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Evaluation of adverse effects of EMLA (lidocaine/prilocaine) cream for the placement of jugular catheters in healthy cats

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Hospitalized veterinary patients undergo a number of potentially painful procedures such as venipuncture and catheter placement. In human pediatric patients, topical anesthetics are gaining popularity in the prevention of pain associated with such minor invasive procedures. A cream containing a mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA cream®, AstraZeneca, Wilmington, DE, USA) has been shown to provide effective local analgesia for catheter placement, venipuncture, vaccinations, lumbar spinal taps, circumcision, and skin mass removals in adults, children, and neonates (Hallen & Uppfeldt, 1982; Manner *et al.*, 1987; Rosdahl *et al.*, 1988; Gupta & Sibbald, 1996; Koscielniak-Nielsen *et al.*, 1998; Halperin *et al.*, 2000).

EMLA is an abbreviation for Eutectic Mixture of Local Anesthetics; a eutectic mixture allows solubilization of the anesthetic agents in a form that permits local absorption without the use of organic solvents (Lener *et al.*, 1997). Analgesia is due to high local concentrations of lidocaine and prilocaine in the skin, with minimal systemic absorption. EMLA cream is well tolerated in most human patients, even neonates (Taddio, 2001). Common side effects include blanching of the skin or local erythema (Lener *et al.*, 1997). Methemoglobinemia or neurologic toxicity have been reported less commonly, generally within 1–3 h of cream removal when EMLA has been applied to a large surface area or for prolonged periods of time (Lener *et al.*, 1997; Rincon *et al.*, 2000).

For human pediatric patients, a conservative maximum EMLA dose of 1–2 g over 10 cm^2, with an application time of 1–1.5 h under occlusion, has been recommended (Chang *et al.*, 1994). There is only one report of the use of EMLA cream in cats, in which EMLA was apparently well tolerated for the placement of peripheral cephalic catheters in dogs, cats, and rabbits in an experimental setting (Flecknell *et al.*, 1990). No adverse effects were observed in these animals, although the degree of systemic absorption was not measured. The purpose of this pilot study was to determine the degree of systemic absorption and clinical adverse effects during the use of EMLA cream in the placement of jugular catheters in healthy cats.

Ten healthy young adult cats (five male, five female) without previous jugular venipuncture were used for the study. The study protocol was approved by the IACUC at the University of Wisconsin-Madison. For each cat, 1 g (1 cc) of EMLA cream® (Astra Pharmaceuticals) was applied in a thick layer to a 2×5 cm area of closely shaved skin (#40 blade) overlying one jugular vein. The treated area was then covered with a 6×7 cm occlusive bandage (Tegaderm™; 3M Corp., St Paul, MN, USA). Clinic personnel wore exam gloves during cream application. After 1 h, the occlusive bandage was removed and the EMLA cream was gently wiped away with 70% ethanol. A routine sterile scrub of the area was performed, and a 19-gauge, 20.3 cm jugular catheter (Intracath; Becton Dickinson, Cockeysville, MD, USA) was placed on the treated side.

As jugular catheters in cats are generally placed under sedation in our hospital, all cats were monitored by the technician for discomfort during catheter placement, to include: (i) struggling against restraint, (ii) biting or scratching, or (iii) loud vocalization. If one or more of these signs were observed, the procedure was stopped, and the cat was sedated for subsequent jugular catheter placement with midazolam (0.1 mg/kg, i.m.) and butorphanol (0.4 mg/kg, i.m.).

Four categories of adverse effects were evaluated: local irritation, systemic absorption of lidocaine or prilocaine, development of methemoglobinemia, and clinical evidence of gastrointestinal, neurologic, or cardiovascular complications. For evaluation of local irritation, the treated area was examined for the presence of erythema, swelling, or pruritis (as evidenced by scratching) after cream and bandage removal. For evaluation of systemic absorption, blood samples [0.5 mL each in ethylenediaminetetraacetic acid (EDTA)] were obtained for the determination of serum lidocaine and prilocaine concentrations,

both prior to EMLA cream application, and through the jugular catheter at the time of catheter placement (i.e. approximately 1 h after cream application), as well as at 2, 4, and 6 h after cream application. In addition, whole blood in EDTA (0.1 mL) was analyzed for methemoglobin using co-oximetry (Watcha *et al.*, 1989; Rausch-Madison & Mohsenifar, 1997) at the same time points. Finally, cats were monitored for clinical signs of gastrointestinal upset (vomiting, salivation, and diarrhea), tremors or twitching, cyanotic mucous membranes, dyspnea, or tachycardia, with hourly monitoring of heart rate, respiratory rate, mucus membrane color, and demeanor, for 6 h after cream application.

Lidocaine and prilocaine were extracted from plasma using a tetracaine internal standard and modifications of a published method (Vickers *et al.*, 1997). Recovery of lidocaine and prilocaine from feline plasma was complete, and the limit of quantitation for each assay was 0.3 μg/mL. Inter-assay CVs over the concentrations relevant to this study ranged from 10.8 to 18.9% for lidocaine and from 12.7 to 19.7% for prilocaine; intra-assay CVs ranged from 8.9 to 13.4% for lidocaine and from 7.3 to 15.5% for prilocaine. Both lidocaine and prilocaine standards were stable in feline serum at −80 °C over the duration of the study.

