

# Serum levetiracetam concentrations and adverse events after multiple dose extended release levetiracetam administration to healthy cats

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**Background:** Multiple dose administration of antiepileptic drugs to cats presents a challenge for owners. Extended release levetiracetam (XRL) has once daily recommended dosing interval, but multiple dose administration of XRL has not been evaluated in cats.

**Objective:** Evaluate serum levetiracetam concentrations and adverse clinical effects after 11 days of once daily XRL administration to healthy cats.

**Animals:** Nine healthy privately owned cats, body weight  $\geq 5$  kg

**Methods:** Extended release levetiracetam (500 mg/cat) was administered PO q24h for 10 days. On day 11, blood was collected at trough, 4, 6, and 8 hours after tablet administration. Owners maintained records of adverse effects throughout study. Levetiracetam was quantitated in serum using immunoassay validated in cats.

**Results:** Median dose 94.3 mg/kg q24h. Median (range) trough, 4, 6, and 8 hour serum levetiracetam concentrations were 7.0 (2.3-14.1), 82.6 (7.8-125.3), 92.3 (13.3-97.3), and 72 (22.8-96.4)  $\mu\text{g}/\text{mL}$ , respectively. Peak was not observed in 4 cats because of missed samples ( $n = 2$ ) and failure to reach maximal concentration ( $C_{\text{max}}$ ) by 8 hours ( $n = 2$ ). Median time of maximal concentration ( $T_{\text{max}}$ ) for the remaining 5 cats 5.2 (range 4-6) hours. Adverse effects were minimal and included ataxia ( $n = 1$ ), sedation ( $n = 1$ ), and vomiting or regurgitation ( $n = 1$ ). All signs resolved without dose adjustment or additional treatment.

**Conclusions and Clinical Importance:** Mean trough serum levetiracetam concentrations were  $\geq 5$   $\mu\text{g}/\text{mL}$  and adverse effects were minimal throughout dosing period, indicating that the drug was well tolerated. Once daily XRL (500 mg/cat) administration may provide an easier alternative to 3 times daily dosing of intermediate-release levetiracetam for epileptic cats.

## KEYWORDS

antiepileptic drug, feline, Keppra, seizures

**Abbreviations:** AED, antiepileptic drug;  $C_{\text{max}}$ , maximum concentration; IRL, immediate-release levetiracetam;  $T_{\text{max}}$ , time of maximum concentration; XRL, extended-release levetiracetam

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## 1 | INTRODUCTION

Epileptic seizures are the most common reason cats are presented to veterinary neurologists<sup>1,2</sup> and often antiepileptic drugs (AED) are recommended for long-term seizure control regardless of the etiologic diagnosis. Although many cats have favorable seizure control with PO administration of phenobarbital<sup>3</sup> and intermediate-release levetiracetam (IRL),<sup>4</sup> administration 2–3 times daily long-term may be difficult for owners, leading to poor compliance.

Levetiracetam is an AED with a novel mechanism of action.<sup>5,6</sup> Currently 2 formulations are available for use in the USA: IRL and extended release levetiracetam (XRL). The current recommended dosing interval for IRL in cats is every 8 hours. Extended-release formulations are designed to allow for less frequent dosing intervals compared to intermediate release formulations.<sup>7</sup> However, only 500 and 750 mg XRL tablet sizes are commercially available. Reformulation of an extended-release product is not possible and therefore 500 mg XRL tablets were chosen. After single-dose pharmacokinetic analysis in healthy cats, the recommended dosing interval for 500 mg XRL was once daily.<sup>8</sup> The purpose of our study was to evaluate serum levetiracetam concentrations and adverse clinical effects after 11 days of once daily 500 mg XRL administration in healthy cats. The specific aims were: (1) determine trough and peak serum levetiracetam concentrations in healthy cats on day 11 and (2) identify adverse clinical and biochemical effects in cats after 10 days of q24h PO XRL administration.

