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Disposition of Extended Release Levetiracetam in Normal Healthy Dogs After Single Oral Dosing

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Background: Levetiracetam is an anticonvulsant used for control of canine epilepsy. An extended release preparation should improve dosing convenience.

Objectives: To determine the disposition of extended release levetiracetam in normal dogs after single dosing.

Animals: Pharmacokinetic study: 16 healthy, adult dogs.

Methods: Using a partially randomized crossover study, levetiracetam (30 mg/kg) was administered intravenously (IV) and orally (PO) as extended release preparation with or without food. Blood was collected for 24 hours (IV) or 36 hours (PO). Serum levetiracetam was quantitated by immunoassay and data were subjected to noncompartmental analysis.

Results: Pharmacokinetic parameters for fasted versus fed animals, respectively, were (mean ± SEM): C_{max} = 26.6 ± 2.38 and 30.7 ± 2.88 μ/mL, T_{max} = 204.3 ± 18.9 and 393.8 ± 36.6 minutes, $t_{1/2}$ = 4.95 ± 0.55 and 4.48 ± 0.48 hours, MRT = 9.8 ± 0.72 and 10 ± 0.64 hours, MAT = 4.7 ± 0.38 and 5.6 ± 0.67 hours, and F = 1.04 ± 0.04 and 1.26 ± 0.07%. Significant differences were limited to T_{max} (longer) and F (greater) in fed compared to fasted animals. Serum levetiracetam concentration remained above 5 μ/mL for approximately 20 hours in both fasted and fed animals.

Conclusions and Clinical Importance: Extended release levetiracetam (30 mg/kg q12h), with or without food, should maintain concentrations above the recommended minimum human therapeutic concentration.

Key words: Anticonvulsants; Antiepileptics; Seizures.

Seizures are among the most common neurologic disorders affecting companion animals, and their control generally requires lifelong daily medication.[1–3] The life span of dogs with epilepsy is shorter than dogs without epilepsy; antiepileptic medication adverse effects or inadequate seizure control lead to an even shorter life span.[4] Although phenobarbital and bromide are common choices for long-term seizure management in dogs, the failure rate for sole or combination treatment remains 15–30%.[5,6]

Levetiracetam is a new antiepileptic drug found to be both safe and effective in dogs.[7–12] Favorable characteristics include a unique mechanism of action[13] (binding to the synaptic vesicle protein 2A), minimal metabolism,[14] few documented drug-drug interactions,[15] and multiple administration routes (IV, PO, IM, per rectum).[7–16] Currently, based on previous studies in dogs, an average 3-hour half-life requires 8-hour dosing intervals. Furthermore, drug concentrations will fluctuate >75% during a dosing interval,[a] which may contribute to poor seizure control. An extended release levetiracetam product approved for use in humans has lengthened the dosing interval from 12 to 24 hours in human epileptic patients.[17–20] However, previous studies have indicated that dosing regimens for slow or extended release products approved for use in humans cannot accurately be extrapolated to dogs.[21] This necessitates testing of extended release products intended for use in humans, in dogs, before their use in canine

Abbreviations:

AR	accumulation ratio
AUC_{IV}	area under the curve for intravenous administration
AUC_{oral}	area under the curve for oral administration
Cl	clearance
C_{max}	maximum concentration
C_o	plasma drug concentration at time 0
$Dose_{IV}$	dose for intravenous administration
$Dose_{oral}$	dose for oral administration
F	bioavailability
Kel	elimination rate constant
K	terminal elimination rate constant
MAT	mean absorption time
MRT_{IV}	mean residence time for intravenous administration
MRT	mean residence time
MRT_{oral}	mean residence time for oral administration
SEM	standard error of the mean
$t_{½}$	half-life
tau	dosing interval
T_{max}	time to maximum concentration
V_d	volume of distribution

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epileptic patients. Differences may reflect particle sizes allowed through the human versus canine pylorus and shorter gastrointestinal transit time in dogs.[22,23]

The goal of this study was to describe the pharmacokinetic parameters of extended release levetiracetam[b] in neurologically normal, healthy dogs after a single dose, to determine the effects of food on its disposition, and to establish a dosing interval, which would maintain serum levetiracetam concentrations above the minimum therapeutic concentration established in humans (5 μg/mL) throughout the proposed dosing protocol.

