

Methemoglobinemia Induced by Lidocaine-Prilocaine Cream

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ABSTRACT: With growing awareness of the importance of pain control in all procedures, the use of lidocaine-prilocaine cream (EMLA) for all ages is increasing. Lidocaine-prilocaine cream has been implicated as a cause of methemoglobinemia. Diagnostic clues may be oxygen-resistant cyanosis and an oxygen “saturation gap” between arterial blood saturation and pulse oximetry. Treatment with intravenous methylene blue is often effective. Since EMLA is often mistakenly considered risk-free it is routinely applied by medical staff in the emergency room. Subsequent to the case of EMLA-induced methemoglobinemia in an 8 year old girl we wish to alert the medical community to this phenomenon, and in this work review the relevant literature.

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KEY WORDS: EMLA, methemoglobinemia, lidocaine-prilocaine, seizures

Methemoglobin is an oxidized and non-oxygen binding form of hemoglobin. Increased levels in the blood can cause the clinical syndrome of methemoglobinemia. Etiology can be both congenital (defects in hemoglobin synthesis or metabolism) or acquired, mostly drug induced [1].

Lidocaine and prilocaine are sodium channel-blocking local anesthetics [2]. A eutectic mixture of local anesthetics (EMLA, lidocaine-prilocaine cream) is widely used in pediatrics as a pain-reducing agent before venipuncture, intravenous cannulation and other procedures [3]. We encountered a previously healthy 8 year old girl who developed generalized tonic-clonic seizures and oxygen-resistant cyanosis during laser hair removal therapy. Prior to therapy, a large amount of EMLA was applied. Following the diagnosis of EMLA-induced methemoglobinemia (meth-Hb levels of 20.4%, normal range 0–1.5%) she was treated with methylene blue and her symptoms resolved. Although EMLA-induced methemoglobinemia is a well-documented adverse effect, it is often mistakenly considered free of risk and is routinely applied by medical staff in the emergency room.

We conducted a MEDLINE search of the English-language

literature from 1 January 1985 to 17 October 2013. Using the keywords “EMLA and methemoglobinemia,” “Lidocaine-Prilocaine and methemoglobinemia” and “Lidocaine-Prilocaine and cream and methemoglobinemia,” we screened for previously published human case reports of lidocaine-prilocaine cream (EMLA)-induced methemoglobinemia.

Our search yielded 13 case reports. Table 1 presents all 13 cases, as well the patient we had encountered. Ten patients were females, 4 patients were without underlying conditions, and 5 were neonates. EMLA was applied before laser therapy in four and before circumcision in two. Five patients had previous skin lesions, four presented clinically with seizures. Six patients were treated with intravenous methylene blue. All cases resolved completely and patients were discharged without further treatment. One patient (case 2) experienced rebound after 8 hours, with levels increasing from 6% to 14%.

PATHOGENESIS AND RISK FACTORS

The ferrous iron of hemoglobin is exposed continuously to oxidative stress from normal metabolism, causing Fe²⁺ of the heme group to be oxidized to Fe³⁺. This converts hemoglobin to meth-Hb, a non-oxygen-binding form of hemoglobin that binds a water molecule instead of oxygen [4]. Meth-Hb reduction is performed mainly within the red cell by enzyme systems cytochrome-b5 reductase (major pathway) and NADPH meth-Hb reductase (minor pathway). These enzyme systems normally maintain meth-Hb levels at below 1% of total hemoglobin. Exposure to exogenous oxidizing drugs and their metabolites may accelerate formation of meth-Hb 100–1000 times the normal rate, overwhelming the protective enzyme systems and raising meth-Hb levels [4–6]. Excessive replacement of hemoglobin with meth-Hb leads to functional anemia [6] and tissue hypoxia [7].

The prevalence of EMLA-induced methemoglobinemia has not been established. The annual report of the American Association of Poison Control Centers, published in December 2012, revealed only two cases of toxic methemoglobinemia, neither of which were EMLA-related [8]. Benzocaine, a similar local anesthetic, has long been reported as a precipitant of

Lidocaine-prilocaine cream, a widely used analgesic in pediatrics, may cause methemoglobinemia

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meth-Hb = methemoglobin

Table 1. Summary of reported cases of lidocaine-prilocaine cream-induced methemoglobinemia