## 2 | MATERIALS AND METHODS

This study was designed as a prospective clinical trial. Nine cats, owned by University of Wisconsin School of Veterinary Medicine or Veterinary Care Hospital staff or students, were enrolled in the study. Cats were considered healthy if their physical and neurologic examinations did not identify any clinically relevant abnormalities and their packed cell volume, total protein concentration and serum biochemical analysis (sodium, potassium, chloride, total CO<sub>2</sub>, anion gap, glucose, urea nitrogen, creatinine, total protein, albumin, globulin, alanine amino transferase, and alkaline phosphatase) results were within the normal reference range. Informed consent was obtained from all owners. The study was approved by the University of Wisconsin's Institutional Animal Care and Use Committee. Enrollment criteria included: (1) no history of epileptic 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) a minimum body weight of 5 kg. A single 500 mg XRL tablet (Solco Healthcare US, Cranbury, New Jersey) was administered PO with food q24h at home by owners for 10 days. All owners were requested to keep a daily log on a provided record form, including the time of XRL tablet administration, if consumption of food occurred with tablet administration, and observed adverse effects during the study period. Owners were informed of the adverse effects noted after single dose XRL administration healthy cats, but were instructed to record all adverse events, regardless if they had been reported previously.

On day 11 before to administration of the morning dose of medication, cats were hospitalized, and a blood sample (3.0 mL) was taken from a peripheral vein (medial saphenous or jugular vein). This sample was used for the trough (time 0) serum levetiracetam concentration and repeated serum biochemistry analysis. Packed cell volume was not repeated on day 11. The XRL tablet was administered by study personnel, and cats were provided immediate access to food. Subsequent blood samples (1.5 mL each) were collected by peripheral venipuncture (medial saphenous or jugular vein) into sterile tubes at 4, 6, and 8 hours after tablet administration for serum levetiracetam concentration assay. A neurologic examination also was repeated on day 11. Cats were released to their owners and returned home after the final blood sample. Owners were instructed to administer one 500 mg XRL tablet on day 13 and 15 as a weaning protocol to minimize the risk of withdrawal epileptic seizures.

### 2.1 | Measurement of serum levetiracetam concentration

After clotting at room temperature, blood samples were centrifuged for 10 minutes at 1100g within 2 hours of collection. Serum samples were shipped to the Auburn Clinical Pharmacology Laboratory overnight, not on ice, for sample analysis. Upon receipt by the laboratory, serum was harvested and frozen at –20°C until analysis.

At the time of sample analysis, samples were thawed at room temperature and then vortexed to assure homogeneity. Levetiracetam was detected and quantitated in feline serum using a Food and Drug Administration immunoassay approved for humans on a general chemistry analyzer, which is described elsewhere.<sup>5,9</sup> The system was validated in feline serum using pooled feline serum to which had been added known concentrations of levetiracetam. During the validation process all control samples prepared with feline serum, produced results within 10% of the target serum concentration. Subsequent analysis was based on the manufacturer's levetiracetam calibrator and control kits. The upper and lower limits of quantitation were 100 and 2 µg/mL, respectively.<sup>9</sup> The coefficients of variation (CV[%]) for the low, medium and high controls of 7.5, 30, and 75 µg/mL in feline serum were 4.7%, 3%, and 3%, respectively.

Descriptive statistics were determined using commercially available software (Microsoft Excel, 2013). Data were reported for each time point using median and range serum levetiracetam concentrations. The time to maximal concentration ( $T_{max}$ ) and maximal concentration ( $C_{max}$ ) reported were based on sampling times in our study and may not represent true  $T_{max}$  or  $C_{max}$ . Successful outcome was defined as trough serum levetiracetam concentrations  $\geq 5$  µg/mL and minimal to no adverse effects at peak serum concentrations. No therapeutic reference interval has been established for cats and therefore the therapeutic reference interval in humans (5–45 µg/mL) was used for reference.

