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Levetiracetam Rectal Administration in Healthy Dogs

R.K. Peters, T. Schubert, R. Clemmons, and T. Vickroy

Background: Levetiracetam is used to manage status epilepticus (SE) and cluster seizures (CS) in humans. The drug might be absorbed after rectal administration and could offer a practical adjunct to rectal administration of diazepam in managing SE and CS.

Hypothesis: Levetiracetam is rapidly absorbed after rectal administration in dogs and maintains target serum concentrations for at least 9 hours.

Animals: Six healthy privately owned dogs between 2 and 6 years of age and weighing 10–20 kg.

Methods: Levetiracetam (40 mg/kg) was administered rectally and blood samples were obtained immediately before (time zero) and at 10, 20, 40, 60, 90, 180, 360, and 540 minutes after drug administration. Dogs were observed for signs of adverse effects over a 24-hour period after drug administration.

Results: C_{LEV} at 10 minutes was 15.3 ± 5.5 μg/mL (mean, SD) with concentrations in the target range (5–40 μg/mL) for all dogs throughout the sampling period. C_{max} (36.0 ± 10.7 μg/mL) and T_{max} (103 ± 31 minutes) values were calculated and 2 disparate groups were appreciated. Dogs with feces in the rectum at the time of drug administration had lower mean C_{max} values (26.7 ± 3.4 μg/mL) compared with those without (45.2 ± 4.4 μg/mL). Mild sedation was observed between 60 and 90 minutes without other adverse effects noted.

Conclusions and Clinical Importance: This study supports the use of rectally administered levetiracetam in future studies of clinical effectiveness in the management of epileptic dogs.

Key words: Anticonvulsant; Cluster; Epilepsy; Status.

Epileptic seizures occur in 0.5–5.7% of dogs,[1,2] with some reports exceeding 40% of idiopathic epileptic dogs experiencing cluster seizures (CS; 2 or more seizures within a 24-hour period) or status epilepticus (SE; continuous seizures or multiple seizures with incomplete recovery lasting longer than 5 minutes).[3–5] Prolonged seizure activity can be life threatening and often requires veterinary attention for seizure control. Emergency interventions can be cost prohibitive to owners and will often lead to euthanasia.[6–9] Rectal administration of diazepam allows owners to help control seizures at home, which is thought to have contributed to the quality of life of epileptic pet owners by allowing control of frightening seizures and providing economic benefits from fewer emergency visits.[10] This has become a standard part of the home-therapeutic protocol for managing status and cluster seizures in dogs.[11] Although diazepam is effective in early seizure interruption, frequent dosing or adjunctive use of other longer acting anticonvulsants can be required for continued seizure control owing to the relatively short half-life. In addition, prolonged seizures are thought to alter the $GABA_A$-receptor composition and number leading to benzodiazepine resistance.[12] Other drugs might therefore be required in those cases to achieve seizure control. Historically, phenobarbital administered IV or PO has been considered optimal for long-acting treatment of seizures in dogs with SE or CS. Newer generation drugs, zonisamide and levetiracetam, are being used increasingly as a result of a therapeutic profile that includes perceived clinical efficacy, limited adverse effects, and decreasing cost of generic formulations.

Abbreviations:

$AUC_{0-\infty}$	the area under the curve from zero to infinity
AUC_{0-t}	the area under the curve from zero to the end of the sampling period
C_{LEV}	the serum concentration of levetiracetam at a given time point
C_{max}	the maximal serum concentration of levetiracetam recorded (μg/mL)
CNS	central nervous system
CS	cluster seizures
LEV	levetiracetam
SE	status epilepticus
$T_{1/2}$	the calculated half-life
T_{max}	the time point at which C_{max} was measured (minutes)
V_d	the volume of distribution

