Levetiracetam (s-\(\alpha\)-ethyl-2-oxo-1-pyrrolidine acetamide) is among the newest of the anticonvulsant drugs approved for use in humans, with proven efficacy for many types of seizure disorders. Although its mechanism of action is incompletely understood, it is novel, compared with that for the classical AEDs. Levetiracetam interacts with neuronal synaptic vesicular (SV2A) receptors, thereby modulating calcium-dependent exocytosis of neurotransmitters.\(^1\) It also suppresses the inhibitory effect of Zn\(^{2+}\) on \(\gamma\)-aminobutyric acid and glycine-gated currents.\(^2\) In addition to its anticonvulsant effects, levetiracetam has been found to be neuroprotective when administered prophylactically to rodents with experimentally induced cerebral ischemia and head trauma.\(^3,4\)

The safety and efficacy of levetiracetam in humans have been extensively evaluated. During the clinical development of levetiracetam, 3 multicenter, double-blinded placebo-controlled trials conducted in the United States and Europe established its safety and efficacy as an adjunct treatment for refractory partial seizures in adults\(^5-8\) and children.\(^9\) Clinical trials have revealed levetiracetam to be effective as the sole treatment for control of myoclonic\(^10\) and primary generalized tonic-clonic seizures\(^11,12\) in patients with idiopathic epilepsy. The most common adverse effects with administration of levetiracetam in adults are related to the CNS and include somnolence, fatigue, dizziness, and headache.\(^13\) In children, the most commonly reported adverse effects are aggressive behavior, nervousness, and hyperkinesia.\(^14\-17\)

In studies\(^14-17\) of pharmacokinetics of levetiracetam administered in accordance with recommended dose regimens to dogs, rodents, and rabbits, investigators have not reported adverse effects, which supports
its potential safety. In all of the species evaluated, levetiracetam is almost exclusively excreted as the unchanged compound by the kidneys.15,16 In dogs, pharmacokinetics of levetiracetam support its long-term use as an anticonvulsant because it is well absorbed after oral administration, is minimally protein bound, distributes well into the brain, and has linear pharmacokinetics.14,15 Furthermore, it is excreted by the kidneys, which minimizes the risk of disease and interactions involving the liver. One potential disadvantage of levetiracetam in dogs is a T1/2 of approximately 3 to 4 hours, which necessitates administration every 8 hours.14-16

A number of novel, second-generation AEDs have been developed that are effective and tolerated well in humans. However, neither safety nor efficacy in humans can be used to predict effects in dogs or cats. Differences in pharmacodynamics (including therapeutic or adverse responses) or pharmacokinetics can be profound. Cost may also be a limiting factor. Among these newer drugs, gabapentin, zonisamide, and levetiracetam have been found to be of benefit as adjunctive treatments in refractory canine patients.19–21 Few scientific reports regarding the use of second-generation AEDs in cats are available. Levetiracetam has been used as an adjunct treatment22 and as the sole treatment23 in AEDs in cats are available. Levetiracetam has been shown to be effective in dogs and cats. Although no important adverse effects have been reported in cats or other species, caution should be exercised when administering this drug to cats without knowledge of a scientifically derived dose. This may be particularly true for cats, a species for which unique pharmacokinetics and pharmacodynamics have been determined for many drugs. However, kinetic differences focus principally on metabolism, which suggests fewer adverse effects may be expected after administration of levetiracetam. Nonetheless, the potential risk for inappropriate use of an anticonvulsant drug mandates that use in any species, including cats, be supported with scientific studies, including pharmacokinetic studies.

The objective of the study reported here was to describe the time course of levetiracetam after a single dose administered IV or orally to cats to determine a dose and dosing interval that would achieve and maintain therapeutic concentrations described in humans (5 to 45 µg/mL)24 throughout the dosing interval. Furthermore, the study was intended to assess tolerability of levetiracetam after oral and IV administration of a single dose.