Materials and Methods

Experimental Protocol

Sixteen privately owned adult (age 1–5 years) dogs weighing a minimum of 15 kg (average weight, 34 kg; range, 20.4–50 kg) were volunteered for this study and were assessed to be apparently healthy based on normal physical and neurologic examination, CBC, serum biochemistry, and urinalysis. They were studied using a nonrandomized, crossover study (IV followed by PO), but dogs were randomized to be fasted or receive food with the PO dose. All procedures were approved by Auburn University's Institutional Animal Care and Use Committee (IACUC) and Clinical Research Review Committee (CRRC). Owners signed a client informed consent (CIC) form before their pet's participation in the study.

The current dosing protocol for regular release levetiracetam results in a total of 60 mg/kg/day administered. Therefore, in an initial pilot study using 4 dogs, half received 30 mg/kg in anticipation of a 12-hour dosing interval, and half received 60 mg/kg in anticipation of a 24-hour dosing interval, to determine the dosage that would be studied in the remaining dogs. Based on these first 4 animals, a dosage of 30 mg/kg was chosen for the remaining 12 dogs because the 60 mg/kg dosage caused sedation and did not offer an advantage in terms of duration because serum levetiracetam concentrations were below the low end of the therapeutic range at 24 hours.

All remaining 12 dogs received approximately 30 mg/kg of levetiracetam first as a single IV dose[c] followed by PO extended release dose[b] separated by approximately 26.3 hours (approximately 8.7 half-lives). For each dog, the IV dose was given first to assure that the PO dose could be given without concern of residual levetiracetam, thus allowing the entire study for each animal (IV and PO dose) to be performed using a single IV catheterization. The IV dose was diluted 1 : 1 with 0.9% NaCl[d] and administered over approximately 2 minutes. Dogs randomized to be administered their PO dose with food were fed their provided home diet immediately after PO administration of the tablet. Those randomized to be fasted were not fed for at least 12 hours before and 4 hours after manual PO administration and then fed their home diet. Immediately before the study, cephalic (for drug administration) and lateral saphenous (for blood sampling) catheters were placed using topical lidocaine/prilocaine anesthetic[e] and manual restraint. The pilot study protocol differed only in that the dogs received IV doses of 20 mg/kg and PO doses of either 30 or 60 mg/kg instead of equal doses IV and PO (to the closest tablet size) of approximately 30 mg/kg.

Blood samples (3 mL) were collected immediately before and at 5, 10, 15, 20, 40, 60, 90, 120, 150, 180, 240, 300, 360, 480, 600, 720, and 1,440 minutes after IV and 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720, 900, 1,080, 1,260, 1,440, 1,800, and 2,160 minutes after PO administration. Catheters were irrigated after collection with an equivalent volume of 0.9% NaCl and with heparinized saline (0.1 U/mL)[f] when more than 4 hours lapsed among sample collections. Samples were placed in glass red top tubes.[g] Based on the US prescribing information from UCB Pharmaceuticals, the tablets should not be "chewed, broken or crushed."[24] Because of this, dogs were dosed to the nearest 30 mg/kg, with the actual mean dose being 32.67 mg/kg (range, 29.4–35.7 mg/kg).

Each dog was visually monitored throughout the study period for evidence of adverse drug reactions. In addition, physical and neurologic examinations, CBC, serum biochemistry, and urinalysis were performed on each dog at the completion of the study to compare to the preadministration results.

