

## Standard Article

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## Pharmacokinetics of Single Oral Dose Extended-Release Levetiracetam in Healthy Cats

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**Background:** Repeated PO dosing of anti-epileptic drugs may contribute to poor compliance in treated cats. Intermediate-release levetiracetam has been used safely in cats, but must be given q8h to maintain serum concentrations in the therapeutic interval for humans (5–45 µg/mL). Approved extended-release levetiracetam (XRL) for human use may require less frequent dosing, but the large dosing unit has limited its use in cats.

**Hypotheses:** In healthy cats, serum levetiracetam concentration will remain above 5 µg/mL for at least 24 hours after administration of a single dose of XRL PO and will be well tolerated.

**Animals:** 7 healthy cats.

**Methods:** Extended-release levetiracetam (500 mg) was administered PO. Blood was collected and neurologic examination findings recorded at scheduled times over 30 hours. Serum levetiracetam concentration was quantitated by an immunoassay validated in cats. Data were subjected to noncompartmental analysis. Descriptive statistics were reported.

**Results:** The median dosage of 86.2 mg/kg, (range, 80–94.3) achieved a mean maximum concentration ( $C_{\max}$ ) of  $89.8 \pm 25.8$  µg/mL at  $4.9 \pm 1.57$  hours. Serum levetiracetam was  $>5$  µg/mL in all cats by 90 minutes. Mean concentrations were  $43.7 \pm 18.4$  and  $4.9 \pm 3.4$  µg/mL at 12 and 24 hours, respectively. The half-life was  $4.1 \pm 1.0$  hours. The drug was well tolerated.

**Conclusions and Clinical Importance:** A single 500 mg PO dose of XRL safely maintained serum levetiracetam concentration  $\geq 5$  µg/mL in healthy cats for at least 21 hours. Clinical efficacy studies in epileptic cats receiving XRL are indicated; however, monitoring should be implemented for individual cats.

**Key words:** Anti-epileptic drug; Feline; Keppra; Seizures.

Anti-epileptic drug (AED) treatment is recommended for cats with frequent or prolonged seizures to minimize secondary brain damage. Many cats are resistant to frequent administration of medications PO throughout the day, leading to poor treatment adherence by clients and resultant wide fluctuations in serum concentrations.<sup>1–3</sup>

Levetiracetam is an AED approved for use in humans. Its novel mechanism of action coupled with minimal reported adverse effects makes it an appealing drug for seizure control in cats.<sup>4,5</sup> Pharmacokinetics of intermediate-release levetiracetam (IRL)-administered PO in cats support a 20–25 mg/kg dosage, but the short elimination half-life of  $2.95 \pm 0.95$  hours necessitates a q8h dosing regimen, decreasing owner compliance.<sup>4,6,7</sup> An extended-release formulation of levetiracetam is specially formulated to result in a lower maximal drug concentration ( $C_{\max}$ ), a longer time to maximal

### Abbreviations:

AED	anti-epileptic drug
AR	accumulation ratio
AUC	area under the curve
$C_{\max}$	maximum concentration
IRL	immediate-release levetiracetam
MRT	mean residence time
$t_{1/2}$	disappearance half-life
$T_{\max}$	time of maximum concentration
XRL	extended-release levetiracetam

concentration ( $T_{\max}$ ) and less fluctuation in serum concentrations in humans when compared to IRL.<sup>1</sup> Its use in cats has not been evaluated previously. One of the reasons it has not been evaluated is likely that the smallest tablet size is 500 mg. Cutting, crushing, or breaking the tablets compromises the extended-release properties. The PO dosage administered to a cat would result in a dosage of approximately 100 mg/kg/d in an average 5-kg cat. Yet, clinically, based on therapeutic drug monitoring data, levetiracetam may be safe enough for this dose to be well tolerated (personal communication, Dawn Boothe, May 2017).

The purposes of our study were to describe the disposition of a single 500 mg dose of XRL in healthy cats and document clinical adverse effects after administration. Our hypotheses were that serum levetiracetam concentrations would remain  $\geq 5$  µg/mL for 24 hours postpill administration, and the drug would be well tolerated by healthy cats.