Materials and Methods

Animals—Ten healthy adult domestic shorthair cats were included in the study. There were 2 castrated males and 8 spayed females. Age of the cats ranged from 18 months to 5 years, and body weight ranged from 2.45 to 4.42 kg (mean, 3.44 kg). All procedures were approved by the Auburn University Institutional Animal Care and Use Committee.

A baseline health assessment that included physical and neurologic examinations, a CBC, serum biochemical profile, and urinalysis was performed. On the day prior to each period of the study, each cat was weighed and then sedated (15 mg of ketamine/kg, 0.4 mg of butorphanol/kg, and 0.03 mg of medetomidine/kg, IM) so that an indwelling catheter could be aseptically placed in a jugular vein. At the conclusion of each period of the study, the baseline health assessment was repeated and the indwelling catheter was removed.

Pharmacokinetic evaluation—The study was conducted prospectively as a randomized, crossover design involving 2 periods with a 7-day washout between each period. Each cat initially received a single dose of levetiracetam (20 mg/kg) IV or orally in the first period and then received the same dose via the alternative route in the second period. For IV administration, the calculated dose of the commercial IV preparation of levetiracetam was diluted in 5 mL of sterile saline (0.9% NaCl) solution and administered over a 5-minute period through the indwelling catheter inserted in a jugular vein. The commercially available levetiracetam oral suspension was used for oral administration. A blood sample (3 mL) was collected from the jugular vein (via the indwelling catheter) and placed into collection tubes 0, 10, 20, and 40 minutes and 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours after administration. At least 2 catheter volumes of blood were aspirated and discarded prior to collection of each sample. After each sample was collected, indwelling catheters were flushed with heparinized saline solution. Blood samples were maintained on ice until centrifugation at 50 × g for 15 minutes at 4°C; plasma was harvested and stored frozen (−70°C) until analysis.

Evaluation for adverse effects—Each cat was monitored at each time point at which plasma samples were obtained for 24 hours after levetiracetam administration. Cats were observed for evidence of adverse drug reactions. In addition, a physical examination, CBC, serum biochemical profile, and urinalysis were performed for each cat immediately before and 24 hours after IV and oral administration.

Sample analysis—Plasma samples were thawed at 21°C and then mixed to assure homogeneity. Levetiracetam was detected in feline plasma via high-performance liquid chromatography by use of methods described elsewhere, with slight modifications (the column used was 230 mm instead of 150 mm). Sample preparation was accomplished by use of solid-phase extraction. Samples were eluted from the columns with methanol. The eluent was dried (evaporated) under nitrogen gas and reconstituted with the mobile phase, which was a mixture composed of 3% acetonitrile, 6% methanol, and 89% 3mM potassium phosphate buffer containing triethylamine to adjust the pH to 6.5. Flow rate was set at 1.0 mL/min. Drug was detected by use of UV spectroscopy at 205 nm. Drug concentrations in samples were quantitated by comparing the UV signal in unknown samples with the signal for standards prepared by the addition of known amounts of levetiracetam to feline plasma. Concentrations of the standard curve ranged from 1 to 300 µg/mL. The linear correlation coefficient was 0.9994. Control samples spanning the concentrations of the standard curve revealed results within 15% of the expected concentrations (intra-assay and interassay variability), which
yielded a lower and upper limit of quantitation of 1 and 300 μg/mL, respectively.

Data analysis—Plasma levetiracetam concentrations obtained after IV or oral administration (logarithm of concentration vs time curves) were analyzed by use of noncompartmental linear regression analysis,* with use of AUC determined to infinity via the trapezoidal method. For IV administration, peak plasma concentrations were extrapolated to the y-intercept, whereas for oral administration, the actual Cmax detected at Tmax was calculated. In addition, MRT and T1/2 were determined. Bioavailability after oral administration was determined by use of the equation (AUC after oral administration/AUC after IV administration) × 100.