Measurement of Serum Levetiracetam Concentration

After clotting at room temperature, samples were centrifuged for 10 minutes at 1,900 × *g* within 2 hours of collection. Serum was harvested and frozen at −20°C until analysis. At the time of sample analysis, serum samples were thawed at room temperature and then vortexed to assure homogeneity. Levetiracetam was detected and quantitated in canine serum by a Food and Drug Administration human-approved immunoassay[h] on a general chemistry analyzer,[i] which is described elsewhere.[25] The system was validated in canine serum using pooled canine serum to which had been added known concentrations of levetiracetam. Subsequent analysis was based on the manufacturer's levetiracetam calibrator and control kits[j] which were designed for human serum. The package insert for the assay indicates a lack of cross-reactivity with the major metabolite (L057/PBA).[26] Furthermore, this metabolite represents only 2–9% of the dose (based on urinary excretion) in dogs compared to 24% of the dose in adult humans.[14,27] The upper and lower limits of quantitation are 100 μg/mL and 2 μg/mL, respectively.[26] The coefficient of variation based on canine controls was <14% for the low and <7% for the high range control. After validation in canine serum, manufacturer's controls are the basis for quality assurance. These are characterized by CV ≤ 10% for all controls.[a]

Data Analysis

Serum levetiracetam concentration versus time data was subjected to noncompartmental analysis[k] with area under the curve (AUC) determined to infinity by the trapezoidal method. For IV administration, peak serum concentrations were extrapolated to the *y*-intercept (C_0), whereas for PO administration, the actual maximum concentration (C_{max}) occurring at time to maximum concentration (T_{max}) was determined. In addition, mean residence time (MRT), elimination half-life ($t_{1/2}$), disappearance rate constant (k_d), and, after IV administration, clearance (Cl) and volume of distribution (V_d) were determined. Mean absorption time (MAT) was determined for PO doses based on the equation: $MAT = MRT_{oral} - MRT_{IV}$. Absolute bioavailability (F) of PO administered levetiracetam was determined from the following equation: $(AUC_{PO} \times Dose_{IV})/(AUC_{IV} \times Dose_{PO})$. Data were included from the pilot study for $t_{1/2}$, k_d, V_d, Cl, MRT, and F because these variables are independent of the dose administered. Only data from the 12 main study dogs were used for C_{max}, T_{max}, C_o, AUC, and MAT because these variables are dependent on dose administered.

Pharmacokinetic data are reported as mean ± SD as determined by use of commercially available software.[k] A Student's *t*-test was used to compare pharmacokinetic parameters obtained for PO administration with and without food and a paired *t*-test was used to compare IV and PO data by commercially available software[l] because the variances were found to be equal based on folded $F > 0.05$. Values of $P < .05$ were considered significant.

Results

Adverse Effects

All dogs in the pilot and main study appeared to tolerate all doses well. Adverse effects apparently, were limited to transient mild sedation after the 60 mg/kg PO extended release dose in the pilot study. A single dog in the pilot study vomited 22 hours after IV administration of levetiracetam (at 20 mg/kg), but continued the study without further problems. Clinicopathologic data (results of CBC, serum biochemistry, and urinalysis) obtained after administrations were within normal limits and no clinically relevant changes were seen when compared to preadministration results for all animals.

