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Methemoglobinemia Following Topical Application of EMLA® Cream

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Case Report: A 19-year-old male presented to the emergency department with shortness of breath, light-headedness, and cyanosis of his lips and nail beds. The patient stated that he applied “10 tubes of EMLA® cream” to his groin area prior to a hair removal procedure. He developed symptoms soon after and washed the cream from his skin before coming to hospital. His initial pulse oximeter oxygen saturations were 84%; administration of 100% oxygen produced only a slight improvement. The emergency physician consulted with the BC Drug & Poison Information Centre and the opinion was the patient was suffering from local anesthetic induced methemoglobinemia. Approximately 90 minutes after coming to hospital, co-oximetry measurement of hemoglobin oxygen saturations revealed a methemoglobin fraction of 24.5% (normal <1%). The patient was treated with 1 mg/kg intravenous methylene blue and his symptoms immediately improved. Three hours later the patient’s methemoglobin fraction had decreased to 3.6 percent.

DISCUSSION

EMLA® cream is a eutectic mixture of local anesthetics consisting of 2.5% lidocaine and 2.5% prilocaine. It is available without a prescription (behind the counter) at pharmacies. EMLA® cream is commonly employed as a topical anesthetic prior to painful dermal procedures. Local anesthetics are well known for their central nervous system and cardiovascular toxicities following supratherapeutic intravenous doses. Perhaps less well known is the ability of some of these agents to alter hemoglobin oxygen saturation by inducing methemoglobinemia.

Oxidizing potential of local anesthetics: The oxidizing properties of local anesthetics can be attributed to their chemical structure. Benzocaine is metabolized to strong oxidizers like aniline, phenylhydroxylamine, and nitrobenzene. In one study, the use of benzocaine 20% spray in hospitals was associated with mean peak methemoglobin levels of 43.8 percent in 5

patients. Prilocaine is derived from aniline and metabolized in the liver to *ortho*-toluidine, another potent oxidizer. Several published case reports have associated methemoglobinemia with topical application of EMLA® cream in both adults and children. Cases of methemoglobinemia are primarily associated with overuse of the product by applying it to large surface areas or leaving it on for too long. Applying EMLA® to broken skin or mucous membranes or the use of occlusive dressings also increases the risk of toxicity. Methemoglobinemia is also documented following subcutaneous administration of prilocaine during circumcision in male neonates. The potential for other local anesthetics to induce methemoglobinemia is not well demonstrated.

Methemoglobinemia: Methemoglobin is an altered state of hemoglobin where the ferrous (Fe^{2+}) irons of heme are oxidized to the ferric (Fe^{3+}) state. The ferric irons are unable to bind oxygen resulting in impaired oxygen delivery to tissues. The observed cyanotic skin colour is imparted by the oxidized hemoglobin and not from impaired oxygen delivery to tissues. The presence of methemoglobin is measured by examining hemoglobin oxygenation fractions using a co-oximeter. Normally, the methemoglobin fraction is less than 1%, while the oxyhemoglobin fraction approaches 100%. The half-life of methemoglobin following acute exposures to oxidants is 1 to 3 hours. With continuous exposure the half-life is prolonged.

Signs and symptoms: Cyanosis and low oxygen saturation that does not respond to supplemental oxygen are the first observed signs. These typically occur when methemoglobin fractions exceed 10 to 15%. Headache, dizziness, fatigue, dyspnea, exercise intolerance, and weakness occur at levels above 20%. More serious symptoms such as tachypnea, chest pain, dysrhythmias, seizures, and CNS depression occur at fractions above 50% and death is associated with methemoglobin levels exceeding 70%. Patients with pre-existing anemia may become symptomatic at lower methemoglobin fractions due to an already reduced oxyhemoglobin concentration. Acute hemolysis may occur 1 to 3 days after an episode of methemoglobinemia.

Management: Methemoglobinemia is typically managed with intravenous administration of methylene blue, a basic thiazine dye. In the presence of cellular NADPH methylene blue is reduced to leukomethylene blue, which, in turn, reduces methemoglobin to hemoglobin. Treatment is not usually required unless methemoglobin fractions exceed 10%. Symptomatic patients with methemoglobin fractions between 10 and 25 percent should receive 1 to 2 mg/kg methylene blue. All patients with documented methemoglobin fractions exceeding 25% should receive treatment regardless of symptoms. Methylene blue is infused intravenously over 5 minutes followed immediately by a saline flush of 15 to 30 mL to reduce injection site pain. Symptoms generally improve within 15 to 30 minutes. Repeat doses are usually not required.

EMLA® CREAM AND LASER HAIR REMOVAL

Although EMLA® cream is frequently used to avoid pain during laser hair removal, some authors suggest that many patients can be treated without anesthetics. EMLA® cream has not

been adequately studied for this indication, and its use in laser hair removal should be considered off-label. As stated in the product monograph, EMLA should only be used for the approved indications because maximum safe doses for other uses are not known. Serious adverse events including methemoglobinemia, CNS toxicity, and cardiovascular collapse have occurred when EMLA® cream was used for laser hair removal. In one case, EMLA® was applied to an area of intact skin measuring only 5 cm x 5 cm for 30 minutes. The application of heat from the laser may have increased the absorption of EMLA®. Thermal injury due to excessive laser application under EMLA® anesthesia has also been reported.

RECOMMENDATIONS

Methemoglobinemia is a serious blood disorder associated with overuse of EMLA® cream. The use of EMLA® cream prior to laser hair removal should be considered off-label, and patients requesting EMLA® for laser hair removal or requesting large quantities should be cautioned about the possibility of methemoglobinemia. Procedures involving large quantities over a large skin area must be conducted where staff trained and equipped to deal with toxicities are present. Patients should always be instructed to apply the cream to the smallest possible skin surface area and not to leave the cream on for longer than necessary. Patients reporting symptoms of methemoglobinemia should be immediately referred to a hospital emergency department.

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See also:

Morena Higuera M, et al. Methemoglobinemia induced by local anesthetic administration previous to laser depilation. *Med Clin (Barc)*. 2008; 131: 198-9.

Garcia-Saura PL, et al. *Rev Esp Anesthesiol Reanim*. 2012. [Epub ahead of print]

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We are grateful to all the First Nations who have cared for and nurtured the lands and waters around us for all time, including the xʷmʷkʷyʷm (Musqueam), Skʷwxʷwʷmesh Uʷxwumixw (Squamish Nation), and sʔlʔilwʔtaʔ (Tsleil-Waututh Nation) on whose unceded and ancestral territory our centre is located.

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