Case # authors (yr) [Ref]	Age, gender	Underlying condition	Body area of EMLA application	Procedure	Treatment	Meth-Hb* levels at diagnosis (%)	Reevaluated meth-Hb levels (%)/ interval between measurements (hr)	CNS manifestations	Outcome
Case 1 Current report	8 yr Female	None	Lower limbs	Hair-removing laser therapy	IV MB 1.3 mg/kg	20.4	1.4/6	Seizures	CR
Case 2 Larson (2013) [2]	4 mo Female	Port wine stains	Torso and lower limbs	Laser therapy	Anti-convulsant medication IV MB 1.5 mg/kg	22.8	3.4/18*	Seizures	CR
Case 3 Shachor-Meyouhas (2008) [22]	28 days Female	None	Lower back	Preparation for lumbar puncture	IV MB 0.3 mg/kg	32	5/8	None	CR
Case 4 Elsaie (2007) [23]	37 yr Female	None	5.5 cm ² on left cheek	Hair-removing laser therapy	NA	NA	NA	Tinnitus	CR
Case 5 Raso et al. (2006) [24]	4 yr Female	Atopic dermatitis, molluscum contagiosum	Left anterior hemithorax, axilla and left arm	None	IV MB 1 mg/kg	19	2.5/NA	Headache, instability in walking, blurry vision	CR
Case 6 Parker et al. (2004) [25]	3 yr Female	Eczema	Back	Allergy skin testing	Oxygen	17.7	1.4/NA	Seizures	CR
Case 7 Hahn et al. (2004) [26]	30 yr Female	Sertraline and oral contraceptive use	Lower limbs below the knees	Hair-removing laser therapy	IV MB 1 mg/kg	20	2.7/NA	Light-headedness	CR
Case 8 Sinisterra et al. (2002) [27]	7 mo Female	Pulmonary hypertension, left diaphragmatic hernia, nitric oxide therapy	Both groins to cover an area of ~8 cm ²	Preparation for central vein insertion	Double dose of IV MB 2 mg/kg	16	1.6/NA	None	CR
Case 9 Touma & Jackson (2001) [28]	3 yr Female	Molluscum contagiosum	Lower & upper limbs, anterior & posterior trunk	Curettage of skin lesions	None	20.5	2.1/24	Drowsy & lethargic	CR
Case 10 Rincon et al. (2000) [18]	21 mo Female	Molluscum contagiosum	Neck, trunk, abdomen, extremities & back	Curettage of skin lesions	Anti-convulsant medication, mechanical ventilation	8	NA	Seizures	CR
Case 11 Couper (2000) [29]	4 days Male	None	Penis	Circumcision	None	16	0.6/36	None	CR
Case 12 Elsner & Dummer (1997) [30]	7 days Female	Cavernous and papillary hemangioma	10 cm ² on sacrum, right buttocks, upper leg	Laser therapy	None	NA	NA	Sleepiness	CR
Case 13 Kumar (1997) [31]	2 days Male	None	Penis	Circumcision	Oxygen	16	< 2.1/24	None	CR
Case 14 Jakobson & Nilsson (1985) [14]	12 wk Male	Preoperative treatment with trimetoprim-sulphamethoxazole mixture due to resolved pyelitis	Back of the hands & in cubital regions	Re-implantation of right ureter	IV MB 1 mg/kg	28	NA	None	CR

*Rebound appeared 8 hours after treatment: meth-Hb levels increased from 6% to 14%
 meth-Hb = methemoglobin, IV = intravenous, MB = methylene blue, NA = data not available, CR = complete recovery

methemoglobinemia, with an estimated methemoglobinemia incidence of 1 case per 7000 benzocaine exposures reported [9]. Other drugs related to meth-Hb formation are nitroglycerin, dapsone, phenacetin, phenytoin, primaquine, sulfonamides, and prilocaine metabolites [10,11]. Methemoglobinemia resulting from accidental occupational exposure to chemicals is rare and usually not severe. Occupational cases were described in aniline dye production, in pharmaceutical, pesticide or rubber manufacture, in the electronics industry, and during transportation or waste disposal of meth-Hb-forming agents [12].

Unintentional drug-induced methemoglobinemia in children was also reported. An example is benzocaine, an over-the-counter analgesic prescribed to relieve teething pain, mouth or gum soreness and canker sores. Its use was related to meth-Hb formation [13]. Infants and young children are at increased risk for the development of methemoglobinemia secondary to topical anesthetics, even when appropriate dosing guidelines are followed. This is due to their increased body surface area to body mass ratio as compared to adults, resulting in a greater proportion of drug absorbed per kilogram body weight.

Neonates have a lower activity of NADH-dehydrogenase and are therefore more susceptible to “oxidative stress” and to develop EMLA-induced methemoglobinemia [7,14]. Some studies, however, suggest that the use of EMLA in this age group is safe. Brisman et al. [15] performed a double-blind placebo-controlled randomized trial to assess the safety of 1 g EMLA cream 5% used on intact skin in term neonates. Meth-Hb concentrations were significantly higher in the EMLA group but were below potentially harmful levels. Law and colleagues [16] reported a statistically significant increase in meth-Hb after application of EMLA to the foreskin of 10 normal newborns to reduce pain associated with circumcision, but the levels were normal and there were no clinical signs.