### Materials and Methods

Seven apparently healthy cats, between 2 and 17 years of age (median, 9.08 years) and weighing 5.3–6.25 kg (median, 5.8 kg),

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owned by University of Wisconsin School of Veterinary Medicine or Veterinary Care Hospital staff or students, were studied. Cats were considered apparently healthy if their physical and neurologic examinations did not identify any clinically relevant abnormalities and they had packed cell volume, total protein concentration, and serum biochemical analysis results within the normal reference interval. Informed consent was obtained from all owners. This pharmacokinetic clinical study was approved by the University of Wisconsin's Institutional Animal Care and Use Committee. Enrollment criteria included (1) no history of seizures or other neurologic disease, (2) no concurrent medications other than heartworm or flea control products, (3) no concurrent participation in ongoing clinical studies or participation within the preceding 30 days, and (4) minimum body weight of 5 kg. Pilot data were collected in 2 cats to establish the most appropriate sampling times.

All cats were fasted for a minimum of 10 hours and then sedated with alfaxalone (2 mg/kg) IM and butorphanol (0.1 mg/kg) IM to facilitate aseptic jugular vein catheter placement for blood collection. A 16 g (5Fr) single lumen long-term IV catheter<sup>a</sup> was placed in the left or right jugular vein. A complete neurologic examination was performed a minimum of 3 hours after recovery from sedation. Once the neurologic examination findings returned to normal, a single 500 mg XRL tablet<sup>b</sup> was administered PO, followed by free access to food and water throughout the study period. Blood samples then were collected into sterile tubes<sup>c</sup> at 0, 30, 60, and 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, and 36 hours. These were modified for the full study to 0, 30, 60, and 90 minutes, and 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, and 30 hours. For all cats, at each sampling time, the first 1 mL of blood withdrawn from the catheter was returned to the cat and the catheter was irrigated with 1–2 mL of 0.9% NaCl<sup>d</sup> after sampling. Repeated general physical and neurologic examinations were performed at 4, 8, 12, 18, and 24 hours. Any adverse effects were noted throughout the sampling period. Intravenous catheters were removed after collection of blood samples, and cats were returned to their owners.

### Measurement of Serum Levetiracetam Concentration

After clotting at room temperature, samples were centrifuged for 10 minutes at 1,100 g within 2 hours of collection. Serum samples were shipped overnight on ice to Auburn University's Clinical Pharmacology Laboratory for sample analysis. Upon receipt by the laboratory, serum was frozen at  $-20^{\circ}\text{C}$  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 feline serum by a Food and Drug Administration-approved immunoassay for use in

humans on a general chemistry analyzer, which is described elsewhere.<sup>8</sup> The assay had been previously validated in cats.<sup>6</sup> The upper and lower limits of quantitation are 100 and 2  $\mu\text{g/mL}$ , respectively.<sup>8</sup> The coefficient of variation using the manufacturer's quality controls for the time period our samples were analyzed was <14% for the low and <7% for the high-range control.

### Data Analysis

Descriptive statistics (range) were determined by commercially available software.<sup>e</sup> All pharmacokinetic data are reported as mean  $\pm$  SD. The minimum therapeutic reference range for humans was used as a target for minimal serum levetiracetam concentration (5  $\mu\text{g/mL}$ ) in our study.<sup>9</sup> Serum levetiracetam concentration versus time data was subjected to noncompartmental analysis with area under the curve (AUC) determined to infinity by the log-linear trapezoidal method. The actual maximal concentration ( $C_{\text{max}}$ ) occurring at time to maximal concentration ( $T_{\text{max}}$ ) was recorded. Because levetiracetam was not given IV, the terminal component of the drug concentration versus time curve could not be confirmed to be solely due to elimination and thus both the elimination rate constant and half-life were reported as disappearance. Other parameters included mean residence time (MRT) and the percent of the AUC that was extrapolated.

