Transdermal absorption of a liposome-encapsulated formulation of lidocaine following topical administration in cats

Boel A. Fransson, DVM, MS; Kenneth E. Peck, MS; Jennifer K. Smith, BS; Janice A. Anthony, BA; Katrina L. Mealey, DVM, PhD

Objective—To determine plasma disposition after dermal application of a liposome-encapsulated formulation of lidocaine in cats.

Animals—6 healthy adult cats with a mean (± SD) body weight of 4.1 ± 0.44 kg.

Procedure—CBC determination and biochemical analysis of blood samples were performed for all cats. Cats were anesthetized by use of isoflurane, and catheters were placed IV in a central vein. The next day, blood samples were obtained from the catheters before and 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after applying a 4% liposome-encapsulated lidocaine cream (15 mg/kg) to a clipped area over the cephalic vein. Plasma concentrations of lidocaine were analyzed with a high-performance liquid chromatography assay.

Results—Two cats had minimal transdermal absorption of lidocaine, with lidocaine concentrations below the sensitivity of the assay at all but 1 or 2 time points. In the other 4 cats, the median maximum plasma concentration was 149.6 ng/ml, the median time to maximum plasma concentration was 2 hours, and the median area under the concentration versus time curve from zero to infinity was 1014.5 ng-h/ml.

Conclusions and Clinical Relevance—Maximum plasma concentrations of lidocaine remained substantially below toxic plasma concentrations for cats. On the basis of these data, topical administration of a liposome-encapsulated lidocaine formulation at a dose of 15 mg/kg appears to be safe for use in healthy adult cats. (Am J Vet Res 2002;63:1309–1312)

Lidocaine is a local anesthetic agent that acts by inhibiting voltage-gated sodium channels and, thus, blocks the conduction of nerve impulses. Typically, it is injected locally, but this route of administration has several disadvantages, particularly for use in cats. First, injection of lidocaine is poorly tolerated in any species because of pain (probably pH-related) but particularly so in cats. Cats handle restraint and painful procedures particularly poorly, compared with other species, often leading to stress manifested as aggression and marked attempts to escape. Second, cats have been reported to be sensitive to the neurologic adverse effects of lidocaine. Serious adverse effects of local anesthetics involve primarily the CNS, manifested by convulsions, at lower doses, and cardiovascular collapse at higher doses. In cats, IV administration of lidocaine at a mean (± SD) dose of 11.7 ± 4.6 mg/kg has been shown to induce convulsions. Mean toxic plasma concentration of lidocaine for onset of seizures was 139.9 ± 68.6 µg/ml in one study. The recommended dose for therapeutic use of lidocaine IV in cats is 0.25 to 0.75 mg/kg, which is only a sixteenth to a fourth of the recommended dose in dogs.

Alternatives to local injection of lidocaine for local analgesia or anesthesia have been used in pediatric patients for more than 20 years. One such alternative is a eutectic mixture of local anesthetics (EMLA). An EMLA cream consists of a mixture of lidocaine and prilocaine together with an emulsifier. In people, the cream has to be left in contact with the skin for at least 30 to 60 minutes and covered by an occlusive dressing to provide effective local anesthesia. A preliminary study in laboratory animals, including cats, indicated that a similar duration of treatment is necessary when using EMLA cream in animals. Study results indicated that topical application of EMLA cream enabled venipuncture in cats with substantially less signs of pain or discomfort than placebo. Several disadvantages exist regarding the use of EMLA in cats. The restraint associated with placement of the occlusive bandages was resented in some cats. Furthermore, prilocaine, one of the active ingredients in EMLA cream, has been associated with methemoglobin formation in infants after topical application. Feline hemoglobin is more susceptible to denaturation by oxidants, compared with other species, and the cat spleen is less efficient in removal of the denatured hemoglobin. Therefore, a drug combination containing prilocaine seems less attractive for use in cats.

