Gabapentin, a structural analogue of GABA, has been used as an adjunctive antiepileptic drug to treat partial seizures in humans.\(^1,2\) Gabapentin has been used to treat all types of neuropathic pain,\(^3\) and it also can be used to reduce postoperative pain and the amount of postoperative opioids required in humans.\(^4\) Although gabapentin resembles GABA, it does not interact with GABA\(_A\) or GABA\(_B\) receptors, nor does it inhibit GABA uptake. It is not metabolized into GABA or a GABA agonist.\(^5\) Data suggest that it binds to the \(\alpha_2\beta\delta\) accessory subunit of voltage-dependent calcium channel complexes\(^6\) and has an inhibitory effect on voltage-gated calcium channels.\(^7\) To date, there has been no consensus on the mechanism of action of gabapentin.

In cats, there are a limited number of options for drugs that provide analgesia without undesirable adverse effects. Opioids are controlled substances and their use can lead to dysphoria, whereas NSAIDs can cause toxic effects in cats.\(^8\) Alternative analgesic drugs for oral administration are needed.

**Objective**—To determine the pharmacokinetics of gabapentin in cats after IV and oral administration.

**Animals**—6 healthy female adult domestic shorthair cats.

**Procedures**—Gabapentin was administered IV (4 mg/kg) or orally (10 mg/kg) in a crossover randomized design. Blood samples were obtained immediately before gabapentin administration and at various times up to 960 minutes after IV administration or up to 1,440 minutes after oral administration. Blood samples were immediately transferred to tubes that contained EDTA and were centrifuged at 4\(^{\circ}\)C. Plasma was harvested and stored at \(-20^\circ\)C until analysis. Plasma concentrations of gabapentin were determined by use of liquid chromatography–mass spectrometry. Gabapentin concentration-time data were fit to compartment models.

**Results**—A 3-compartment model with elimination from the central compartment best described the disposition of gabapentin administered IV to cats, but a 1-compartment model best described the disposition of gabapentin administered orally to cats. After IV administration, the mean ± SEM apparent volume of the central compartment, apparent volume of distribution at steady state, and clearance and the harmonic mean ± jackknife pseudo-SD for terminal half-life were 90.4 ± 11.3 mL/kg, 650 ± 14 mL/kg, 3 ± 0.2 mL/min/kg, and 170 ± 21 minutes, respectively. Mean ± SD systemic availability and harmonic mean ± jackknife pseudo-SD terminal half-life after oral administration were 88.7 ± 11.1% and 177 ± 25 minutes, respectively.

**Conclusions and Clinical Relevance**—The disposition of gabapentin in cats was characterized by a small volume of distribution and a low clearance. (Am J Vet Res 2010;71:817–821)
Gabapentin has several features that make it attractive for use as an analgesic in cats. Gabapentin is not a controlled substance and is widely available as an oral formulation. Also, gabapentin has few toxic effects in several species. Although gabapentin has been used increasingly in cats, the authors are not aware of any published data on the pharmacokinetics of this drug in this species. Without such data, it is difficult to make rational dosing recommendations. Therefore, the purpose of the study reported here was to characterize the pharmacokinetics of gabapentin in cats after IV and oral administration.

**Materials and Methods**

**Animals**—Six healthy adult spayed female domestic shorthair cats were used in the study. Mean ± SD body weight of the cats was 3.7 ± 0.3 kg. Cats were allowed ad libitum access to food and water during the study. The study was approved by the Institutional Animal Care and Use Committee at the University of California-Davis.

**Instrumentation and drug administration**—The day before an experiment, cats were anesthetized by administration of isoflurane in oxygen. A 22-gauge, 10-cm catheterb was placed in a jugular vein. A light bandage was placed over the catheter, and the cats were allowed to recover from anesthesia.