Levetiracetam is a pyrrolidine-derivative anticonvulsant that was approved in 1999 for adjunctive treatment of partial-onset seizures in adult humans. The drug has since gained broader approvals for treatment of a variety of partial and generalized seizure conditions, including those in pediatric patients.[13,14] Levetiracetam has a therapeutic profile closer to ideal than most other anticonvulsants[15] and the parenteral form is now used increasingly to manage cluster seizures and status epilepticus in the very young, elderly, and critically ill humans.[16–20]

In the authors' (RP, TS, and RC) experience, dogs might be obtunded, inappetant, or otherwise difficult to medicate during an episode of SE or CS. In these

From the Small Animal Clinical Sciences (Peters, Schubert, Clemmons); and the Department of Physiological Sciences (Vickroy), College of Veterinary Medicine, University of Florida, Gainesville, FL. *This study was supported by the University of Florida, College of Veterinary Medicine Resident Intramural Competitive Grants Program.*

Corresponding author: R.K. Peters, DVM, Department of Small Animal Clinical Sciences, University of Florida, 2015 SW 16th Avenue, Gainesville, FL 32608; e-mail: krupkar@ufl.edu.

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cases it can be very difficult for owners to administer necessary drugs, especially those that require oral administration. Pharmacokinetic studies with oral and parenterally administered levetiracetam in dogs have demonstrated that this drug undergoes rapid absorption and has excellent tolerance and bioavailability via oral, intramuscular, and subcutaneous routes of administration.[a,6,21–27] Although the serum half-life for these routes is similar to that of rectally administered diazepam metabolites, the resident half-life of levetiracetam in the cerebrospinal fluid can be considerably longer. In view of its excellent bioavailability and longer duration of action in the CNS, levetiracetam is a good candidate for parenteral administration to dogs experiencing an episode of CS. Although intramuscular or subcutaneous routes can be used as alternatives to oral dosing, both might be difficult for owners and painful for some dogs because of the need to administer the drug with a hypodermic needle. As an alternative, levetiracetam might be well suited for rectal administration as it is so well absorbed via other routes with little to no hepatic metabolism,[28] and it might be well absorbed via that route in humans.[b,29] The purpose of this study was to evaluate the feasibility of using rectally administered levetiracetam to rapidly achieve and maintain target blood concentrations in healthy dogs.

Materials and Methods

Animals

Six privately owned mixed-breed dogs (5 spayed females and 1 neutered male) were included in the study. Dogs were 2–6 years of age, weighing 20–40 pounds, and with a benign medical history, normal physical and neurologic examinations, and no abnormalities on a complete blood count, chemistry panel, and urinalysis. Dogs were 3.7 ± 1.1 years of age and weighing 14.5 ± 1.45 kg. All dogs had a body condition score between 4 and 6 (5.0 ± 0.6) on an established 9-point scale.[30] This study had IACUC approval, and informed consent was obtained from all owners before enrollment into the study.

Experimental Protocol and Sample Collection

The initial protocol included a 16-hour fast and oral administration of 5 mg bisacodyl[c] 12 hours before the study to promote fecal clearance. Bisacodyl use was based on other studies using laxatives, enemas, and fecal extraction to help limit complications from feces in rectal absorption studies.[31,32] Additional enema was not used here in an effort to limit rectal irritation before drug administration. This protocol was followed in 2 dogs. A digital rectal exam after drug administration in the first dog revealed formed feces in the rectum despite these measures. The dose was not repeated and blood samples were evaluated with the suspicion of inadvertent injection of the drug into fecal material. Although the second dog did not have fecal material palpable on rectal exam, it was presumed that the bisacodyl would not be uniformly effective at clearing the rectum of fecal material for the study. The remaining dogs were therefore only fasted with bisacodyl withheld to limit any complications from to-date uncharacterized interactions with levetiracetam or changes in rectal absorptive capacity. All remaining dogs received a limited digital rectal exam and extraction of fecal material as necessary immediately before drug administration.