A newer topical anesthetic agent contains lidocaine as the single active ingredient. Use of lidocaine in classic topical anesthetic preparations have been ineffective when applied to intact skin and can only be used to anesthetize mucous membranes. The new generation of lidocaine for topical administration uses a liposomal encapsulation that facilitates penetration of the active ingredient through intact skin and has shown effective local analgesic properties similar to EMLA cream. This formulation of lidocaine has a faster onset of peak pain control than EMLA cream (20...
of efficacy of topical use of lidocaine for laryngeal potentially could lead to systemic effects. Evaluations of topical use of lidocaine for laryngeal desensitization in cats are available, as well as a report of toxicosis after topical administration of lidocaine on the trachea in cats. No data exist regarding dermal application of a liposome-encapsulated form of lidocaine in cats. The purpose of the study reported here was to determine the plasma disposition after dermal application of a liposome-encapsulated form of lidocaine in cats. In addition, the purpose was to evaluate whether clinical signs of lidocaine toxicosis were observed after dermal application.

**Materials and Methods**

**Animals**—The Washington State University Institutional Animal Care and Use Committee approved our study. Six apparently healthy cats (mean [± SD] body weight, 4.1 ± 0.44 kg) of unknown age were studied. Dental examination revealed complete dental arcades with no or mild tartar; therefore, cats were assumed to be young adults. Prior to enrollment in our study, physical examinations of the cats were performed as well as CBC determination and biochemical analysis of blood samples obtained from the jugular vein. A few hematologic abnormalities were detected in some cats (mild lymphocytosis or lymphopenia, mild eosinophilia), but they were not considered to represent a pathologic state that would either endanger the cat by participation in our study or interfere with results.

One cat had mildly high serum alanine aminotransferase and alkaline phosphatase activities and a high cholesterol concentration, which could indicate liver disease. This cat had a good appetite and was clinically normal in terms of thirst, urination, and defecation. The cat had no clinical signs of disease and other measurements influenced by liver function, including BUN, blood glucose, and serum albumin concentrations, were within reference range. The blood glucose concentration was mildly high in 3 cats, most likely as a result from the stress of restraint associated with blood collection.

Twelve hours prior to our study, food was withheld but water remained available ad libitum. Cats were fed 4 to 6 hours after recovery from anesthesia and thereafter fed according to their regular schedule.

On day 1 of our study, cats were anesthetized by use of isoflurane. A 22-gauge 8-in IV catheter was placed through a 19-gauge needle into the medial saphenous vein. The catheter was secured by taping the needle cover to the skin and was thereafter protected from mutilation by application of an occlusive layer covered with cast padding and bandaging tape. The catheter was flushed (with physiologic saline [0.9% NaCl] solution containing 10 U/ml heparin) after insertion into the central catheter and at 2 and 8 hours after application. Heart rate was monitored before application of the cream and at 2 and 8 hours after application.

The blood samples were immediately placed on ice, and plasma was separated from cells by centrifugation. The plasma was transferred to 2-ml plastic tubes and immediately frozen at −18°C. The samples were transported frozen by high-priority overnight shipping to the Texas State Veterinary Medicine Diagnostic Laboratory, where the samples were analyzed by use of a high-performance liquid chromatography (HPLC) assay.

**Analysis of plasma lidocaine concentrations**—An HPLC with a diode array detector and a narrow bore high carbon load C18 column was used to determine plasma concentration of lidocaine. The solvent consisted of a 50:50 ratio of acetonitrile-to-aqueous, with a flow rate of 0.4 ml/min; the aqueous phase consisted of 1.5% tetrahydrofuran and triethylamine (vol/vol), with the pH adjusted to 6.5 with phosphoric acid. Wavelengths monitored were 213 nm (used for quantitation) and 254 nm. Lidocaine (retention time, 6.1 minutes) was well resolved, with baseline separation and without interference from other coextracted compounds. The external standard method of calibration by peak area was used in the computer-generated report of lidocaine concentration.