When applied to undamaged skin in adults, prilocaine in a eutectic mixture is absorbed to a very small extent [14]. Studies of EMLA absorption in patients with eczema and psoriasis have shown much greater absorption in diseased skin as compared with normal controls [2]. The literature is consistent with this notion, where 5 of the 13 reported patients had previous skin lesions.

Another risk factor for the development of methemoglobinemia is metabolic acidosis, which inhibits reduction of meth-Hb to hemoglobin. Thus, correcting patients' pH is considered part of the treatment [17].

CLINICAL PRESENTATION

Methemoglobinemia induced by local anesthetics typically develops within 20 to 60 minutes after exposure but could be delayed for up to 2 hours [6,7]. The clinical effects of methemoglobinemia result from a state of functional anemia caused by the inability of meth-Hb to bind oxygen, and by an increase in the affinity of the remaining ferrous heme for oxygen. Symptoms are directly related to the hemoglobin's compromised oxygen-carrying capacity, although patients can present with varying degrees of hypoxia [6,11].

Diagnostic clues are oxygen-resistant cyanosis and an oxygen “saturation gap” between arterial blood saturation and pulse oximetry

Healthy patients who are not anemic usually have minor symptoms with meth-Hb levels below 15%. Levels higher than 15% are associated with cyanosis and levels of 20–45% may result in mental status changes, headache, lethargy, tachycardia, weakness, dizziness and syncope. Levels exceeding 50% are associated with dysrhythmias, seizures, coma, and death. The occurrence of neurological abnormalities and death is proportional to the degree of methemoglobinemia [4,11,18].

In the literature, four patients with meth-Hb levels of 8–23%, which do not correlate with severe hypoxemia, had seizures. This may be the result of an additive effect of both components of EMLA cream: prilocaine metabolites may cause methemoglobinemia and lidocaine can produce generalized tonic-clonic seizures at high levels (> 7.5 g/ml) [19].

DIAGNOSIS

A thorough history should be taken, especially regarding exposure to substances known to cause methemoglobinemia. A history of underlying conditions that may cause cyanosis is also important. The presence of an oxygen-resistant cyanosis, and no history of cardiopulmonary disease, is a diagnostic clue [1]. Several blood tests are needed. Arterial blood gases are measured in order to find an oxygen “saturation gap” between pulse oximetry and blood gas analysis. A gap of more than 5% is another diagnostic clue [4,17]. The “saturation gap” is caused by the inability of pulse oximetry to detect different types of abnormal Hb. Multiple wavelength CO-oximetry can provide accurate measurements of the true oxygen-carrying status since it assesses all hemoglobin species [20]. Because anemia is known to exacerbate symptoms, a complete blood count is essential. Lactate level and acid base balance, as

As treatment with intravenous methylene blue is often effective, awareness and early diagnosis are crucial

reflected by the blood gases, will estimate tissue ischemia and are therefore also important [1]. The blood of patients with methemoglobinemia is described as chocolate-brown or very dark red. This chocolate-brown color does not disappear when blood is exposed to oxygen, in contrast to the dark red/violet of deoxygenated blood [20,21]. Laboratory diagnosis of methemoglobinemia is based on analysis of its absorption spectrum. This test can be performed in most hospital laboratories along with other standard blood workup tests. A fresh specimen should always be obtained since meth-Hb levels tend to increase with storage [11].

TREATMENT

Mild or asymptomatic cases require monitoring, removal of the offending agent and administration of high flow oxygen, which will accelerate the conversion of meth-Hb to hemoglobin. Moderate to severe cases are defined as patients who are symptomatic with any elevation in meth-Hb levels, meth-Hb levels > 10% in patients with co-morbidities, or meth-Hb levels > 30% despite being asymptomatic. These patients should be treated with intravenous methylene blue at a dose of 1–2 mg/kg over a 5 minute period. Methylene blue activates meth-Hb reduction by using NADPH dehydrogenase [20].

Electrons transfer start with the pentose-phosphate shunt via glucose-6-phosphate-dehydrogenase, and in its absence hemolytic anemia occurs [17]. Thus, methylene blue is contraindicated in patients with G6PD deficiency [15]. Testing of G6PD deficiency before administration of methylene blue is often impractical. Therefore, if clearly indicated, even when information regarding G6PD status is lacking, it should be used. In patients known to have G6PD deficiency, ascorbic acid should be used [1]. One dose of methylene blue is usually sufficient. However, signs of cyanosis should be monitored up to 12 hours after administration for rebound methemoglobinemia and to assess the need for further dosing and intervention [4,7]. If methemoglobinemia persists, the dose may be repeated after one hour. An exchange transfusion may become necessary if the level of meth-Hb in the blood remains high [5,7]. Differential diagnosis of failure of methylene blue to resolve methemoglobinemia includes inadequate dose of methylene blue and variability among individuals in rates of absorption, enterohepatic circulation and metabolism. Furthermore, drug metabolites may also cause methemoglobinemia and can result in persistent disease. Examples are aniline and dapsone, which metabolize to phenylhydroxylamine and hydroxylamine, respectively. Both metabolites are inducers of meth-Hb formation. In addition, several congenital conditions should be suspected in treatment failure. Such diseases include NADPH dehydrogenase deficiency, G6PD deficiency, or a hemoglobin variant such as HbM [20].

