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 μg/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 μg/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 action13 (binding to the synaptic vesicle protein 2A), minimal metabolism,7,8,10–12 and few documented drug-drug interactions,15 and multiple administration routes (IV, PO, IM, per rectum).1–6 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,8 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
epileptic patients. Differences may reflect particle sizes allowed through the human versus canine pylorus and shorter gastrointestinal transit time in dogs.\(^2^2\)\(^2^3\)

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 \(\mu\)g/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 dosages 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\(^d\) 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\(^e\) 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 fasted their PO dose. Immediately before the study, cephalic (for drug administration) and lateral saphenous (for blood sampling) catheters were placed using topical lidocaine/prilocaine anesthetic\(^f\) and manual restraint. The pilot study protocol differed only in that the dogs included from the pilot study for the remaining 12 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 predosing results.

**Measurement of Serum Levetiracetam Concentration**

After clotting at room temperature, samples were centrifuged for 10 minutes at 1,900 \(\times\) \(g\) within 2 hours of collection. Serum was harvested and frozen at \(-20^{\circ}\)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.\(^2^3\) 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\(^i\) which were designed for human serum. The package insert for the assay indicates a lack of cross-reactivity with the major metabolite (L057/PBA).\(^2^6\) 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.\(^1^4\),\(^2^7\) The upper and lower limits of quantitation are 100 \(\mu\)g/mL and 2 \(\mu\)g/mL, respectively.\(^2^6\) 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 \(\leq 10%\) for all controls.\(^6\)

**Data Analysis**

Serum levetiracetam concentration versus time data was subjected to noncompartmental analysis\(^8\) with area under the curve (AUC) determined to infinity by the trapezoidal method. For IV administration, peak serum concentrations were extrapolated to the \(t\)-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: \(\text{MAT} = \text{MRT}_{oral} – \text{MRT}_{IV}\). Absolute bioavailability (F) of PO administered levetiracetam was determined from the following equation: \((\text{AUC}_{PO} \times \text{Dose}_{PO})/(\text{AUC}_{IV} \times \text{Dose}_{IV})\) Data were included from the pilot study for \(t_{1/2}, k_{d}, V_d, \text{Cl, MRT, and F}\) because these variables are independent of the dose administered. Only data from the 12 main study dogs were used for \(C_{max}, T_{max, Cl, \text{AUC, and MAT because these variables are dependent on dose administered.}}\)

Pharmacokinetic data are reported as mean \(\pm\) SD as determined by use of commercially available software.\(^6\) 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\(^b\) 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\text{max}) was measured (t\text{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 t\text{max}}) 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\text{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 = .038). When comparing IV data to PO fed data, significant differences included MRT (P < .001), AUC (P = .017) and k\text{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 µg × 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 (non-fed) 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 |
|------------------------|---------------|-------------------------|--------------------------|-----------------------|
| C0 (µg/mL)             | 70.0 ± 9.3    | 65–75                   | NA                       | NA                    |
| t\text{max} (hours)    | 4.0 ± 1.4     | 3.3–4.7                 | .065                     | .20                   |
| k\text{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 (µg × h/mL)        | 306 ± 79.4    | 262–349                 | .038*                    | .017*                 |
| V\text{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\text{1/2}, k\text{d}, MRT, V\text{d}, and CL only (n = 16). Variables marked with an (*) represent statistically significant differences between IV and fasted or fed groups.

t\text{1/2}, disappearance half-life; k\text{d}, disappearance rate constant; MRT, mean residence time; AUC, area under the curve; V\text{d}, apparent volume of distribution; CL, serum clearance.
sent statistically significant differences between fasted and fed groups. The long half-life 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 abstractm 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 µg × h/mL and with extended release 230 µg × 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 levetiracetam9 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

### 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 |
|--------------------|------------------|-------------------------|---------------|--------------------------|---------------------------|
| \(C_{\text{max}}\) (µg/mL) | 26.6 ± 5.8       | 21–31                   | 30.7 ± 7.1    | 25–36                    | .30                       |
| \(T_{\text{max}}\) (hours)* | 3.4 ± 0.8        | 2.7–4                   | 6.6 ± 1.5     | 5.4–7.8                  | .0010*                    |
| \(t_{1/2}\) (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 \(k_d\); \(t_{1/2}\); disappearance rate constant; MRT, \(F\) (n = 16). Variables marked with an (*) represent statistically significant differences between fasted and fed groups. \(C_{\text{max}}\), maximum plasma drug concentration at time = \(t_{\text{max}}\); \(t_{1/2}\), 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.
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. Furthermore, the results reported here are specific to the studied preparation 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

1. Personal communication, Auburn University Clinical Pharmacology Laboratory
2. Keppra XR, 500 and 750 mg tablets, UCB Pharmaceuticals, Brussels, Belgium
3. Keppra, parental 100 mg/mL formulation, UCB Pharmaceuticals, Brussels, Belgium
4. 0.9% NaCl 1 Liter bags, Abbott Laboratories, Abbott Park, IL
5. Lidocaine & Prilocaine cream, 2.5%/2.5%, Fougera Pharmaceuticals, Melville, NY
6. Heparin (1,000 U/mL), Sagent Pharmaceuticals Inc, Schaumburg, IL
7. Kendall Monoject Blood Collection Tubes, 5 ml Red top, Kendall, Munsfield, Maine
8. ARK Diagnostic Levetiracetam Immunoassay, Sunnyvale, CA
9. Siemens Dimension Xpand Plus, New York, NY
10. ARK Diagnostic Levetiracetam Calibrator Kit, Sunnyvale, CA
11. WinNonLin Professional, version 4.1, Pharsight Corp, Mountain View, CA
12. SAS for Windows, version 9.2, SAS Institute Inc, Cary, NC
13. 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.