Pharmacokinetics

Table 1 delineates serum pharmacokinetics (mean ± SD) and *P* values comparing IV to PO administration and Table 2 delineates serum pharmacokinetics (mean ± SD) after PO administration with *P* values comparing fasted to fed administration. Mean serum concentrations remained >5 μg/mL for minimum of 9.5 hours after IV administration (Fig 1). For PO administration, serum levetiracetam achieved the minimum therapeutic concentration of 5 μg/mL by 100 minutes in fasted dogs and 200 minutes in fed dogs. At 12 hours, levetiracetam concentrations (μg/mL; mean ± SD) were higher ($P < .0001$) after PO (n = 12; 15.5 ± 5.3) compared to IV (n = 12; 5.5 ± 2.2) administration. Within the PO group, concentrations at 12 hours were lower ($P = .03$) in fed (n = 6; 12.3 ± 3.1) compared to fasted animals (18.6 ± 5.3) because of the delayed peak in serum concentrations after PO administration with food. Concentrations remained above the minimum therapeutic concentration for a mean of 19.8 hours (range, 15–24.2 hours) in fasted animals and 20.7 hours (range, 16.7–28.7 hours) in fed animals (Fig 1). Fluctuation in drug concentrations from the time at which peak (C_{max}) was measured (t_{max}) to 24 hours averaged 11.2-fold (range, 5.3–15.8) in fasted and 13.7-fold (range, 5.3–26.4) in fed animals after single dose administration. However, fluctuation was decreased to 2.4-fold (range, 1.9–3.2) in fasted and 1.8-fold (range, 1.4–2.7) in fed animals when measured to 12 hours. The accumulation ratio (AR) was calculated by the equation $AR = 1/(1 - e^{-K \times tau})$ for a 12- and 24-hour dosing interval. In fasted animals, the mean AR was 1.27 for 12-hour and 1.05 for 24-hour dosing intervals. In fed animals, the mean AR was 1.21 for 12-hour and 1.04 for 24-hour dosing intervals.

Statistical Analysis

Statistically significant differences between fasted and fed groups included t_{max}, which was longer ($P = .001$) and *F*, which was greater ($P = .02$) in fed compared to fasted dogs (Table 2). When comparing IV data to PO fasted data, significant differences included MRT ($P < .001$) and AUC ($P = 0.038$). When comparing IV data to PO fed data, significant differences included MRT ($P < .001$), AUC ($P = .017$) and k_d ($P = .043$). MRT was significantly longer (9.8 ± 2.0 and 10.8 ± 1.8 hours versus 5.4 ± 1.4 hours [$P < .001$]) and AUC significantly larger (335.4 ± 74.3 and 393.4 ± 138.3 versus 306.4 ± 79.4 μ × h/mL) in fasted and fed PO compared to IV. Elimination half-life did not differ between IV and either fasted or fed PO.

Discussion

According to the Food and Drug Administration Orange Book, at least 12 different extended release products are approved for use in humans and thus available for extra label veterinary use in dogs. Although each will have been demonstrated to be bioequivalent in humans, this assurance cannot be extrapolated to dogs because extended release preparations formulated for humans are not always slowly released in dogs.[21] Flip-flop pharmacokinetics often are attributed to extended release preparations implying that the rate of absorption is slower than the rate of elimination causing them to occur simultaneously, which causes the rate of absorption to determine the slope of the decline rather than the rate of elimination. Although significant differences could not be demonstrated in either disappearance rate constants or half-life between PO (nonfed) and IV administration (the former reflecting an

Table 1. Pharmacokinetics of levetiracetam in serum after IV (mean ± SD: 32.5 ± 2.1) administration of as single dose of levetiracetam to dogs (n = 12).

Variable	Mean ± SD	95% Confidence Interval	*P* Value Versus PO Fasted	*P* Value Versus PO Fed
Co/*y*-intercept (μ/mL)	70.0 ± 9.3	65–75	NA	NA
$t_{½}$ (hours)	4.0 ± 1.4	3.3–4.7	.065	.20
k_d (hours)	0.16 ± 0.4	−0.05 to 0.4	.31	.043*
MRT (hours)	5.4 ± 1.4	4.7–6.1	<.001*	<.001*
AUC (μ × h/mL)	306 ± 79.4	262–349	.038*	.017*
V_d (L/kg)	0.6 ± 0.1	0.58–0.66	NA	NA
CL (mL/kg/h)	114 ± 25.6	101–126	NA	NA

Data from 4 pilot animals receiving 20 mg/kg IV were included for $t_{1/2}$, k_d, MRT, V_d, and CL only (n = 16). Variables marked with an (*) represent statistically significant differences between IV and fasted or fed groups.

$t_{1/2}$, disappearance half-life; k_d, disappearance rate constant; MRT, mean residence time; AUC, area under the curve; V_d, apparent volume of distribution; CL, serum clearance.

