

Methemoglobinemia Induced by Application of an Anesthetic Cream

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PRACTICE POINTS

- Consideration should be given to patients applying anesthetic creams to areas with high absorption capacity.
- Dermatologists should be aware of methemoglobinemia as a serious adverse effect of local anesthetics and guide patients accordingly, as patients do not tend to consider these products to be drugs.

To the Editor:

Methemoglobinemia (MetHb) is a condition caused by elevated levels of methemoglobin in the blood, which leads to an overall reduced ability of red blood cells to release oxygen to tissues, causing tissue hypoxia. Methemoglobinemia may be congenital or acquired. Various antibiotics and local anesthetics have been reported to induce acquired MetHb.¹ We describe an adult who presented with MetHb resulting from excessive topical application of local anesthetics for painful scrotal ulcers.

A 54-year-old man presented with multiple scrotal and penile shaft ulcers of a few weeks' duration with no systemic concerns. His medical history included chronic hepatitis C virus (HCV) and lumbar disc disease. Physical examination revealed multiple erosions and ulcers on an erythematous base involving the scrotal skin and distal penile shaft (Figure). Histopathology revealed acute leukocytoclastic vasculitis, and a laboratory workup was positive for mixed cryoglobulinemia that was thought

to be HCV related. The patient was started on a systemic corticosteroid treatment in addition to sofosbuvir-velpatasvir for the treatment of HCV-related mixed cryoglobulinemic vasculitis. Concomitantly, the patient self-treated for pain with a local anesthetic cream containing lidocaine 2.5% and prilocaine 2.5%, applying it excessively every few hours daily for 2 weeks. He also intermittently used occlusive dressings.

After 2 weeks of application, the patient developed lightheadedness and shortness of breath. He returned and was admitted for further evaluation. He had dyspnea and tachypnea of 22 breaths per minute. He also



Multiple scrotal and penile ulcers that the patient self-treated with a local anesthetic cream containing lidocaine 2.5% and prilocaine 2.5%.

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had mild tachycardia (109 beats per minute). He did not have a fever, and his blood pressure was normal. The oxygen saturation measured in ambient room air by pulse oximetry was 82%. A neurologic examination was normal except for mild drowsiness. The lungs were clear, and heart sounds were normal. A 12-lead electrocardiogram also was normal. A complete blood cell count showed severe macrocytic anemia with a hemoglobin level of 7 g/dL, which was a severe decline from the patient's baseline level of 14 g/dL (reference range, 13–17 g/dL). A MetHb blood level of 11% was reported on co-oximetry. An arterial blood gas analysis revealed a pH of 7.46; partial pressure of carbon dioxide of 41 mm Hg; and partial pressure of oxygen of 63 mm Hg. The haptoglobin level was low at 2.6 mg/dL (reference range, 30–200 mg/dL). An absolute reticulocyte count was markedly elevated at $0.4 \times 10^6/\text{mL}$ (reference range, $0.03\text{--}0.08 \times 10^6/\text{mL}$), lactate dehydrogenase was elevated at 430 U/L (reference range, 125–220 U/L), and indirect bilirubin was high at 0.9 mg/dL (reference range, 0–0.5 mg/dL), consistent with hemolytic anemia. Electrolyte serum levels and renal function tests were within reference range. A diagnosis of MetHb induced by the lidocaine-prilocaine cream was rendered, and intravenous methylene blue 72 mg (1 mg/kg) was administered over 10 minutes. Within the next 60 minutes, the patient's drowsiness and arterial desaturation resolved. A subsequent MetHb measurement taken several hours later was reduced to 4%. The patient remained asymptomatic and was eventually discharged.

Methemoglobinemia is an altered state of hemoglobin where the ferrous (Fe^{2+}) ions of heme are oxidized to the ferric (Fe^{3+}) state. These ferric ions are unable to bind oxygen, resulting in impaired oxygen delivery to tissues.¹ Local anesthetics, which are strong oxidizers, have been reported to induce MetHb.² In our patient, the extensive use of lidocaine 2.5%–prilocaine 2.5% cream resulted in severe life-threatening MetHb. The oxidizing properties of local anesthetics can be attributed to their chemical structure. Benzocaine is metabolized to potent oxidizers such as aniline, phenylhydroxylamine, and nitrobenzene.³ Prilocaine and another potent oxidizer, ortho-toluidine, which is a metabolite of prilocaine, can

oxidize the iron in hemoglobin from ferrous (Fe^{2+}) to ferric (Fe^{3+}), leading to MetHb.^{2,3}

Cases of anesthetic-induced MetHb primarily are associated with overuse of the product by applying it to large surface areas or using it for prolonged periods of time. In one case report, the occlusive dressing of the lidocaine-prilocaine cream applied to skin of the legs that was already abraded by laser epilation therapy resulted in MetHb.⁴ In our patient, applying the topical anesthetic to the eroded high-absorptive mucosal surface of the scrotal skin and the use of occlusive dressings increased the risk for toxicity. Absorption from scrotal skin is 40-times higher than the forearm.⁵ The face, axillae, and scalp also exhibit increased absorption compared to the forearm—10-, 4-, and 3-times higher, respectively.

In recent years, the use of topical anesthetics has greatly expanded due to the popularity of aesthetic and cosmetic procedures. These procedures often are performed in an outpatient setting.⁶ Dermatologists should be well aware of MetHb as a serious adverse effect and guide patients accordingly, as patients do not tend to consider a local anesthetic to be a drug. Drug interactions also may affect free lidocaine concentrations by liver cytochrome P450 metabolism; although this was not the case with our patient, special attention should be given to potential interactions that may exacerbate this serious adverse effect. Consideration should be given to patients applying the anesthetic to areas with high absorption capacity.

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