On the day of an experiment, gabapentin was administered IV as a bolus (4 mg/kg) in a medial saphenous vein or orally (10 mg/kg). Immediately before IV administration, gabapentin was dissolved in water to achieve a solution with a concentration of 10 mg/mL. The solution was filtered through a 0.2-μm filter. For oral administration, 100-mg gabapentin capsules were reformulated to contain a dose of approximately 10 mg of gabapentin/kg so that 1 capsule containing an individual’s dose was administered to each cat. Blood samples (1.5 mL) were obtained via the jugular catheter prior to gabapentin administration and 1, 2, 4, 8, 15, 30, 60, 120, 240, 480, and 960 minutes after IV administration or 5, 10, 20, 30, 45, 60, 90, 180, 360, 720, and 1,440 minutes after oral administration. Collected blood samples were inserted into tubes that contained EDTA; tubes were immediately placed on ice and then centrifuged at 3,901 × g for 10 minutes at 4°C. Plasma was harvested and stored at −20°C until analyzed for gabapentin concentrations.

After a 2-week washout period, each cat was given gabapentin via the other route of administration. The order of treatments for each cat was determined by use of a randomization procedure (random number list generated by a computer programd).

**Gabapentin analysis**—Gabapentin was quantitated in feline plasma by use of LC-MS analysis of extracted plasma samples. Calibration standards were prepared. Stock solutions were made by dissolving 10.0 mg of gabapentin standard in 10.0 mL of acetonitrile. Working solutions were prepared by dilution of the gabapentin stock solution with acetonitrile to achieve concentrations of 10.0, 1.0, and 0.1 mg/mL. Plasma calibrators were prepared by dilution of the working gabapentin solutions with drug-free plasma to achieve concentrations of 0.3, 2.0, 5.0, 10, 25, 50, 100, 500, 1,000, 2,000, 5,000 10,000, 20,000, and 30,000 ng/mL. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality control samples (plasma fortified with analytes at concentrations at the midpoint of the standard curve) were routinely included as an additional evaluation of accuracy. The concentration of gabapentin in each sample was determined via the internal standard method by use of the peak area ratio and linear regression analysis.

Quantitative analyses were performed on a mass spectrometer coupled with an LC system. Chromatography involved the use of a 50 × 2.1-mm, 3-mm column and a linear gradient of acetonitrile in water with a constant flow of 0.2% formic acid at a rate of 0.4 mL/min. The acetonitrile concentration was maintained at 2% for 0.3 minutes and then increased up to 98% during a period of 2 minutes.

Prior to analysis, all plasma samples were extracted by use of solid-phase extraction cartridges (200 mg, 3 mL, octadecyl, endcapped, sorbent type C18 cartridges). Aliquots of 0.4 mL of plasma were treated with 2.0 mL of phosphate buffer (pH, 7.0) fortified with 4 ng of internal standard in an extraction procedure developed to elute gabapentin and baclofen in a single fraction. The injection volume was 30 μL.

Detection and quantification involved full-scan LC-MS-MS transitions of initial product ions for gabapentin (m/z, 172.1). The response for the major product ion for gabapentin (m/z, 134.1) was plotted, and peaks at the proper retention time were integrated with a computer program. The same computer program was also used to generate calibration curves and quantitate the analytes in all samples.

The concentration of gabapentin in each sample (eg, calibrators, quality control samples, and unknown plasma samples) was determined via an internal standard method by use of the peak area ratio and linear regression analysis. The response for gabapentin was linear and yielded values of R² ≥ 0.99. The technique was optimized to provide a limit of detection of 0.5 ng/mL and limit of quantitation of 2.0 ng/mL. Intraday accuracy was 94% and 98% for 25 and 500 ng/mL, respectively. Interday accuracy was 92% and 96% for 25 and 500 ng/mL, respectively. Intraday precision (percentage of relative SD) was 2.7% and 1.8% for 25 and 500 ng/mL, respectively. Interday precision (percentage of a nominal concentration) was 0.4% and 5.5% for 25 and 500 ng/mL, respectively.