Methemoglobinemia was measured with an IL 482 Co-Oximeter (Instrumentation Laboratories, Lexington, MA, USA), using a normal range established from duplicate samples from 10 adult cats (pets of VMTH staff) with no history of oxidant drug exposure. In addition, to establish the linear range of the instrument for feline methemoglobin, normal feline erythrocytes were spiked with 25% *o*-toluidine (final concentration, 80 mg/dL), which oxidizes feline hemoglobin to methemoglobin (Onji & Tyuma, 1965), and were incubated from 0 to 2 h at room temperature to generate a linear range of methemoglobin concentration from 0.1 to 55%. In the EMLA-treated cats, mean whole blood methemoglobin levels at each time point were compared with baseline and to the established normal range using repeated measures ANOVA.

There were no signs of local erythema, swelling, blanching, or pruritus at the site of EMLA application in any of the 10 cats. Plasma lidocaine and prilocaine concentrations were undetectable (<0.3 μg/mL) at all time points from 0 to 6 h after EMLA cream application in all 10 cats. Whole blood methemoglobin concentrations for the treated cats are shown in Fig. 1, with 10 normal cats (used for co-oximetry validation) used for comparison. No cat developed an abnormal whole blood methemoglobin level at any time point after EMLA cream application. Cats remained comfortable throughout the study, with no signs of gastrointestinal upset, neurologic signs, cyanosis, or distress.

In addition, although evaluation of efficacy was not the purpose of this pilot study, jugular catheters were successfully placed in six of these young healthy cats without sedation. These six cats did not respond to the venipuncture with any signs of tensing, struggling, or vocalization. The remaining four cats were sedated due to struggling against restraint; three of these cats were fearful and agitated prior to any intervention. Therefore, EMLA cream appeared subjectively, in at least six cats, to eliminate the usual signs of discomfort associated with venipuncture.

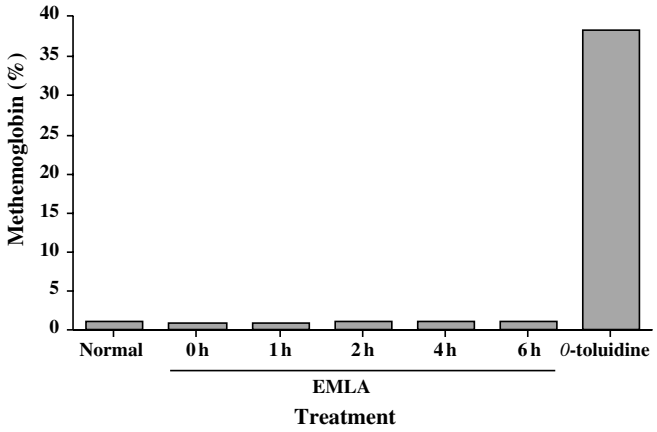

Fig. 1. Whole blood methemoglobin levels in 10 cats treated with topical EMLA cream with occlusion for 1 h, and monitored for 6 h after application. Normal represents whole blood methemoglobin in 10 untreated healthy staff-owned cats. *o*-Toluidine represents a positive control in which normal feline erythrocytes were incubated *in vitro* for 1 h with 80 mg/dL of the oxidant agent *o*-toluidine.

Since the initiation of this study, another group evaluated the degree of absorption of lidocaine from a liposome-encapsulated formulation of lidocaine (15 mg/kg total dose) applied to a 3 × 7 cm area over the cephalic vein in cats. Although methemoglobin levels were not measured, plasma lidocaine concentrations, which peaked at 2–4 h after cream application, did not exceed 0.2 μg/mL (Fransson *et al.*, 2002). In our study, EMLA cream was not associated with any systemic absorption (>0.3 μg/mL) or any observed adverse effects in healthy cats, using a protocol that has been reported for use in human neonates. Cats in this study received 1 g of a 2.5% lidocaine/2.5% prilocaine cream (i.e. 25 mg of each anesthetic per gram of cream) over a 10 cm^2 surface area. This is equivalent to 5 mg/kg of dosage of each anesthetic for a 5-kg cat. Although this would be a high intravenous dose for a cat (Muir, 1991), this dose applied topically was expected to be safe, based on low systemic absorption reported in humans (Haugstvedt *et al.*, 1990).

In humans, toxicity from EMLA cream has been associated with improper administration practices, such as application to a large surface area, prolonged contact time, application to damaged skin, or application to mucous membranes (Onji & Tyuma, 1965; Olson & McEvoy, 1981; Rincon *et al.*, 2000). One potential concern about the use of EMLA cream in cats is the presence of prilocaine (Fransson *et al.*, 2002), which itself can cause methemoglobinemia in infants (Frey & Kehrer, 1999). In addition, cats appear to be more susceptible to oxidant injury to hemoglobin than are human and dogs (Harvey & Kaneko, 1976). However, we found no evidence of methemoglobinemia in healthy cats using this specific EMLA protocol.

Although the optimal use of EMLA cream requires occlusion for an hour prior to a procedure, the cats in this study tolerated

occlusive bandaging well. Should EMLA prove to be an effective analgesic in veterinary patients, possible indications for EMLA cream would include elective, potentially painful procedures, such as jugular catheter placement, skin mass removal, skin biopsies, arterial blood gas measurements, or repeated blood draws (e.g. serial blood glucose measurements). EMLA has been shown to penetrate intact skin to a depth of 3–5 mm in humans, and provides analgesia for 3.5–12 h, depending on application techniques (Egekvist & Bjerring, 1997; Kopecky *et al.*, 2001). EMLA is not recommended at this dosage for use on mucous membranes, as this route is associated with enhanced systemic absorption (Olson & McEvoy, 1981). We conclude from the results of this pilot study that EMLA cream, when applied as a 1 g dose to a 10 cm^2 area of shaved skin with 1 h of occlusion, does not lead to significant systemic absorption, methemoglobinemia, or observed clinical adverse effects in healthy cats. We are now evaluating the efficacy and tolerability of this regimen in client-owned, hospitalized cats.

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