Table 2. Pharmacokinetics of extended release levetiracetam in serum after PO (mean ± SD: 32.67 ± 2.35 mg/kg) administration of a single dose to dogs (n = 12).

Parameter	Mean ± SD Fasted	95% Confidence Interval	Mean ± SD Fed	95% Confidence Intervals	*P* Values Fed Versus Fasted
C_{max} (μ/mL)	26.6 ± 5.8	21–31	30.7 ± 7.1	25–36	.30
T_{max} (hours)*	3.4 ± 0.8	2.7–4	6.6 ± 1.5	5.4–7.8	.0010*
$t_{½}$ (hours)	4.4 ± 2.1	3.8–6	4.2 ± 1.1	3.5–5.4	.53
k_d (hours)	0.16 ± 0.04	0.13–0.18	0.17 ± 0.03	0.15–0.19	.72
MRT (hours)	9.8 ± 2.0	8.4–11	10.8 ± 1.8	9.5–12	.31
MAT (hours)	4.7 ± 0.9	4–5.4	5.6 ± 1.7	4.3–6.9	.31
AUC (μ × h/mL)	335.4 ± 74.3	276–393	393.4 ± 138.3	282–503	.39
F (%)*	1.0 ± 0.1	0.96–1.1	1.3 ± 0.2	1.12–1.39	.02*

Data from 4 pilot animals were included for $t_{1/2}$, k_d; disappearance rate constant; MRT, *F* (n = 16). Variables marked with an (*) represent statistically significant differences between fasted and fed groups.

C_{max}, maximum plasma drug concentration at time = t_{max}; $t_{1/2}$, disappearance half-life; k_d, disappearance rate constant; MRT, mean residence time; MAT, mean absorption time; AUC, area under the curve; *F*, % bioavailability.

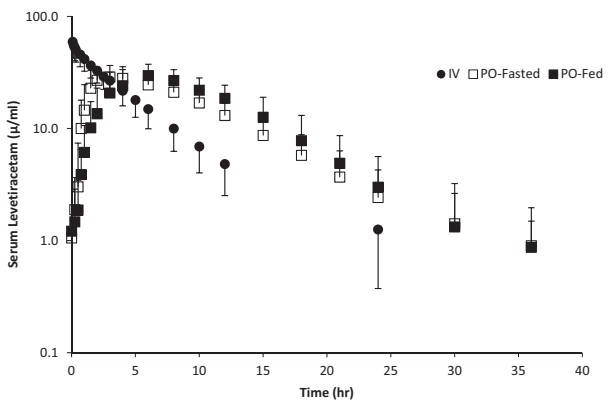

Fig 1. Mean ± SD serum levetiracetam concentrations (n = 12) at various times after IV (black circle) administration of levetiracetam and oral fasted (white square; n = 7) and oral fed (black square; n = 7) administration of extended release levetiracetam (mean 32.67 mg/kg [range 29.4–35.7 mg/kg]). Time of levetiracetam administration was designated as time 0.

extended release preparation), this may only be a reflection of small sample size. The terminal slope of the line (k_d) measured on log concentration versus time plots was significantly steeper with IV[c] compared to PO extended release formulation[b] when administered with food, but not when administered to a fasted animal, suggesting that the presence of food slowed absorption sufficiently to allow the extended release preparation to have a longer exposure in the animal. That PO slow release resulted in a longer exposure time is demonstrated by significant differences in MRT, which was longer after PO versus IV administration; as was AUC when compared to both PO administrations and IV administration. This observation is further supported by graphic representation of the data showing a longer time within therapeutic concentrations with the extended release product[b] (Fig 1). This finding, however, does not support true pharmacokinetic flip-flop principles, but may be clinically relevant to the prescriber of this medication in recommending the medication be given with food.