For all dogs, a 19 g, 25 cm central-line catheter[d] was placed in the saphenous vein for blood sampling. The dogs were permitted to acclimate to the environment before a single dose of 40 mg/kg of parenteral levetiracetam[e] was administered approximately 1.5 inches into the rectum using a syringe fitted with a plastic teat cannula.[f] Venous blood samples were obtained from the catheter immediately before drug administration and at 10, 20, 40, 60, 90, 180, 360, and 540 minutes thereafter. All blood samples were collected into red-top tubes, and serum was separated within 20 minutes by centrifugation at 27°C ($3{,}500 \times g$, 8 minutes) and then immediately frozen at −20°C. A small meal was provided after drug administration and small treats were given at each blood sampling time. Before each blood collection, heart and respiratory rates were recorded and dogs were assessed for any signs of adverse reaction. The dogs were initially observed from a distance while approaching the cage and a Phase One Sedation response score was assigned according to the scale depicted in Table 1. A loud hand-clap was then performed near the dog before opening the cage door and a Phase Two Sedation score was assigned. The cage door was then opened and the dog was permitted to walk around the room while the researcher (1 of 2 investigators) looked for signs of ataxia or weakness. Observation periods were videotaped for subsequent evaluation and comparison with baseline recordings before drug administration. Throughout the day, dogs were observed for any signs of nausea or other gastrointestinal upset. After the final blood sampling at 540 minutes, the IV catheter was removed and the dogs were released home to their owner for continued observation. Owners were instructed to record any abnormalities in behavior, strength and coordination, or gastrointestinal signs. The animals were cared for according to the principles outlined in the NIH Guide for the Care and Use of Laboratory Animals.

Table 1. Patient Assessment Scoring System.

Sedation
Phase One
0: Typical alert posture
1: Mild sedation but easily responsive to the researcher approaching the cage
2: Laterally recumbent but will easily rise to sternal recumbency
3: Tends to remain laterally recumbent
Phase Two
0: Normal response compared to baseline
1: Weakened reaction
2: Very delayed and weak reaction
3: No reaction
Ataxia
0: None; normally strong and coordinated
1: Very slight or brief ataxia
2: Mild and persistent
3: Moderate but ambulatory
4: Unable to walk
Nausea
0: None, good appetite
1: Transient hypersalivation with good appetite
2: Salivation, swallowing, or poor appetite
3: Single episode of vomiting
4: Multiple vomiting events

Measurement of Serum Levetiracetam Concentration

Serum samples were stored frozen at −20°C for periods of up to 3 weeks before analysis for levetiracetam content. In separate studies with levetiracetam spiked samples of control canine serum, there was no significant decline (less than 5%) in levetiracetam concentrations when samples were stored at −20°C or 4°C up to 6 weeks. Levetiracetam concentration in serum samples was determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection according to a modified version of a method reported previously.[22] A reference standard of pure levetiracetam was obtained from the manufacturer[g] and dissolved in distilled water to produce a 1 mg/mL stock solution that was stored in a tightly sealed, light-resistant vial refrigerated at approximately 4°C. As needed, the stock solution was diluted further in mobile phase and added to control serum from dogs to produce calibration standards with levetiracetam concentrations from 0.5 to 100 μg/mL. The mobile phase for HPLC analysis consisted of a 95 : 5 mixture of 0.01 M phosphate buffer (pH 5.5):acetonitrile, which was prepared fresh and degassed each day. The HPLC system consisted of a quaternary solvent delivery system (flow rate, 1 mL/min) with autosampler and a UV/visible detector[h] set at a fixed wavelength of 205 nm. Aliquots (80 μL) of extracted serum samples were injected onto a reversed-phase analytical column[i] that was maintained at ambient temperature. Sample chromatograms were integrated with a computer program[j] and peak areas corresponding to analyte were converted into levetiracetam concentrations by linear regression comparison to an 8-point standard curve (0.5–100 μg/mL). All incurred, calibration, and control plasma samples were prepared in an identical manner for HPLC analysis. Solid-phase extraction cartridges[k] were conditioned with 1 mL of methanol followed by 2 mL of distilled water. Aliquots of canine serum (1 mL) were transferred onto individual conditioned cartridges and allowed to pass through the cartridge by gravity flow. Cartridges were washed with 1 mL of distilled water before final elution into a clean glass tube with 1 mL of methanol. Eluates were dried at elevated temperature (65°C) and reconstituted in 1 mL of distilled water by sequential vortex mixing (20 seconds), sonication (15 minutes), and vortex mixing. Reconstituted samples were subjected to low-speed centrifugation (10 minutes at 2,500 × *g*) at room temperature and passed through a syringe filter (0.45 μm) into autosampler vials for HPLC analysis. Within the window of time for levetiracetam elution (10.7–11.1 minutes), there were no detectable interfering peaks present in extracted control serum samples. The limit of quantification for levetiracetam in canine serum was 0.05 μg/mL. System suitability and performance criteria included a relative standard deviation below 3.9% (6 injections of 5, 10, and 50 μg/mL standards) and a linear regression coefficient (r^2 value) greater than 0.97 for all individual standard curves.