## 3 | RESULTS

All 9 cats completed the study. All doses were administered in the morning at home. No administration difficulty was reported by owners

**TABLE 1** Calculated parameters for 9 healthy cats after 11 days of once daily administration of XRL (500 mg)

Parameters	Mean	SD	Median	Range
$T_{max}$ (hours) [5]	6.0	1.1	5.2	4.0–6.0
$C_{max}$ ( $\mu\text{g/mL}$ )				
Overall [5]	102.5	13.4	97.3	92.7–125.3
Ate [2]	114.45	15.3	114.5	103.6–125.3
Did not eat [3]	94.6	2.4	95.0	2.4
Trough ( $\mu\text{g/mL}$ ) [9]	8.0	4.15	7.0	2.3–14.1
Hour 4 ( $\mu\text{g/mL}$ ) [8]	74.0	41.8	82.6	7.8–125.3
Hour 6 ( $\mu\text{g/mL}$ ) [8]	81.0	37.6	92.3	13.3–97.3
Hour 8 ( $\mu\text{g/mL}$ ) [8]	68.7	30.5	72.0	22.8–96.4

Unclear. Numbers in [bracket] = number of cats included in the measured parameter. No n number listed?

during the 10-day period. Two cats had medication placed in commercial canned food and were able to consume the pill without crushing it. All remaining cats swallowed the tablets whole after direct administration to the oropharynx. All cats were reported to have eaten food with, or shortly after XRL administration on days 1–10. Physical and neurologic examinations were normal for all cats at enrollment and on day 11. No clinically relevant change was noted in serum biochemistry results between enrollment and day 11. On day 11, food was consumed within 2 hours of drug administration by 4 of 9 cats; the remaining 4 cats did not consume food on day 11 within 2 hours of XRL tablet administration.

Median weight and age were 5.3 kg (range, 5.1–6.6) and 9.3 years (range, 3.3–13.9), respectively. Median dosage was 94.3 (range, 75.7–98.0) mg/kg PO q24h. See Table 1 and Figure 1 for  $C_{max}$ ,  $T_{max}$ , and mean, standard deviation (SD) and median (range) serum concentrations at each time point. Peak was not observed for 4 cats because of missed samples ( $n = 2$ ) and failure to reach  $C_{max}$  by 8 hours ( $n = 2$ ). Poor cat cooperation resulted in unattained serum levetiracetam concentrations at 4 (cat 6), 6, and 8 hours (cat 7). Therefore, data reported at these time points is from 8 cats. Reported adverse clinical effects included mild ataxia (1 cat, day 1 only), sedation (1 cat, day 2 only), and vomiting or regurgitation (1 cat, days 3, and 7 only). All signs resolved without dose adjustment or additional treatment.

## 4 | DISCUSSION

Our results indicate that median serum levetiracetam concentrations at day 11 were above the minimum therapeutic range used in humans (5  $\mu\text{g/mL}$ ) at all time points and the drug was well tolerated throughout the treatment period. Three sampling times (4, 6, and 8 hours) were used to estimate peak serum concentration based on the previously determined mean (SD)  $T_{max}$  of 4.9 (1.6) hours after single dose XRL administration in healthy cats.<sup>8</sup> However, peak serum concentrations were not achieved in 2 cats by 8 hours, suggesting a wide inter-animal variation of  $T_{max}$ . Mean (SD) serum levetiracetam concentrations at trough were 8.0 (4.15)  $\mu\text{g/mL}$ , indicating minimal drug accumulation. Therapeutic drug monitoring of serum levetiracetam concentrations at trough should be considered to establish a therapeutic range for a

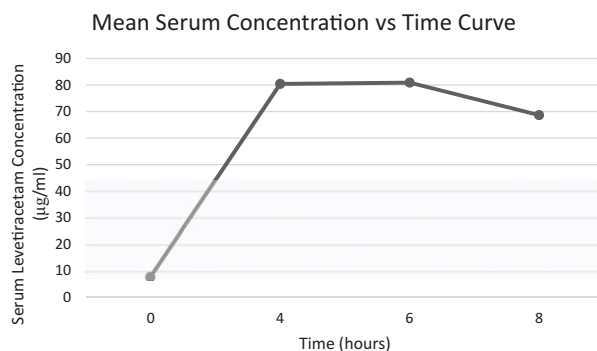
given individual, especially if therapeutic success is not achieved or an increase in adverse events is noted.