Lidocaine was extracted from feline plasma samples (200 µl) by solid phase extraction. Samples underwent extraction in triplicate and were randomly assayed. For each replicate, 20 µl of plasma was added to 700 µl of 0.2M phosphate buffer (pH, 6.5) and loaded onto a preconditioned (1 ml of methanol followed consecutively by 1 ml of HPLC grade water, 0.3 ml of 1 N acetic acid, and 0.3 ml of 0.2M phosphate buffer [pH, 6.5]) 50-g C8-benzene sulfonic acid mixed-bed solid phase extraction column. The column was rinsed with 1 ml of 0.2M phosphate buffer (pH, 6.5), followed by 0.3 ml of 1 N acetic acid. The column was dried for 3 minutes under nitrogen (10 to 15 in Hg) and washed with 1 ml of hexanes, followed by 1 ml of methanol. Lidocaine was eluted with dichloromethane, methanol, and ammonium hydroxide in a ratio of 60:40:4. Samples were dried under nitrogen at 45°C then resuspended in 60 µl of HPLC solvent. Plasma calibrators were prepared in duplicate by addition of 200, 100, 80, 60, 40, 20, and 10 ng of lidocaine (1 mg diluted with 100 ml of methanol) each to 200 µl of pooled blank feline plasma. Calibrators were extracted by solid phase extraction in triplicate as described. Correlation coefficient was > 0.990 for all curves.

Within day coefficient of variation, 1-way ANOVA estimates for lidocaine at 150, 90, and 30 ng in 200 µl of plasma
were 8.2, 6.9, and 4.9%, respectively; the between day coefficient of variation were 17.2, 13.5, and 13%, respectively. Recovery (spiked in 200 µl of pooled blank feline plasma and extracted as described, compared with the corresponding amount directly injected into the HPLC) of lidocaine (150 and 30 ng/200 µl) was 94.3 ± 8.6 and 93.0 ± 6.2%, respectively. Limit of quantification (<20% limit from target value) for lidocaine was 50 ng/ml (10 ng/200 µl).

**Pharmacokinetic calculations**—Because lidocaine was administered by an extravascular route, the only pharmacokinetic variables calculated were maximum plasma concentration (C_{MAX}), time to maximum plasma concentration (T_{MAX}), and area under the concentration versus time curve from zero to infinity (AUC). The trapezoidal method was used to calculate AUC. Values for T_{MAX} and C_{MAX} were determined from the plasma concentration versus time curve. Because of the low number of cats, normal distribution of data could not be assumed, and the results were described as median values.

**Results**

During our study, none of the cats had any neurologic signs indicating adverse effects from lidocaine. Heart rates during our study did not increase or decrease more than 10% from rates monitored prior to the experiment in any of the 6 cats.

Because the limit of quantitation of the assay was 50 ng/ml, lidocaine concentrations below this concentration were not used for analyses. Two of the 6 cats studied apparently had limited transdermal absorption of lidocaine. The plasma concentration of lidocaine from 1 of these cats was greater than the limit of detection at only 2 time points (3 and 4 hours) and from another at only 1 time point (2 hours). Pharmacokinetic analyses were performed by use of data from the remaining 4 cats (**Table 1**). Median T_{MAX}, C_{MAX}, and AUC were 2 hours, 149.5 ng/ml, and 1014.5 ng/h/ml, respectively. A mean plasma lidocaine concentration versus time curve for 4 cats was created (**Fig 1**).

Evaluation of clinical efficacy was not an aim of our study. However, one of the investigators did perform multiple needle punctures to the skin, after temporary removal of the protective bandage, to which the lidocaine cream had been applied 1 hour earlier. A 22-gauge hypodermic needle was rapidly inserted into the skin approximately 1 millimeter (partial thickness) several times. Subjectively, it appeared that none of the cats reacted adversely.

