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STANDARD ARTICLE

Serum levetiracetam concentrations after transdermal levetiracetam administration, 3 times daily, to healthy cats

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Background: Repeated oral administration of antiepileptic drugs can be challenging for cat owners, resulting in reduced compliance, poor seizure control, and reduced quality of life for cats. Levetiracetam (LEV) has several properties that make it an appealing drug for transdermal application.

Objectives: The aims were to (1) determine if transdermal LEV, in a lipophilic, liposomic cream vehicle, resulted in serum concentrations above 5 μg/mL; (2) identify clinical adverse effects; and (3) evaluate the concentration of LEV in a lipophilic liposomic cream at set intervals.

Animals: Six healthy, client-owned cats weighing ≤5 kg.

Methods: Prospective clinical trial. Transdermal LEV was applied to the inner pinna at a dosage of 60 mg/kg (400 mg/mL concentration) at home for 6 days. Day 7, cats were hospitalized for blood sample collection for LEV concentration at times 0 (before dose administration), 0.5, 1, 2, 3, and 4 hours after administration.

Results: Median (range) timed serum concentrations were 16.6 (8.6-39.6) μg/mL, 16.1 (6.8-34.4) μg/mL, 15.4 (10.1-36.7) μg/mL, 17.4 (9.2-32.7) μg/mL, 15.1 (8.3-25.9) μg/mL, and 14.8 (11.9-28.4) μg/mL, respectively. Adverse events were limited to sedation (1/6 cats) and pinna crusting (1/6 cats). The LEV, in the proposed vehicle, retained concentration above 95% at 400 mg/mL up to 5 weeks.

Conclusions and Clinical Importance: Thrice daily transdermal LEV resulted in median serum concentrations ≥5 μg/mL throughout the sampling period and clinical adverse events were minimal. Transdermal LEV can provide an alternative for cats resistant to administration of other forms of anticonvulsant medication.

KEYWORDS

anticonvulsant, feline, levetiracetam, pharmacokinetic, transdermal

1 | INTRODUCTION

Seizures in cats make up 0.5%-3.5% of all referrals to veterinary teaching hospitals.[1–3] Several anticonvulsant drugs are available for use in cats with daily administration ranging from 1–3 times daily.[4–7] To achieve greater seizure control, antiseizure medications should be given at the same time every day, often long term. However, repeated oral administration in cats can be challenging for owners resulting in reduced compliance, poor seizure control, and reduced quality of life for both the cat and owner. All these factors can negatively affect the established human animal bond.[5,8]

Transdermal formulations have been utilized to decrease the difficulty associated with oral medication administration in cats. Phenobarbital, in a lipophilic, liposomic cream (Lipoderm, PCCA Pharmacy), was previously reported to achieve therapeutic concentrations after transdermal administration in healthy cats; however, this medication is not suitable for all cats.[5] Some epileptic syndromes are better

Abbreviations: LEV, levetiracetam; LEV-L, levetiracetam in lipophilic liposomic cream.

managed with other anticonvulsant medications, such as patients with reflex seizures.[9] Levetiracetam (LEV) is a newer anticonvulsant drug with seizure control ranging from 50% to 100% when administered as prescribed, PO, for epileptic cats.[9,10] Levetiracetam has several properties that make it a promising candidate for transdermal administration: it is water soluble, has lipophilic properties (thus promoting absorption across the stratum corneum), and is a small molecule (170.1 g/mol). These are all characteristics of drugs that have been successfully formulated for transdermal administration.[5,11] The primary aim of this clinical trial was to determine if transdermal levetiracetam in lipophilic, liposomic cream vehicle (Lipoderm, PCCA Pharmacy; LEV-L), resulted in serum concentrations above the minimum human therapeutic concentration (5 μg/mL)[6,12] and to identify adverse clinical effects in healthy cats. A secondary aim was to evaluate the concentration of LEV-L at 1, 3, and 5 weeks at room temperature. Our hypotheses were that serum LEV concentrations would be above 5 μg/mL at all time points after 6 days of administration, clinical adverse effects would be minimal and comparable to known adverse effects of LEV in cats, and that LEV-L would maintain a concentration above 95% at room temperature for a minimum of 5 weeks.