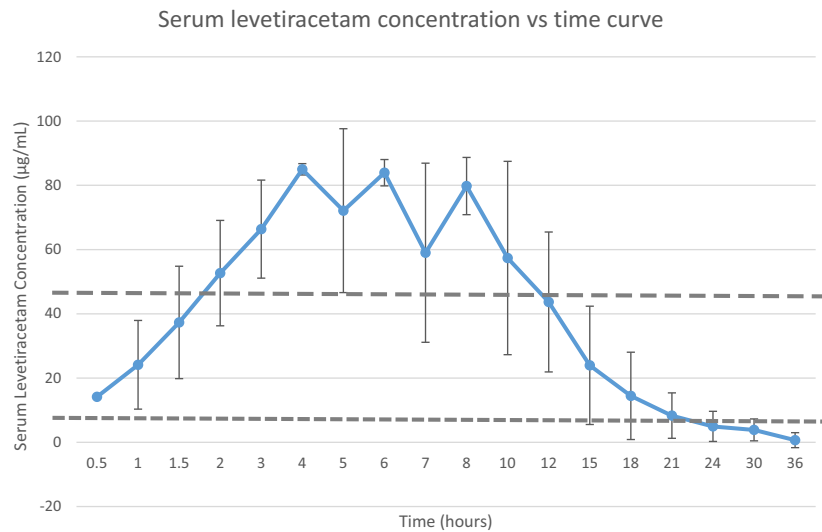
### Results

All 7 cats completed the study. Physical and neurologic examination findings, serum biochemistry, and PCV/TP were normal for all cats at enrollment. Cats were given a median dose of 86.2 mg/kg, (range, 80–94.33 mg/kg) of XRL PO. Food was consumed by 6 of 7 cats immediately after pill administration. One cat (cat 8) did not consume food or water until 8 hours post-pill administration. Serum concentrations  $>5$   $\mu\text{g/mL}$  were achieved in all cats by 90 minutes after administration of the tablet. Mean  $C_{\text{max}}$  ( $\pm$ SD) of  $89.8 \pm 25.8$   $\mu\text{g/mL}$  was achieved at  $4.9 \pm 1.57$  hours. Mean serum concentration ( $\pm$ SD) at 12 and 24 hours was  $43.7 \pm 18.4$   $\mu\text{g/mL}$  and  $4.9 \pm 3.4$   $\mu\text{g/mL}$ , respectively. A summary of the pharmacokinetic analysis can be found in Table 1. A time versus serum levetiracetam concentration curve can be found in Figure 1. Based on the half-life, an approximately 75% fluctuation would be expected with a 12-hour dosing interval and approximately 93% fluctuation would be expected with a 24-hour dosing interval.

**Table 1.** Pharmacokinetic analysis of serum levetiracetam concentration after administration of 500 mg extended-release levetiracetam tablet in cats ( $n = 7$ ).

Parameter	Median (range)	Mean ( $\pm$ SD)	95% CI
$C_{\text{max}}$ ( $\mu\text{g/mL}$ )	80.9 (63.3–138.6)	89.8 (25.8)	66.0, 113.6
$T_{\text{max}}$ (h)	4.0 (4.0–8.0)	4.9 (1.6)	204.1, 378.7
AUC/dose (Observed) ( $\mu\text{g} \times \text{h/mL/mg/kg}$ )	615.2 (494.3–1077.2)	676.5 (205.1)	486.9, 866.2
AUC (Observed) ( $\mu\text{g} \times \text{h/mL}$ )	49215.4 (40383.9–96184.4)	58565.0 (19455.4)	40571.8, 76558.2
AUC (%extrapolated)	1.6 (0.5–2.8)	1.5 (0.8)	0.8, 2.2
$T_{1/2}$ (h) <sup>a</sup>	4.3 (3.1–5.6)	4.1 (1.0)	3.3, 5.2
MRT (h)	8.9 (7.5–10.8)	8.9 (1.0)	476.9, 591.1
$\lambda$	0.002 (0.002–0.003)	0.002 (0.0)	0.0, 0.0

<sup>a</sup>Represents harmonic mean  $\pm$  pseudo-SD.  $T_{\text{max}}$ : time to maximal concentration; AUC, area under the curve; MRT, mean residence time;  $\lambda$ , disappearance rate constant; SD, standard deviation.



**Fig 1.** Mean ( $\pm$ SD) serum concentration of levetiracetam ( $\mu\text{g/mL}$ ) versus time (hours) for 7 cats after a single 500 mg extended-release levetiracetam tablet. Reference range in humans is delineated by dashed lines.

All cats tolerated the drug with no obvious serious adverse events. One cat had diarrhea at 24 hours post-pill administration and mild sedation appeared to occur in 2 cats (at 2 hours and between 2–6 hours) post-administration. Neurologic examination findings remained normal for all cats at all points evaluated throughout the study. No difficulty with tablet administration was noted.