References

1. Thomas WB, Dewey CW. Seizures and narcolepsy. In: Dewey CW, ed. A Practical Guide to Canine and Feline Neurology. 2nd ed. Ames, IA: Wiley-Blackwell Publishers; 2008:237–253.
2. International Veterinary Information Service website. Braund’s clinical neurology in small animals: Localization, diagnosis and treatment. Berendt M. Epilepsy. Available at: http://www.ivis.org/advances/Vite/berendt/chapter_frm.asp?LA=1. Accessed November 10, 2013.
3. Zimmermann R, Hulsmeyer VI, Sauter-Louis C, Fischer A. Status epilepticus and epileptic seizures in dogs. J Vet Intern Med 2009;23:970–976.
4. Berendt M, Gredal H, Ersboll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med 2007;21:754–759.
5. de Lahunta A, Glass E. Seizure disorders: Narcolepsy. In: de Lahunta A, Glass E, eds. Veterinary Neuroanatomy and Clinical Neurology, 3rd ed. St. Louis, MO: Saunders Elsevier; 2009:454–468.
6. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. J Am Vet Med Assoc 2012;240:1073–1083.
7. Volk HA, Matiasak LA, Felus-Pascual AL, Platt SR, Chandler KE. The efficacy and tolerability of levetiracetam in pharma-coresistant epileptic dogs. Vet J 2008;176:310–319.
8. Thomas WB. Idiopathic epilepsy in dogs and cats. Vet Clin North Am Small Anim Pract 2010;40:161–179.
9. Patterson EE, Goel V, Cloyd JC, et al. Intramuscular, intravenous and oral levetiracetam in dogs: Safety and pharmacokinet-ics. J Vet Pharmacol Therap 2008;31:253–258.
10. Moore SA, Munana KR, Papich MG, Nettifee-Osborne J. The pharmacokinetics of levetiracetam in healthy dogs following single and multiple oral doses. Am J Vet Res 2010;71:337–341.
11. Veterinary Information Network website, Steinberg M, Faisstler D. Levetiracetam therapy for long-term idiopathic epilep-tic dogs. ACVIM Oral Presentation 2004. Available at: http://www.ivi.com/Members/Proceedings/Proceedings.plx?CID=ACVIM2004&PID=6247&O=Generic. Accessed November 10, 2013.
12. Bailey KS, Dewey CW, Boothe DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. J Vet Emerg Crit Care 2008;18:153–157.
13. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci USA 2004;101:9861–9866.
14. Benedetti MS, Coupez R, Whomsley R, et al. Comparative pharmacokinetics and metabolism of levetiracetam, a new anti-epileptic agent, in mouse, rat, rabbit and dogs. Xenobiotica 2004;34:281–300.
15. Moore SA, Munana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. J Vet Pharmacol Ther 2010;34:31–34.
16. Peters RK, Schubert T, Clemmons R, Vickroy T. Levetirac-etam rectal administration in healthy dogs. J Vet Int Med 2014;28:504–509.
17. Routis E, Burton I, Guenole E, et al. Pharmacokinetics of levetiracetam XR 500 mg tablets. Epilepsia Res 2009;84:224–231.
18. Peltola J, Coetzee C, Jimenez F, et al. Once-daily extended-release levetiracetam as adjunctive treatment of partial-onset sei-zures in patients with epilepsy: A double-blind, randomized, placebo-controlled trial. Epilepsia 2009;50:406–414.
19. Richy FF, Banerjee S, Brabant Y, Helmers S. Levetiracetam extended release and levetiracetam immediate release as adjunctive treatment for partial-onset seizures: An indirect comparison of treatment-emergent adverse events using meta-analytic techniques. Epilepsy Behav 2009;16:240–245.
20. Ulloa CM, Towfigh A, Saffieh J. Review of levetiracetam, with a focus on the extended release formulation, as adjunctive therapy in controlling partial-onset seizures. Neuropsychiatr Dis Treat 2009;5:467–476.
21. Brown SA, Forrester SD. Serum disposition of oral clorazepate from regular-release and sustained-delivery tablets in dogs. J Vet Pharmacol Ther 1991;14:426–429.

22. Martinez MN, Papich MG. Factors influencing the gastric residence of dosage forms in dogs. J Pharm Sci 2009;98:844–860.

23. Sutton SC. Companion animal physiology and dosage form performance. Adv Drug Deliv Rev 2004;56:1383–1398.

24. UCB website. UCB US prescribing information Keppra® XR extended release tablets. Available at: http://www.ucb.com/_up/ucb_com_products/documents/Keppra_XR_%2006_2012.pdf. Accessed June 20, 2012.

25. Carnes MB, Axlund TW, Boothe DM. Pharmacokinetics of levetiracetam after oral and intravenous administration of a single dose to clinically normal cats. AJVR 2011;72:1247–1252.

26. ARK website. ARK levetiracetam assay. Available at: http://www.ark-tdm.com/pdfs/WEB_LEV/ARK_Levetiracetam_Control_Rev02_August%202012.pdf. Accessed September 19, 2014.

27. Isoherranen N, et al. Pharmacokinetics of levetiracetam and its enantiomer (R)-α-ethyl-2-oxo-pyrrolidine acetamide in dogs. Epilepsia 2001;42:825–830.

28. Patsalos PN, Ghattaura S, Ratnaraj N, Sander JW. In situ metabolism of levetiracetam in blood of patients with epilepsy. Epilepsia 2006;47:1818–1821.