Statistical analysis—Descriptive statistics were calculated by use of commercially available software.† Pharmacokinetic data were reported as the mean ± SD, except for T1/2, which was reported as the harmonic mean and its comparable measure of SD, pseudo-SD. The time that drug concentrations remained in the therapeutic range defined for humans (5 to 45 μg/mL) was determined. Student t tests‡ were used to compare elimination rate constants between routes of administration to detect a flip-flop effect.

Results

Adverse effects after oral or IV administration of a single dose of levetiracetam—All cats appeared to tolerate levetiracetam well; adverse effects were apparently limited to transient mild to moderate hypersalivation after oral administration. Laboratory data (results of a CBC, serum biochemical profile, and urinalysis) obtained 24 hours after administration were compared with preadministration data, and no clinically relevant changes or abnormalities were detected.

Pharmacokinetics after IV administration of a single dose of levetiracetam—Plasma concentrations of levetiracetam within the therapeutic range defined for humans were achieved at the first time point (10 minutes after administration) and remained within the therapeutic range for at least 9 hours in 7 of 10 cats (Figure 1; Table 1). Mean ± SD Cmax (ie, y-intercept) was 37.52 ± 6.79 μg/mL. Mean ± pseudo-SD for T1/2 was 2.86 ± 0.65 hours. Mean ± SD MRT was 4.57 ± 0.94 hours, Vdss was 0.52 ± 0.09 L/kg, and clearance was 2.0 ± 0.60 mL/kg/min.

Pharmacokinetics after oral administration of a single dose of levetiracetam—Plasma concentrations of levetiracetam within the therapeutic range defined for humans were achieved at the first time point (10 minutes after administration) and remained within the therapeutic range for at least 9 hours in 7 of 10 cats (Figure 1; Table 2). Mean ± SD Cmax was 25.54 ± 7.97 μg/mL, and mean Tmax was 1.67 ± 1.73 hours. Mean ± pseudo-SD T1/2 was 2.95 ± 0.95 hours. Mean ± SD MRT was 5.65 ± 1.25 hours, and oral bioavailability was 102 ± 0.39%. The elimination rate did not differ between IV and oral administration.

Discussion

Analysis of results of the study reported here suggested that levetiracetam (20 mg/kg) administered orally or IV to cats every 8 hours should achieve and maintain plasma concentrations within the therapeutic range for humans. The lack of clinically important adverse effects, in conjunction with favorable pharmacokinetics and potential efficacy,§ make use of levetiracetam a reasonable option for seizure management in cats.

Levetiracetam is a structurally novel AED that is used successfully in humans as the sole treatment or
as adjunctive treatment for partial-onset seizures in humans. Levetiracetam has been proven effective after oral administration for the treatment of epilepsy in dogs and has promise for the treatment of epilepsy in cats. Treatment options for seizure disorders in cats are limited, which mandates a need for identification and description of new AEDs for use in cats. Currently, phenobarbital is the most commonly recommended anticonvulsant drug for the treatment of seizure disorders in cats. Although phenobarbital is generally safe and effective, its use is associated with adverse effects, including sedation, polyuria, polydipsia, polyphagia, facial pruritus, bone marrow dyscrasias, and coagulopathies. Additionally, unpredictable relationships between dose and plasma drug concentrations can make safe and effective seizure management much more challenging in cats. Diazepam is often cited as a second drug of choice for epilepsy in cats; however, up to 20% of cats are reportedly unresponsive to diazepam, and the development of acute fatal hepatic necrosis has been reported. Phenobarbital and diazepam are primarily metabolized by the liver, which may preclude their use in animals with hepatic dysfunction and generally increases the risk of drug interactions or hepatic disease. Bromide, a drug that has been used effectively in dogs, has proven variably effective for treatment of seizures in cats; however, the risk for eosinophilic pneumonitis, which may develop in 30% to 40% of cats receiving bromide, precludes its routine use as an anticonvulsant in cats.