The serum concentrations of the extended release PO levetiracetam[b] were ≤5 μg/mL by 20.7 hours (range, 16.7–28.7 hours) after administration with food and 19.8 hours (range, 15–24.2 hours) after administration to a fasted dog. This finding resulted in a total time above minimum therapeutic concentration (in humans of 5 μg/mL) of 18.3 hours in fasted and 17.7 hours in fed animals, respectively. Therefore, this study demonstrates that extended release levetiracetam[b] displays an extended pharmacologic profile in the dog compared to IV formulations. Food did not negatively impact or prohibit absorption; it only slowed the disposition of extended release levetiracetam in dogs, a finding consistent with pharmacokinetics in humans.[17] Food did increase the time to reach maximum concentrations, but at the estimated accumulation, this difference would not be clinically relevant.

Although this study did not compare extended release to PO regular release, a recent abstract[m] did compare the 2 preparations in dogs (n = 5) receiving 20 mg/kg levetiracetam PO over an 8-hour period. The investigators found the absorption half-life to be 7.75-fold longer, the elimination half-life 1.43-fold longer, and the AUC 5-fold greater for the extended compared to regular release tablets. The AUC for regular release was 44.8 μ × h/mL and with extended release 230 μ × h/mL. This AUC for regular release is short when compared to previously published data,[7,9–12,14,15] which may reflect the short sampling period.

On the basis of this study, we recommend the dosage of extended release levetiracetam[b] to be 30 mg/kg q12h. An elimination half-life of 4.5–5 hours based on the pharmacokinetic study indicates that drug concentrations will fluctuate approximately 50–80% during a 12-hour dosing interval with this approach. Monitoring is recommended to determine the most appropriate dosing interval based on an individual's response to serum drug concentrations because the current study used the 5 μg/mL concentration extrapolated from human medicine. Based on this study, 3-hour peak and just before the next dose trough sampling times are recommended.

The extended release profile of levetiracetam is a result of its formulation,[24] and chewing of the tablets

by dogs could negate these properties. Because in situ hydrolysis of levetiracetam (the major metabolic pathway) occurs in plasma, only serum, and neither plasma nor whole blood, should be used for therapeutic drug monitoring.[28] Furthermore, the results reported here are specific to the studied preparation[b] and will not necessarily apply to other extended release levetiracetam products intended for human use. The patent held by UCB Pharmaceuticals expired in September 2011 and many generic extended release levetiracetam products have entered the market. Each of these medications must be tested in dogs (or by therapeutic monitoring in the patient) to ensure the same pharmacokinetic profile as the trade name medication tested in this study.

Future recommendations include prospective clinical trials to ensure the same efficacy and safety profile with extended release levetiracetam as seen with regular release levetiracetam in dogs.

Footnotes

[a] Personal communication, Auburn University Clinical Pharmacology Laboratory
[b] Keppra XR, 500 and 750 mg tablets, UCB Pharmaceuticals, Brussels, Belgium
[c] Keppra, parental 100 mg/mL formulation, UCB Pharmaceuticals, Brussels, Belgium
[d] 0.9% NaCl 1 Liter bags, Abbott Laboratories, Abbott Park, IL
[e] Lidocaine & Prilocaine cream, 2.5%/2.5%, Fougera Pharmaceuticals, Melville, NY
[f] Heparin (1,000 U/mL), Sagent Pharmaceuticals Inc, Schaumburg, IL
[g] Kendall Monoject Blood Collection Tubes, 5 ml Red top, Kendall, Munsfield, Maine
[h] ARK Diagnostic Levetiracetam Immunoassay, Sunnyvale, CA
[i] Siemens Dimension Xpand Plus, New York, NY
[j] ARK Diagnostic Levetiracetam Calibrator Kit, Sunnyvale, CA
[k] WinNonLin Professional, version 4.1, Pharsight Corp, Mountain View, CA
[l] SAS for Windows, version 9.2, SAS Institute Inc, Cary, NC
[m] Platt SR, Kent M, Freeman AC, et al. Pharmacokinetic evaluation of extended release levetiracetam in dogs. J Vet Intern Med 2011; 25(4): 729 (ACVIM abstracts)

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Conflict of Interest Declaration: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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