2 | MATERIALS AND METHODS

This study was designed as a multidose, prospective, clinical trial. Six healthy cats owned by Veterinary Medical Teaching Hospital students or staff were enrolled. Cats were enrolled if they (1) had a normal physical and neurologic examination performed by either a board-certified neurologist (HBH) or neurology resident (CS); (2) had PCV/TS and a serum biochemistry panel within the reference range; (3) did not meet any exclusion criteria. Cats were excluded if they (1) had a history of seizures; (2) were currently enrolled in another clinical trial or had involvement in any drug administration clinical trial in the previous 30 days; (3) received medication other than flea/tick/heartworm preventative treatments; or (4) if significant physical or neurologic examination findings or blood work abnormalities were detected at enrollment. A cat-specific therapeutic range for LEV is not available; therefore, the human therapeutic range (5-45 μg/mL) was extrapolated for this study. All owners provided informed consent, and the study was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Wisconsin-Madison.

Levetiracetam (Levetiracetam USP, Fagron) in proprietary lipophilic liposomic cream (Lipoderm, PCCA; LEV-L) was compounded by a clinical pharmacist (Nicole Reif) at the University of Wisconsin-Madison Veterinary Pharmacy Hospital for transdermal administration. Maintenance of concentrations was analyzed using spectrophotometry at an FDA registered laboratory (Eagle Analytical Services, Houston, Texas) at room temperature and protected from light for drug concentrations of 350 and 400 mg/mL. Samples were analyzed at 1, 3, and 5 weeks after production.

Based on the analysis, cats were prescribed 400 mg/mL transdermal LEV-L at a dosage of 60 mg/kg every 8 hours to be applied to the inner pinna for 6 days. This dosage at 3 times the standard oral dose was selected based on a previous transdermal phenobarbital study in which interim analysis suggested a dose escalation of 3 times the standard oral dosage.[5] Owners were instructed to apply the prescribed amount to a gloved finger and to rub the LEV-L into the inner pinna (or to divide the dose over 2 pinnae) until the cream could no longer be visualized on the gloved finger or inner pinna. Owners were asked to keep a compliance log of dosage times and clinical adverse effects noted throughout the study period. On day 7, cats were hospitalized before administration of the morning dose. Although the median time to steady state is less than 1 day, the study was extended over 7 days to allow for adequate drug absorption as well as to provide a longer observation period for detection of adverse clinical effects.[6] A repeat physical and neurologic examination was performed. Blood sampling was performed at time 0 (trough) and at 0.5, 1, 2, 3, and 4 hours after the morning dose. Transdermal LEV was administered immediately after collection of the trough (time 0) serum sample. The cat's LEV-L was applied using a gloved finger to 1 or both pinnae and rubbed into the pinnae until the gel was no longer observed. At each time point, 1.5 mL of blood was collected via peripheral venipuncture. After collection, blood was allowed to clot for a minimum of 10 minutes followed by centrifugation and manual separation and refrigerated until drug quantification. After the final sample collection, cats were returned to their owners. Transdermal administration of LEV was tapered to every 12 hours on days 7 and 8, and once daily on day 9 before discontinuation of the medication to minimize the risk of withdrawal seizures. Serum LEV concentrations were determined using high-performance liquid chromatography at a commercial laboratory using a technique previously described for and validated in cats.[6,13]

2.1 | Statistical analysis

Continuous data were analyzed for all cats using descriptive, non-parametric statistics: median and range for trough and observed peak LEV concentrations, and range of LEV concentrations observed at each time point in each cat. Our measure of a successful outcome was steady-state trough serum LEV concentrations greater than 5 μg/mL with tolerable observed adverse effects at estimated peak concentrations. As the purpose of this study was to determine whether serum drug concentrations remained above an acceptable minimum (5 μg/mL), full pharmacokinetic analysis not performed with this limited sampling protocol.