The lack of clinically relevant serum biochemical changes in our study is consistent with previous observations after multiple dose IRL administration in cats.<sup>6</sup>

Minimal drug accumulation was expected based on the half-life and dosing interval, but our study was conducted over 11 days to allow for a longer assessment of adverse clinical effects. Serious adverse effects of levetiracetam in cats appear to be uncommon, but mild transient ptialism, inappetence, mild lethargy, ataxia, and polydipsia have been reported after IRL administration,<sup>4–6</sup> and sedation and diarrhea were reported after a single dosage of XRL.<sup>8</sup> Although a higher incidence of adverse effects may be expected at high serum concentrations, no correlation between serum concentration and adverse events was found in a previous study of human pediatric epileptic patients.<sup>10</sup> Our findings appear to be in agreement with these findings in children.

A therapeutic range for levetiracetam has been extrapolated from data in humans because a therapeutic range currently is unavailable for cats.<sup>5,6</sup> Therapeutic range reflects the range of serum concentrations of a specific drug in which a therapeutic response can be expected in a given patient population.<sup>11</sup> If serum drug concentrations exceed the upper limit of the therapeutic range, the risk of adverse events may increase. The mean  $C_{max}$  of levetiracetam was above the human therapeutic range in our study. Therefore, despite the lack of adverse effects observed in our study, veterinarians are advised to monitor for adverse effects in cats receiving chronic administration of 500 mg XRL. Few, mild reported adverse effects in our study suggest XRL was well tolerated despite the high  $C_{max}$ . Notably, our study was not designed as a multiple dose toxicity study, and therefore the short observation period may underestimate the true incidence of adverse effects. Prescribing clinicians should be aware of potential adverse effects because of the high  $C_{max}$ , and consider alternative AED if adverse effects are intolerable in an individual cat.

Despite the large tablet size, all 9 cats received the medication successfully without reported difficulty. However, all owners were veterinary students, staff, or faculty and therefore it remains unknown if laypersons treating more fractious cats would encounter greater



**FIGURE 1** Mean serum levetiracetam concentration ( $\mu\text{g/mL}$ ) versus time (hours) curve for 9 healthy cats after 11 days of once daily administration of extended-release levetiracetam (500 mg). Shaded area represents the human reference range

difficulty owing to the large tablet size. No evidence of tablets in feces was noted by owners.

Limitations to our study include the use of a limited number of cats and weight restrictions (body weight  $\geq 5$  kg). Because of the weight restriction inclusion criteria in our study, extrapolation to cats weighing  $<5$  kg is discouraged. This clinical trial was not designed as a toxicity or efficacy study and the short duration of evaluation may have underestimated the incidence of adverse effects, and the clinical effect of XRL remains unknown.

In summary, multidose administration of 500 mg XRL resulted in median serum concentration  $>5$   $\mu\text{g}/\text{mL}$  and few adverse effects. The therapeutic reference range for levetiracetam in cats is unknown and, although once daily dosing resulted in median serum concentrations higher than the minimal reference interval in humans, it remains unknown if epileptic seizure control will be affected. If serum levetiracetam concentrations are above the minimum therapeutic range in humans and the dosage is not clinically effective, a shorter dosing interval (q12h instead of q24h) may be preferred instead of increasing the dosage because of the short half-life. Use of XRL once daily could be considered in cats weighing  $\geq 5$  kg, but trough serum measurements are recommended for monitoring individual cats.

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#### CONFLICT OF INTEREST DECLARATION

The authors declare that they have no conflict of interest with the contents of this article.

#### OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

#### INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

IACUC approval was obtained for this study. IACUC number: V005343-A01.

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