Analysis of results of the present study suggested that the disposition and apparent tolerance of levetiracetam in clinically normal cats support its clinical use at a dose of 20 mg/kg. Its disposition in cats is similar to that in dogs but differs from that in humans. The mean ± SD T 1/2, in cats for oral (2.95 ± 0.95 hours) and IV administration (2.86 ± 0.65 hours) is comparable to that for IV administration in dogs (3.6 ± 0.8 hours) and 4.0 ± 0.82 hours) and is considerably shorter than that in humans (7.16 ± 1.13 hours). Differences in T 1/2 between cats and humans probably reflect differences in clearance, whereas the mean Vdss is similar between dogs, cats, and humans (0.52 ± 0.09 L/kg, 0.43 ± 0.13 L/kg, and 0.56 ± 0.09 L/kg, respectively). Mean clearance is higher in cats (2.0 ± 0.6 mL/min/kg), compared with mean clearance in humans (0.85 ± 0.15 mL/min/kg) and dogs (1.5 ± 0.3 mL/min/kg). The short half-life indicates that levetiracetam concentrations in cats may be expected to decrease by approximately 50%, 75%, and 87% at 2, 4, and 6 hours after administration, respectively, which suggests a need for dosing intervals ≤ 6 hours. However, the pharmacodynamic response to levetiracetam may outlast its presence in plasma, perhaps because of a longer maintenance of concentrations in CSF that has been determined in rats, for which the half-life in the CSF is approximately twice that of plasma. Furthermore, levetiracetam has antiepileptogenic activity in rats that persists long after elimination of the drug from plasma.

The mean ± SD bioavailability was 102 ± 35%, which suggested substantial variation. One cat was a noticeable outlier, with bioavailability calculated at 200%. If results for this cat were removed from the data set, the mean bioavailability would have been 90 ± 15%. Data for this cat were carefully evaluated, and it was noticed that its AUC and Cmax after IV administration were the lowest. This may suggest that its Vdss was much larger, compared with that of the other cats; however, the Vdss should normalize when the drug is given orally (ie, the total amount of drug in the body should not be impacted by an increase in Vdss). On the basis of these data, a possible explanation for the variation is that this cat may have been underdosed for IV administration (eg, part of the dose was inadvertently administered SC), but this was unlikely because of the fact that the AUC was normally distributed. In consideration of this, the bioavailability approached 100%, which is consistent with results of other studies in dogs.

In a recent study, investigators evaluated the efficacy of levetiracetam (20 mg/kg, PO) as an adjunctive treatment to the administration of phenobarbital in cats with refractory seizures. Results of that study suggested that levetiracetam may be a useful adjunctive treatment for refractory epilepsy because 7 of 10 cats had a reduction in seizure frequency of > 50%. Those investigators also reported a limited pharmacokinetic analysis after oral administration. Although only 3 time points were used for plasma drug concentrations in that study, which resulted in the need for some extrapolation of data, the reported pharmacokinetics for oral administration of levetiracetam were similar to the data in the study reported here. The repeatability of both studies to evaluate the pharmacokinetics after oral administration of levetiracetam to epileptic cats and after oral and IV administration to clinically normal nonepileptic cats further validates these results and underscores the potential for safe use of levetiracetam in this species.