Adverse effects of fast intravenous administration of methylene blue or overdose include chest pain, dyspnea, hypertension, diaphoresis, paradoxical increase of meth-Hb and hemolytic anemia. Since the drug is excreted by the kidney, doses should be adjusted to renal functions and the urine may become blue [1].

CONCLUSIONS

As awareness for appropriate pain control management is rising, especially in pediatrics, the use of lidocaine-prilocaine cream is increasing. Although considered safe, lidocaine-prilocaine cream may have adverse side effects, such as methemoglobin-

emia. Cyanosis resistant to oxygen treatment and oxygen saturation gap between arterial sampling and pulse oximetry readings may be diagnostic clues. EMLA cream should be handled like other medications – i.e., doses should not exceed the manufacturers’ instructions and caution is advised. Since treatment is often effective, we wish to alert the medical community to this potentially life-threatening condition.

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G6PD = glucose-6-phosphate-dehydrogenase

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Capsule

Health care-associated infection after red blood cell transfusion

The association between red blood cell (RBC) transfusion strategies and health care-associated infection is not fully understood. Rohde et al. evaluated whether RBC transfusion thresholds are associated with the risk of infection and whether risk is independent of leukocyte reduction. The pooled risk of all serious infections was 11.8% (95%CI, 7.0–16.7%) in the restrictive group and 16.9% (95%CI 8.9–25.4%) in the liberal group. The risk ratio (RR) for the association between transfusion strategies and serious infection was 0.82 (95%CI 0.72–0.95) with little heterogeneity ($I^2=0\%$, $\tau^2 < 0.0001$). The number needed to treat (NNT) with restrictive strategies to prevent serious infection was 38 (95%CI 24–122). The risk of infection remained reduced

with a restrictive strategy, even with leukocyte reduction (RR 0.80, 95%CI 0.67–0.95). For trials with a restrictive hemoglobin threshold of < 7.0 g/dl, the RR was 0.82 (95%CI 0.70–0.97) with NNT of 20 (95%CI 12–133). With stratification by patient type, the RR was 0.70 (95%CI 0.54–0.91) in patients undergoing orthopedic surgery and 0.51 (95%CI 0.28–0.95) in patients presenting with sepsis. There were no significant differences in the incidence of infection by RBC threshold for patients with cardiac disease, the critically ill, those with acute upper gastrointestinal bleeding, or for infants with low birth weight.

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Capsule

Adenoma detection rate and risk of colorectal cancer and death

The proportion of screening colonoscopic examinations performed by a physician that detect one or more adenomas (the adenoma detection rate) is a recommended quality measure. However, little is known about the association between this rate and patients' risks of a subsequent colorectal cancer (interval cancer) and death. Using data from an integrated health care delivery organization, Corley et al. evaluated the associations between the adenoma detection rate and the risks of colorectal cancer diagnosed 6 months to 10 years after colonoscopy and of cancer-related death. They evaluated 314,872 colonoscopies performed by 136 gastroenterologists; the adenoma detection rates ranged from 7.4 to 52.5%. During the follow-up period, they identified 712 interval colorectal adenocarcinomas, including 255 advanced-stage cancers, and 147 deaths from

interval colorectal cancer. The unadjusted risks of interval cancer according to quintiles of adenoma detection rates, from lowest to highest, were 9.8, 8.6, 8.0, 7.0, and 4.8 cases per 10,000 person-years of follow-up, respectively. Among patients of physicians with adenoma detection rates in the highest quintile, as compared with patients of physicians with detection rates in the lowest quintile, the adjusted hazard ratio for any interval cancer was 0.52 (95% confidence interval [CI] 0.39–0.69), for advanced-stage interval cancer, 0.43 (95%CI 0.29–0.64), and for fatal interval cancer, 0.38 (95%CI 0.22–0.65). Each 1.0% increase in the adenoma detection rate was associated with a 3.0% decrease in the risk of cancer (hazard ratio 0.97, 95%CI 0.96–0.98).

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“Two things are infinite: The universe and human stupidity; and I’m not sure about the universe”

Albert Einstein (1879-1955), German-born theoretical physicist and 1921 Nobel Prize laureate who developed the theory of relativity