**Pharmacokinetic analysis**—All pharmacokinetic analyses were performed with a computer program. Nonlinear least squares regression was performed on plasma gabapentin concentrations after IV or oral administration. Data for IV administration were weighted by the reciprocal of the square of the observed plasma gabapentin concentration. Models (1-, 2-, and 3-compartment models) with elimination from the central compartment were fit to the data for IV administration. Data for oral administration were weighted by the reciprocal of the square of the predicted plasma gabapentin concentration. Models (1- and 2-compartment models) with first-order absorption in, and elimination from, the
central compartment and with or without lag time were fit to the data for oral administration. The appropriate model was selected by observation of the residuals plot and by use of the Akaike information criterion. Values for F were calculated from the ratio of the AUC after oral and after IV administration (indexed to their respective dose) by use of the following equation:

\[
F = \left( \frac{\text{AUC}_{\text{oral}} \times \text{dose}_{\text{IV}}}{\text{AUC}_{\text{IV}} \times \text{dose}_{\text{oral}}} \right) \times 100
\]

where AUC_{oral} and AUC_{IV} were the AUC after oral and IV administration, respectively; and dose_{IV} and dose_{oral} were the dose for IV and oral administration, respectively.

Parameters estimated by use of the model were Vc, K10, K12, K21, K31, and K13 for IV administration and Vc/F, K01, and K10 for oral administration. Other pharmacokinetic parameters were calculated by use of standard pharmacokinetic equations. Parameters for oral administration were corrected for F, when appropriate.

Normal distribution of pharmacokinetic parameters was verified by use of the Shapiro-Wilk test. Data were reported as the mean ± SEM (range), and half-lives were reported as harmonic mean ± jackknife pseudo-SD (range), unless specified otherwise.

**Results**

A 3-compartment model best described the decrease in the plasma concentration of gabapentin after IV administration (Figure 1). The mean ± SD Vc, VDss, and CL were 90.4 ± 11.3 mL/kg (range, 64.1 to 132.4 mL/kg), 650 ± 14 mL/kg (range, 567 to 700 mL/kg), and 3.0 ± 0.2 mL/min/kg (range, 2.5 to 3.5 mL/min/kg), respectively, and the harmonic mean ± jackknife pseudo-SD terminal half-life was 170 ± 21 minutes (range, 151 to 198 minutes).

A 1-compartment model best described the decrease in the plasma concentration of gabapentin after oral administration (Figure 1). Data after oral administration for 1 cat were excluded because the data obtained for this cat did not fit any model well. The actual mean ± SD oral dose administered was 10.0 ± 0.3 mg/kg. The mean ± SD F after oral administration was 88.7 ± 11.1% (range, 49.6% to 118.3%), and the harmonic mean ± jackknife pseudo-SD terminal half-life was 177 ± 25 minutes (range, 151 to 211 minutes). Mean ± SD t_{max} after oral administration predicted by use of the model was 100 ± 22 minutes (range, 38 to 175 minutes).

**Discussion**

In the study reported here, we described the pharmacokinetics of gabapentin after oral and IV administration in cats. This information can be used as a basis to design pharmacodynamic studies in cats. Once effective concentrations are determined, the data in this study can be used to design rational protocols for administration of gabapentin to cats.

The pharmacokinetics of gabapentin has been evaluated in humans, dogs, and rats. In humans, gabapentin has a half-life of 6 to 8 hours, is eliminated unchanged by renal clearance, and does not bind to plasma proteins. In rats, the half-life is 2 to 3 hours, and there is minor biotransformation. However, pharmacokinetic studies in dogs have revealed that gabapentin has a half-life of 3 to 4 hours, and it is metabolized to N-methyl-gabapentin.