A therapeutic range for plasma concentrations of levetiracetam has not been defined in cats or dogs. In humans, the therapeutic range is not firmly established but has been reported as 5 to 45 µg/mL on the basis of a typical dosing regimen of 500 to 1,500 mg every 12 hours. Monitoring of therapeutic concentrations of levetiracetam is not routinely performed in humans because a clear relationship between plasma concentrations and efficacy has not been established. For the purposes of the present study, the reported therapeutic range for humans (5 to 45 µg/mL) was used as a basis for the comparison of the pharmacokinetics of levetiracetam in cats. Mean ± SD Cmax of levetiracetam achieved in the present study was 37.52 ± 6.79 µg/mL after IV administration and 25.54 ± 7.97 µg/mL after oral administration. Mean plasma concentrations in 7 of 10 cats were within the therapeutic range for humans for at least 9 hours. On the basis of the T 1/2, a dosing interval of 6 hours may be ideal for cats; however, this is impractical for most pet owners and will result in poor compliance. At a Cmax of 25 µg/mL, with 2 half-lives elapsing during a dosing interval, trough concentrations will be in the low part of the therapeutic range. An initial dose of 20 mg/kg administered IV or orally every 8 hours should be adequate for most cats, given that most of the cats in the present study maintained levetiracetam plasma concentrations within the therapeutic range for humans throughout the dosing interval as well as the fact that the pharmacodynamic effect of
Levetiracetam appears to outlast its presence in plasma. However, for some cats, a trough concentration in the low part of the therapeutic range may be inadequate. To enhance efficacy and maintain an 8-hour dosing interval, every doubling of the dose will add 1 half-life to the dosing interval. Thus, to obtain a target plasma concentration of 10 to 12 g/mL, a dose of approximately 40 mg of levetiracetam/kg every 8 hours may be necessary.

The potential for toxicosis associated with levetiracetam administration is low. In dogs, oral administration of 2,000 mg/kg and IV administration of 1,200 mg/kg result in mild adverse reactions, including salivation, vomiting, tachycardia, and restlessness. In 2 studies of the efficacy of levetiracetam (20 mg/kg, PO, q 8 h), 1 of 18 dogs had mild sedation and 2 of 10 cats had transient lethargy and inappetence. In another study conducted to evaluate the pharmacokinetics and tolerability of levetiracetam (60 mg/kg, IV) in 6 dogs, investigators reported no substantial adverse effects. To our knowledge, there are no data on the toxic effects of levetiracetam in cats; however, on the basis of the disposition of the drug in cats and the data available on toxicoses in dogs, doubling or tripling the dose in cats may prove to be safe and effective. Additional studies are needed to evaluate this possibility.

Levetiracetam is the first of the second-generation AEDs to be formulated as an injectable preparation. Its tolerability and disposition in cats make it suitable for use in clinical settings. This is particularly advantageous for cats that cannot be administered the drug orally because of medical or behavioral reasons. Interestingly, the authors of a recent report described the successful use of the injectable preparation of levetiracetam in the treatment of 18 benzodiazepine-refractory human patients with status epilepticus. In another study in rats with experimentally induced status epilepticus, investigators concluded that IV administration of levetiracetam significantly enhanced the anticonvulsant effects of diazepam administered IV. These data and the disposition of levetiracetam in cats suggest that IV administration of levetiracetam may also be considered as an adjunctive treatment for status epilepticus in cats.

On the basis of the present study, levetiracetam should be considered as an alternative AED for seizure control in cats. The clinical use of levetiracetam in cats as an alternative to standard AEDs, such as phenobarbital, is supported by the fact that levetiracetam has no known clinically relevant drug-drug interactions, does not alter mental function, does not cause substantial sedation, and appears to be tolerated well, and, because of its short half-life, does not accumulate. Because of these factors, any delay in response reflects pharmacodynamic rather than pharmacokinetic accommodation. In the present study, 10 healthy cats tolerated well a single 20 mg/kg dose of levetiracetam administered orally and IV. Plasma concentrations remained within the therapeutic range for humans for at least 9 hours in 7 of 10 cats, which suggested the possibility of daily administration at 8-hour intervals. It is anticipated that some cats may require higher doses of levetiracetam to maintain plasma concentrations in the upper part of the therapeutic range for humans. The increased dose is not anticipated to cause clinical problems. Future studies are warrant-
ed to determine the overall efficacy of levetiracetam in control of seizures in cats as well as for the development of a therapeutic range for plasma concentrations of levetiracetam in cats.

References


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