**Discussion**

To our knowledge, only 1 study using dermal application of lidocaine in cats has been reported. The mean dose of lidocaine in laboratory cats in that study was 15 mg/kg. No adverse effects were observed with this dosage regimen. The application of EMLA cream in that study enabled IV catheterization without apparent painful response in 14 of 16 cats. In the placebo treated group, 10 of 16 cats responded to catheterization. The difference between the treated versus non-treated group was significant. The results from that study suggest that dermal application of lidocaine may be helpful to reduce pain and stress associated with IV catheter placement in cats. However, before administration to client-owned cats, more information is required to determine whether dermal application of lidocaine, to obtain local analgesia or anesthesia, is safe for use in cats.

Previous reports of topical administration of lidocaine to include the use of lidocaine spray to desensitize the larynx. One study reported plasma lidocaine concentrations obtained after topical administration of 20 mg lidocaine/cat, sprayed onto the trachea. The mean peak plasma concentration, calculated with normalization to dose per body weight, in 6 cats was 3.78 µg/ml. Only mild adverse effects associated with apnea were observed in that study. Seizure activity as a manifestation of lidocaine toxicosis in cats was seen with plasma concentrations of approximately 140 µg/ml.

In our study, the use of adult, healthy cats with a heterogeneous background is more consistent with the population of cats seen at our veterinary teaching hospital, compared with the purpose-bred laboratory cats used in the previously mentioned study. We elected to use a preparation containing lidocaine as the sole active ingredient to avoid the prilocaine in EMLA cream, because cats are susceptible to methemoglobin formation.

In 2 of 6 cats, minimal systemic concentrations of lidocaine were detected, suggesting that transdermal absorption of the lidocaine in the liposome formulation is variable between individual cats. In the remain-

**Table 1**—Pharmacokinetic variables for lidocaine after topical administration of a single dose (15 mg/kg) to 4 healthy adult cats

<table>
<thead>
<tr>
<th>Variables</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Median values</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{MAX} (h)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>C_{MAX} (mg/ml)</td>
<td>127</td>
<td>93</td>
<td>197</td>
<td>172</td>
<td>149.5</td>
</tr>
<tr>
<td>AUC (ng/h/ml)</td>
<td>856</td>
<td>652</td>
<td>1422</td>
<td>1173</td>
<td>1014.5</td>
</tr>
</tbody>
</table>

*Two of the 6 cats had minimal absorption of lidocaine, with plasma concentrations exceeding the limit of quantification of the assay at only 1 or 2 time points; therefore, data represents only 4 of 6 cats studied. T_{MAX} = Time to maximum plasma concentration. C_{MAX} = Maximum plasma concentration. AUC = Area under the plasma concentration versus time curve from zero to infinity.**
ing 4 cats, systemic absorption of lidocaine did occur, but the highest peak concentration of lidocaine observed in our study was approximately 0.2 µg/ml (197 ng/ml). This concentration is well below toxic concentrations (139.9 ± 68.6 µg/ml) and is also substantially lower than proposed therapeutic concentrations in dogs and cats (1 to 6 µg/ml).1

The bandages that were used to cover the treated area in our study would, according to a previous report,17 not be necessary for systemic absorption of the lidocaine. However, to prevent cats from licking the applied cream we elected to apply a semicrystalline bandage to cover the cream. It is possible that application of the bandage increased systemic absorption of lidocaine, as this has been reported14 to increase transdermal absorption. Accidental ingestion of the cream could be a potential problem when used in cats. Oral ingestion of lidocaine is generally not associated with toxicosis because the first-pass effect is high, but if the entire dose of 15 mg/kg was to be in contact with the mucus membranes in the oral cavity, a total and rapid absorption could theoretically lead to toxic systemic concentrations. On the basis of our results, application of protective bandages does not appear to increase plasma concentrations to toxic concentrations in neonates. Pharm World Sci 1990;21:173–176.


EMLA cream, Astra Pharmaceuticals Ltd, Wilmington, Del.


References