## Discussion

We demonstrated that levetiracetam was absorbed after PO administration in healthy cats sufficiently enough to achieve and maintain concentrations above the minimal therapeutic concentration for humans of  $5 \mu\text{g/mL}$  for an extended period of time. The  $T_{\text{max}}$  in our study was longer than the previously reported  $T_{\text{max}}$  after a  $20 \text{ mg/kg}$  dose PO of IRL in cats ( $1.67 \pm 1.73$  hours).<sup>6</sup> Extended-release products are designed to have decreased rates of dissolution compared to immediate-release formulations. Such differences, therefore, affect the rate of drug absorption, resulting in more gradual changes in serum drug concentration, including less fluctuation during the dosing interval.<sup>10</sup> This gradual change in serum concentration is proposed to result in fewer undesirable effects as well as to decrease the risk of therapeutic failure arising from subtherapeutic concentrations.<sup>1</sup> Our findings are in agreement with those of previous studies comparing IRL and XRL in dogs and humans.<sup>8,10–12</sup>

The  $C_{\text{max}}$  was higher than the maximal reference interval for humans ( $45 \mu\text{g/mL}$ ) in all cats, but adverse effects were minimal and neurologic examination findings remained normal in all cats, indicating tolerance of the increased  $C_{\text{max}}$ . Reported adverse effects in cats after PO levetiracetam administration include lethargy, anorexia, ataxia, polydipsia, and hypersalivation.<sup>4,6,7</sup> After multi-dose administration of IRL, a reported 18% of cats developed adverse effects, but all signs

resolved within a 2-week period without dose adjustment.<sup>4</sup> None of the cats in our study experienced serious adverse effects despite the much higher actual serum levetiracetam concentration. Despite the large tablet size, difficulty with administration was not encountered in any of the cats in our study. Our findings suggest that a single PO dose of XRL was well tolerated in this healthy, limited population of cats. Only cats  $\geq 5$  kg were enrolled in our study, and therefore, data cannot be extrapolated to cats weighing  $< 5$  kg.

Butorphanol and alfaxalone were selected for sedation based on their rapid metabolism. Minimal to no effect on gastrointestinal motility has been noted after use of butorphanol in dogs and rats.<sup>13</sup> We are unaware of published literature evaluating gastric motility with alfaxalone use, but little to no effect was anticipated based on the mechanism of action of this drug. Although unlikely, it is possible that an adverse effect of alfaxalone may include a change in gastric motility which may result in a change in the gastrointestinal transit time of XRL, but this is considered unlikely.

Concurrent administration of XRL with food may affect absorption. In dogs, a significantly longer  $T_{\text{max}}$  was identified when XRL was administered with food, compared to dogs receiving XRL after fasting.<sup>10</sup> The authors proposed this was due to slowed absorption of levetiracetam rather than delayed elimination. Tablet administration was intended to be with food for our study although only 6 of the 7 cats ate immediately after pill administration. Additional studies should evaluate the effect of food on  $T_{\text{max}}$  and  $C_{\text{max}}$  in cats administered XRL and these parameters should not be extrapolated from the limited data in this study.

In summary, XRL was absorbed sufficiently to allow for detection of serum levetiracetam concentrations in all cats, and minimal adverse effects were noted during the study period. Tablet administration was not difficult, but a multi-dose trial would be needed to further evaluate this finding. The therapeutic range for

levetiracetam is unknown for cats, and therefore, XRL dosages should be adjusted based on an individual cat's seizure control and observed adverse effects. Although once daily administration of XRL is supported by the results of our study, individual variation may warrant twice daily dosing in some cats. A multi-dose trial in healthy cats may be useful to identify adverse effects after longer term dosing and to determine whether drug accumulation occurs. A dosing interval of 24 hours is expected to improve owner compliance and result in improved seizure control in cats.

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### Footnotes

- <sup>a</sup> MILA international, 1610 Florence, KY  
<sup>b</sup> Keppra XR<sup>®</sup>, Lupin Pharmaceutical, Baltimore MD  
<sup>c</sup> BD Vacutainer Sterile 4.0 ML plastic tubes. BD Biosciences, Franklin Lakes NJ  
<sup>d</sup> ZR<sup>®</sup> Flush. Excelsior Medical, Neptune NJ  
<sup>e</sup> Phoenix WinNonlin 7.0, Pharsight, Cetera LL, Princeton NJ
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*Conflict of Interest Declaration:* Authors declare no conflict of interest.

*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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