Analysis of the Data

Plots of levetiracetam serum concentration versus time were constructed and used to estimate standard pharmacokinetic parameters using noncompartmental analysis with a commercial pharmacokinetic software program.[l] Descriptive statistics were calculated, and the data were reported as mean ± SD when Shapiro–Wilk normality and equal variance testing demonstrated normal distribution of the dataset. During data assessment, a difference between groups of dogs with and without palpable fecal material present at the time of drug administration was appreciated. One- and two-tailed student *t*-tests were used to look for statistically significant differences between groups of dogs for these values. Values of $P < .05$ were considered statistically significant when combined with a power analysis of $\pi \geq 0.8$.

Results

Levetiracetam Pharmacokinetics

The serum concentration of levetiracetam was determined at 8 time points after drug administration in 6 dogs (Fig 1). All 6 subjects exhibited a rapid rise in serum levetiracetam concentrations after rectal administration with a concentration of 15.3 ± 5.5 μg/mL (range 8.5–22.5 μg/mL) at 10 minutes. The serum drug concentration remained elevated throughout the sampling period and exceeding the minimum target concentration of 5 μg/mL in all dogs out to 9 hours after drug administration. Pharmacokinetic analysis was carried out to obtain basic descriptive statistics. Analysis of data from the 6 dogs revealed a maximum serum drug concentration (C_{max}) of 36.0 ± 10.7 μg/mL with the time to achieve the maximal concentration (T_{max}) of 103 ± 31 minutes. Visual inspection of the data revealed the possible existence of 2 disparate groups, with 3 dogs exhibiting substantially higher peak levetiracetam concentrations compared with the other 3 subjects. Posthoc review of the study records revealed that increased serum drug concentrations (C_{max} values ranging from 40.2 to 49.6 μg/mL) were present in dogs that had no palpable feces in the rectum at the time of levetiracetam administration (open symbols), whereas 3 subjects with lower peak serum drug concentrations (C_{max} values ranging from 24.5 to 29.1 μg/mL) had palpable feces at the time of levetiracetam administration (closed symbols). In an effort to better evaluate possible differences in serum drug concentrations of dogs with or without palpable feces in the rectum at the time of levetiracetam administration, separate