To our knowledge, the pharmacokinetics of gabapentin in cats has not been reported. In the study reported here, a 3-compartment model best described the disposition of gabapentin when administered IV, whereas a 1-compartment model best described the disposition of gabapentin when administered orally. This difference can be attributable to the addition of the absorption phase when gabapentin is administered orally. The increasing concentration of gabapentin in plasma as a result of absorption may have masked the distribution of gabapentin to peripheral compartments. Although less likely, inadequate timing for collection of blood samples could have contributed to the unobserved distribution to other compartments. The pharmacokinetics of gabapentin after oral or IV administration was characterized by a larger volume of distribution and a higher CL, compared with the mean Vd_{area}.
(0.158 L/kg) and mean Cl (2.27 [mL/min/kg]) reported after IV administration in dogs.\textsuperscript{16} However, both dogs and cats have a relatively small volume of distribution, compared with the mean ± SD for Vd\textsubscript{area} (1.44 ± 0.50 L/kg) and Vd\textsubscript{ss} (1.23 ± 0.28 L/kg) reported after IV administration in rats.\textsuperscript{15,16} This is probably attributable to the relatively low lipid solubility of gabapentin (log\textsubscript{10} octanol-to-water ratio = -1.2).\textsuperscript{15} Gabapentin is extensively distributed in tissues of rats.\textsuperscript{16} However, this could differ from the situation in cats. The mean ± SD Cl after IV administration is also higher in rats (9.5 ± 2.0 [mL/kg]/kg in 1 study)\textsuperscript{15} and 9.27 ± 1.9 [mL/kg]/kg in 1 study\textsuperscript{16}) than in cats and dogs, which results in a shorter half-life in rats (1.7 hours), compared with the half-life in dogs and cats (2.9 and 2.8 hours, respectively). The larger volume of distribution and larger Cl in cats result in a terminal half-life similar to that in dogs.\textsuperscript{15,16} The F in cats (mean ± SD, 88.7 ± 11.1%; range, 49.6% to 118.3%) is higher, compared with the value for F in dogs (mean, 90%);\textsuperscript{16} rats (mean ± SD, 79.0 ± 11%);\textsuperscript{16} and humans (range, 75% to 81%).\textsuperscript{15} The F was extremely good in cats (88.7%), but there was variation among the cats.

After oral administration, C\textsubscript{max} ranged from 4,638 to 10,550 ng/mL and t\textsubscript{max} ranged from 58 to 175 minutes. The t\textsubscript{max} in cats after oral administration was similar to that reported in a study\textsuperscript{15} of humans, rats, and dogs. The high interindividual variability in cats in the study reported here may have been caused by variation in the F of gabapentin. Because food was not withheld from the cats (ie, food was available ad libitum), it is hard to predict whether cats ate close to the time of oral administration of gabapentin. Gastrointestinal transit time of drugs reportedly differs between fed cats and cats from which food is withheld\textsuperscript{15}; thus, the interval between feeding and oral administration of gabapentin could have affected the absorption of gabapentin. Differences in eating habits among cats may have caused variation in the pharmacokinetic parameters measured. Another factor that could have added to the variation is the fact that administration of the gabapentin capsule was not followed by oral administration of a dose of water (ie, a water flush). This may have caused the rate at which a capsule passed through the esophagus to vary. Consistent administration of a water flush could have potentially minimized the variation of transit time through
the esophagus, thereby decreasing the variation in $t_{\text{max}}$ and $C_{\text{max}}$; however, it may be difficult to orally administer a water flush to a cat, especially immediately after oral administration of a capsule.

In humans, an analgesic effect for neuropathic pain was achieved at doses of 1,800 mg of gabapentin/d, 19 and serum concentrations of gabapentin > 2 μg/mL resulted in a reduced frequency of seizures. 20 Simulations were run on a computer program 21 to determine adequate administration that would yield similar concentrations in cats. The pharmacokinetic parameters reported in another study 15 were used to calculate effective plasma concentrations of oral dosages of 1,800 mg/d (600 mg every 8 hours), which were between 4.3 and 8 μg/mL. The pharmacokinetic parameters reported here were used to simulate time-concentration data after administration of doses targeted to yield plasma concentrations similar to the plasma concentrations reported for humans. In cats, an oral administration schedule of 8 mg/kg every 6 hours would be expected to result in plasma concentrations similar to that for an oral administration of 1,800 mg/d in humans. To reach and maintain plasma concentrations of 2 μg/mL, cats should be administered 3 mg of gabapentin/kg PO every 6 hours. Pharmacodynamic studies could be conducted with these dosing regimens to determine whether gabapentin is an effective analgesic in cats.

Gabapentin distribution in cats is characterized by a small volume of distribution and low Cl. Pharmacodynamic studies are needed to determine the correlation between the kinetics of this drug and clinical effects.

References