3 | RESULTS

A loss of up to 10% concentration was found in the 350 mg/mL LEV-L samples, and a loss of up to 5% concentration was found in 400 mg/mL LEV-L samples over the 5-week analysis period. Based on these results, LEV-L was formulated at 400 mg/mL for this clinical trial.

All 6 cats completed the clinical trial. All cats were domestic short-haired cats with median age (range) of 3.09 years (0.58-5.75 years) and median weight (range) of 4.6 kg (2.7-4.9 kg). There were 4 spayed females, 1 intact female, and 1 neutered male cat. All 6 cats enrolled were determined to be healthy based on normal physical and neurologic examination and normal blood work results. Median (range) dose and volume of LEV-L administered was 280 (240-292) mg and 0.70 (0.60-0.73) mL, respectively.

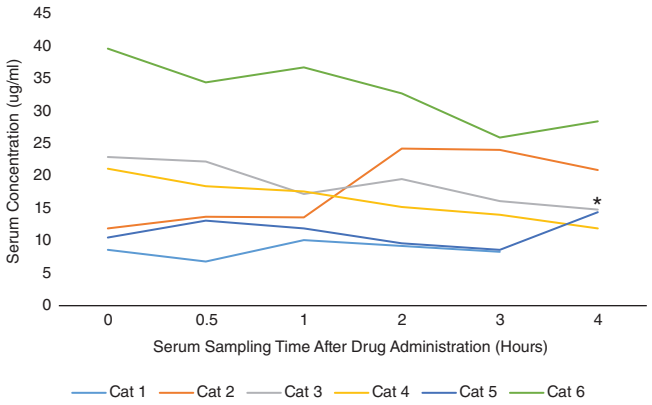

FIGURE 1 Serum levetiracetam concentrations (μg/mL) versus time (hours) for 6 healthy cats after administration of transdermal levetiracetam plus lipophilic, liposomic cream for 6 days. Shaded region represents the human therapeutic range. * indicates sample not obtained

Median (range) serum LEV concentrations at time 0, 0.5, 1, 2, 3, and 4 hours were 16.6 (8.6-39.6) μg/mL, 16.1 (6.8-34.4) μg/mL, 15.4 (10.1-36.7) μg/mL, 17.4 (9.2-32.7) μg/mL, 15.1 (8.3-25.9) μg/mL, and 14.8 (11.9-28.4) μg/mL, respectively (Figure 1). The 4-hour sample was not collected on 1 cat due to poor cat compliance. Median serum LEV concentrations were above the minimum reference concentration (5 μg/mL) at all time points. Median estimated C_{max} and C_{min} (range) were 22.0 (10-39.6) μg/mL and 11.9 (6.8-25.9) μg/mL, respectively.

Adverse effects were limited to mild crusting on the pinnae of 1 cat on day 7 and sedation in 1 cat on day 3. Sedation resolved without dosage adjustment. Physical and neurologic examinations remained normal for all cats on day 7.

4 | DISCUSSION

The results of this study show that serum LEV concentrations greater than 5 μg/mL can be achieved using transdermal LEV-L at a dosage of 60 mg/kg every 8 hours. The dosage selected for this study was 3 times higher than the dosage recommended for oral immediate release LEV (20 mg/g PO q 8h)[6] based on prior experience with transdermal phenobarbital absorption. With transdermal phenobarbital, the dosage of 3 times the standard dosage was required to obtain serum concentrations within the therapeutic range in healthy cats.[5] Lower dosages were not evaluated in our current study to confirm this finding with LEV.

