tolerated. Above this level, signs of hypoxemia, i.e., dyspnea, tachycardia, or altered level of consciousness, appear. Any patient whose methemoglobin level exceeds 60% is in mortal danger from anoxia. Diagnosis is made by demonstrating methemoglobin in the blood by spectrophotometry or by electrophoresis.

In most cases no treatment is required. Administration of pure oxygen increases the amount of physically dissolved oxygen and leads to better tissue oxygenation. In the event of tissue hypoxia, methylene blue, a harmless reducing agent, can be given intravenously. This agent enters the red cell and passes electrons from a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductase to methemoglobin. If methemoglobin levels are high enough to cause life-threatening hypoxia, exchange transfusion is required. The only treatment given to our patient was pure oxygen.

Owing to a calculation error, our patient received 3.5 grams of EMLA. The recommended dose is 1–2.5g;[7] therefore, we assume methemoglobinemia in our patient was a dose-related phenomenon.

Conclusion

If one is presented with a cyanotic neonate who has normal circulation and respiration and is not responding to oxygen therapy, the possibility of methemoglobinemia should be entertained.

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