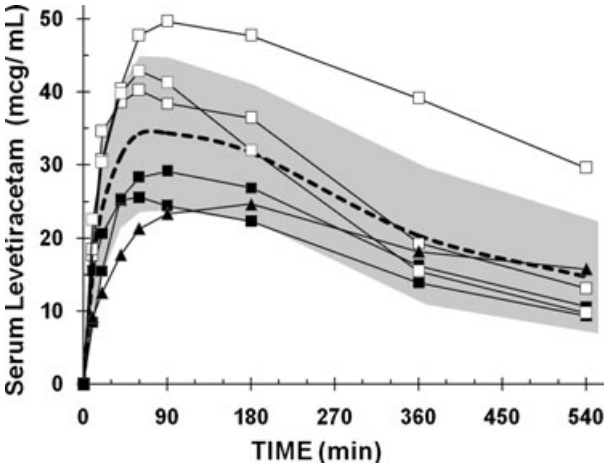

Fig 1. Time course of serum levetiracetam concentration after rectal administration in healthy dogs. Serum drug concentrations in 6 individual levetiracetam-treated (40 mg/kg) dogs are plotted using squares (5 females) and triangles (1 male). Dogs (n = 3) with palpable feces in the rectum at the time of levetiracetam administration are plotted with filled symbols, whereas dogs with no palpable feces (n = 3) are plotted with open symbols. Group mean values (±1 SD) are depicted with a dashed line and shading, respectively.

Table 2. Summary of calculated pharmacokinetic parameters.

	C_{max} (μg/mL)	T_{max} (minutes)	AUC_{0-t} (μg-min/mL)
Entire group	36.0 ± 10.7	103 ± 31	13,300 ± 4,300
Feces group	26.7 ± 3.4	107 ± 27	10,000 ± 430
Nonfeces group	45.2 ± 4.4	99 ± 40	16,500 ± 9,100
P value	.005	.788	.084

pharmacokinetic analyses were carried out for the 2 groups of dogs. The estimated C_{max} for dogs with palpable feces was 26.7 ± 3.4 μg/mL compared to a C_{max} of 45.2 ± 4.4 μg/mL for dogs without palpable feces (Table 2). The values for each group passed Shapiro–Wilk normality and equal variance testing. *P*-values with supporting power analysis for two-tailed ($P = .005$) Student *t*-tests were calculated.

Tolerability

All dogs had signs of slight sedation (Phase One Sedation score of 1) at 1 time point in the period of 60–90 minutes after drug administration. Comparison of the timing of sedation to the recorded serum levels demonstrated a relationship in all dogs between the time of sedation and the period in which serum levetiracetam concentrations were at or near maximal values. No other adverse effects were noted, including stable heart and respiratory rates, and with ataxia and nausea scores of 0/4 throughout the sampling period for all dogs.

Discussion

Our results demonstrate that rectal administration of parenteral levetiracetam produces sustained serum drug concentrations that could be efficacious for management of seizures in dogs. Levetiracetam solution undergoes rapid absorption after rectal administration of a single bolus, and blood concentrations remained well within the reported range for effective seizure control. Although 5–40 μg/mL is the typically reported therapeutic range, these values are extrapolated from human values and the true therapeutic range in both humans and dogs is not well established. There is moderate variability in serum concentrations between individuals with good and poor seizure control and in those with and without evidence of adverse effects.[33] We have therefore used the term "target range" to describe the range currently used as a goal for seizure control with minimal adverse effects in dogs. Levetiracetam was well tolerated in this study with no obvious signs of gastrointestinal discomfort or other physiologic changes, and only a brief period of very mild, transient sedation at or near the time of the peak serum levetiracetam concentration was observed. Sedation scoring was modified from a previously reported system based on the DIVAS assessment scale.[34] Although the dogs in this study were very consistent in the timing and degree of sedative changes observed, use of a nonvalidated sedation scoring system is considered a limitation in objective assessment of the adverse effects.