The stratum corneum is part of the outermost layer of the epidermis. It consists of approximately 40% keratin, 40% water, and the remainder is lipid. The reported thickness is 3-20 μm in cats.[14] Drug absorption is regulated by the stratum corneum; therefore, penetration of this skin layer is the largest hurdle to transdermal drug absorption. Chronic exposure allows for greater emulsification of the stratum corneum and for formation of a drug depot in the subcutis.[15,16] With repeated dosing, absorption is enhanced and formation of a drug depot allows for continuous, slow, steady release into the circulation.[15,16] In these situations, the absorption rate is often slower than the elimination rate resulting in flip-flop kinetics, in which absorption is the primary determinant of drug concentrations in circulation. This is likely the case for LEV-L as total body clearance of LEV is relatively high in cats.[6] The median (±SD) time to steady-state after oral intermediate release LEV administration is 14.74 (4.75) hours.[6] However, this study was extended over 7 days to allow adequate absorption through the epidermis and formation of a drug depot, as well as to provide a longer observation period for detection of adverse clinical effects.[6,15,16] Similar studies of other transdermal drugs in cats have also used a 1-week administration period.[17]

The minimum therapeutic value targeted in this study (5 μg/mL) is the lower end of a commonly referenced therapeutic range that has been extrapolated from humans for use in veterinary species.[6,18] Recent studies in humans have suggested a new target peak range of 12-40 μg/mL and a trough range of 6-20 μg/mL for optimum seizure control using LEV monotherapy.[19] Though serum concentrations were not above 12 μg/mL for all cats in this study, it did exceed 5 μg/mL. This variation can be attributable to differences in absorption or clearance of the drug. A veterinary therapeutic range has not been established for LEV, nor has clinical efficacy been determined for cats or dogs based on any human therapeutic range. It remains unknown if LEV-L is clinically effective at the dosages prescribed in this study, because this study was not designed as an efficacy study.

Levetiracetam results in few dose-dependent adverse clinical effects in cats.[6,9,10,20–22] These findings are consistent with our results in which 2 of 6 cats (33%) experienced minor adverse effects. Crusting of the pinnae might have been secondary to transdermal drug administration; however, the low-frequency observation of this adverse effect and the low number of cats evaluated in this study make the association inconclusive. Although few adverse effects were noted in this study, a longer clinical observation period involving more cats might identify additional adverse effects.

The cost for transdermal LEV, using the formula presented in this study, was notably more expensive than standard oral tablets or oral solution. The cost for a 4.5 kg cat, for 14 days of treatment is approximately $5.70, $4.20, and $227 USD for the oral solution, oral tablets (estimated to closed dose), and transdermal formulation, respectively. The cost difference between transdermal and oral formulations is in part because of the larger required dosage, as well as the cost of compounding the product with the lipophilic liposomic cream.

Limitations for this study include the volume of LEV-L required for administration, the small sample size, and the lack of dosage stratification. The sample size was limited to 6 cats because this was a feasibility pilot study. Although evaluation of novel drugs or products is common in veterinary studies,[4,5,13,23] the authors acknowledge that the small numbers limit extrapolation of the acquired data to larger epileptic cat populations. The volume of LEV-L required for transdermal administration could be a limiting factor for use in epileptic cats. Cats with body weights over 5 kg were not evaluated in this study because of the large volume of LEV required to obtain a 60 mg/kg dosage. A larger sample size would allow for further assessment of any adverse effects. A larger sample size can allow a better assessment of the mean serum concentration at each time point. However, even with a larger sample size, interindividual variation in serum LEV concentrations after transdermal administration could be attributed to many other factors including age, sex, body temperature, and blood

supply, as all these can affect drug absorption.[24] Dosage stratification could increase the utility of LEV-L in cats requiring higher dosages for seizure control and help identify if saturation of the drug depot occurred at the dosage evaluated in this study.

5 | CONCLUSIONS

The results of this study suggest that transdermal administration of LEV to cats resulted in serum drug concentrations above the minimum human therapeutic range and a few adverse effects were identified. Furthermore, LEV-L maintained concentrations up to 5 weeks at a concentration of 400 mg/mL and is the recommended formulation for use. Though minimum human therapeutic concentrations were achieved, transdermal LEV-L dosages should be adjusted based on seizure control and adverse clinical effects until a therapeutic range is established for cats.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Approval from the University of Wisconsin IACUC, number V005942.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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