Despite our attempts to eliminate or substantially reduce the amount of solid material in the rectum with a brief fasting period and administration of a laxative, it was ultimately determined that half of the study subjects had palpable feces in the rectum at the time of drug administration. The entire drug bolus was inadvertently injected into the feces of the first study subject, 1 dog had fecal material digitally evacuated, and the last dog had palpable feces too rostrally located to digitally remove. Although these dogs appeared to have lower C_{LEV} values compared with those without palpable fecal material (C_{max} of 26.7 ± 3.4 versus 45.2 ± 4.4 μg/mL, respectively), all dogs still exhibited serum drug concentrations that were in the reported therapeutic range for the entire 9-hour sampling period. This is clinically important, as dogs requiring rectal administration of levetiracetam for emergency treatment might have fecal material in the rectum at the time of administration. The higher dose used in this study (40 mg/kg) was based on a study in humans that demonstrated reduced drug absorption from the colon compared with the stomach and small intestine.[32] Although the study looked specifically at blood concentrations after absorption from the colon, we hypothesized the effect of rectal absorption to be similar based on physiologic similarities between the structures and the lack of significant first-pass effect in levetiracetam metabolism. A published abstract involving 2 human patients given the drug via rectal administration supported this hypothesis and a decision was made to administer levetiracetam rectally at twice the minimum dose used for oral administration.[b] The C_{max} values obtained in this study after a single 40 mg/kg rectally administered dose are comparable with values observed in dogs given oral or intramuscular doses of 20 mg/kg.[6,22] Although absorption is still quite efficient when using 40 mg/kg, the discrepancy seen here between feces and nonfeces groups raises the concern that the lower end of the general recommended dosing range for levetiracetam (20 mg/kg) might not maintain adequate blood concentrations for the entire 9-hour time period. A separate study evaluating different doses and including IV administration for assessment of bioavailability can support or refute this hypothesis. Although the 40 mg/kg dose might be more reliable in achieving target serum concentrations, the volume required for administration in larger dogs is twice that of the suggested diazepam dosing volume and (nearly 20 mL in a 100-pound dog) might be more likely to stimulate defecation from rectal distension. Suggested dosing might therefore include administering the drug in separate 20 mg/kg boluses, allowing dissipation of the drug volume before repeat dosing.

This study allowed calculation of basic pharmacokinetic parameters of 2 apparently disparate groups; however, a statistical difference could only be supported for the C_{max} values. Although there were calculated differences in the T_{max} and AUC_{0-t} values, these differences were not ultimately statistically significant.

In addition, the mean percent extrapolated AUC for this group of dogs is 33.6% (range: 18.2–51.1%) which precludes reliable interpretation of $AUC_{0-\infty}$, $T_{1/2}$, and V_d. These values were therefore not reported here. Although all the dogs in this study had C_{LEV} values in the target range, there was a substantial range of serum drug concentrations across the 6 animals. Future studies will need to include more animals with sampling at more frequent and extended time intervals to more fully characterize levetiracetam pharmacokinetics after rectal administration in dogs.

Footnotes

[a] Hardy B, Patterson E, Cloyd J, et al. Subcutaneous administration of levetiracetam in healthy dogs. J Vet Intern Med 2011;25:741 (abstract)

[b] Gustafson MC, Penovich PE, Frost MD. Levetiracetam absorption after rectal administration: 2 case reports. Epilepsia 2005;46:211 (abstract)

[c] Bisacodyl 5 mg Tablets–Publix Super Markets, Inc, Lakeland, FL

[d] Milacath 19 g, 25 cm intravenous catheter, Item # PI1910; Mila International, Inc, Erlanger, KY

[e] Levetiracetam 500 mg/5 mL Injection—Sun Pharmaceutical Ind. Ltd, Mumbai, India

[f] Teat cannula—Jorgensen Laboratories, Inc, Loveland, CO

[g] UCB, Inc, Braine l'Alleud, Belgium

[h] Perkin-Elmer 200 series; Perkin-Elmer, Inc, Norwalk, CT

[i] Zorbax RX-C8 column (4.6 × 150 mm, 5 μm particle size), Agilent Technologies, Wilmington, DE

[j] Turbochrom Workstation 2 Software; Perkin Elmer, Inc

[k] Bond Elut C-18 SPE columns (500 mg, 3 mL); Agilent Technologies, Wilmington, DE

[l] PK Solutions Pharmacokinetics Data Analysis; Version 2.0. Summit Research Services, Montrose, CO

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