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Effect of Chronic Administration of Phenobarbital, or Bromide, on Pharmacokinetics of Levetiracetam in Dogs with Epilepsy

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Background: Levetiracetam (LEV) is a common add-on antiepileptic drug (AED) in dogs with refractory seizures. Concurrent phenobarbital administration alters the disposition of LEV in healthy dogs.

Hypothesis/Objectives: To evaluate the pharmacokinetics of LEV in dogs with epilepsy when administered concurrently with conventional AEDs.

Animals: Eighteen client-owned dogs on maintenance treatment with LEV and phenobarbital (PB group, n = 6), LEV and bromide (BR group, n = 6) or LEV, phenobarbital and bromide (PB–BR group, n = 6).

Methods: Prospective pharmacokinetic study. Blood samples were collected at 0, 1, 2, 4, and 6 hours after LEV administration. Plasma LEV concentrations were determined by high-pressure liquid chromatography. To account for dose differences among dogs, LEV concentrations were normalized to the mean study dose (26.4 mg/kg). Pharmacokinetic analysis was performed on adjusted concentrations, using a noncompartmental method, and area-under-the-curve (AUC) calculated to the last measured time point.

Results: Compared to the PB and PB–BR groups, the BR group had significantly higher peak concentration (C_{max}) (73.4 ± 24.0 versus 37.5 ± 13.7 and 26.5 ± 8.96 μg/mL, respectively, $P < .001$) and AUC (329 ± 114 versus 140 ± 64.7 and 98.7 ± 42.2 h*μg/mL, respectively, $P < .001$), and significantly lower clearance (CL/F) (71.8 ± 22.1 versus 187 ± 81.9 and 269 ± 127 mL/h/kg, respectively, $P = .028$).

Conclusions and Clinical Importance: Concurrent administration of PB alone or in combination with bromide increases LEV clearance in epileptic dogs compared to concurrent administration of bromide alone. Dosage increases might be indicated when utilizing LEV as add-on treatment with phenobarbital in dogs.

Key words: Antiepileptic drug; Canine; Drug disposition; Drug interactions; Seizures.

Levetiracetam (LEV) is a structurally novel, second generation antiepileptic drug (AED) that was approved in 1999 for adjuvant treatment of partial-onset seizures in humans. It has a unique mechanism of action involving the selective binding to presynaptic protein SVA2, whereby it modulates the release of neurotransmitters.[1] LEV possesses several favorable pharmacologic properties with respect to its use as an add-on AED, including high bioavailability, limited hepatic metabolism, minimal effect on the disposition of other AEDs and a high therapeutic index.[2] LEV is efficacious in the treatment of partial and generalized seizures associated with several epilepsy syndromes in both adults and children.[3] Based on the promising results in humans, LEV is being used with increasing frequency in veterinary medicine as a treatment for epilepsy.[4–6]

There are several published reports describing the pharmacokinetics of LEV in normal dogs. Studies have evaluated the disposition of a single dose of LEV when administered by the oral, subcutaneous and intravenous routes,[7–10] and after repeated oral dosing.[11] However, the drug is often used as add-on treatment, and the effect of concurrent administration of other AEDS on the pharmacokinetics of LEV has not been fully evaluated in dogs. In healthy laboratory dogs, concurrent administration of LEV and phenobarbital results in a significant increase in LEV oral clearance, with lower peak concentrations and shorter elimination half-life.[12] Information on the disposition of LEV when administered either as a sole agent or as an add-on to dogs with naturally occurring epilepsy is limited.

To explore the potential effect of concomitant AEDs on the disposition of LEV in the clinical setting, we per-

Abbreviations:

AED	antiepileptic drug
$AUC_{0\text{-}Cn}$	area-under-the-curve from time 0 to the last sampling point
AUC	area-under-the-curve
BR	bromide
CL/F	clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
LEV	levetiracetam
PB	phenobarbital
$T_{1/2}$	terminal half-life
T_{max}	time to maximum concentration

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formed a pharmacokinetic study in dogs with naturally occurring epilepsy that were being treated with the conventional AEDs phenobarbital and potassium bromide in conjunction with LEV. The specific aim of the study was to determine whether or not concurrent administration of phenobarbital alone, bromide alone, or phenobarbital and bromide in combination, alters the pharmacokinetics of LEV in epileptic dogs. This information is needed to optimize the use of LEV as an add-on treatment for seizures in dogs.

Materials and Methods

Animals

Eighteen client-owned dogs with epilepsy were enrolled in this nonblinded study. Six dogs were recruited into each of 3 groups based on their established maintenance AED treatment regimen: dogs receiving LEV in combination with phenobarbital only (PB group), dogs receiving LEV in combination with potassium bromide only (BR group), and dogs concurrently receiving LEV, phenobarbital and bromide (PB–BR group). To be eligible for the study, all administered AEDs had to be at steady state concentrations. Owners were required to provide informed consent before their dog's participation in the study. Six dogs presented to NC State University College of Veterinary Medicine for participation in the study, while the remaining 12 dogs presented to one of 10 regional veterinary hospitals for samples to be collected according to standardized study guidelines. The study protocol was approved by the Institutional Animal Care and Use Committee at NC State University.

Sample Collection

Owners were instructed to withhold food from their dog overnight before participation in the study. Dogs presented to the hospital on the morning of the study and were admitted for the day. Blood samples were taken from each dog at 5 time points throughout the day; immediately before administration of the morning dose of LEV (0 hour sample), and at 1, 2, 4, and 6 hours after LEV administration. At each sampling point, approximately 3 mL of blood was collected from either the jugular, cephalic or saphenous vein and placed in a sodium heparin tube. An additional 3 mL of blood was collected at the 0 hour sampling point and placed in a clot tube for measurement of phenobarbital concentration, bromide concentration, or both. Dogs were fed their standard diet between the 4 and 6-hour sample collection. Water was available throughout the study. Dogs were administered other prescribed AEDs in accordance to their established treatment schedule.

Blood samples were centrifuged after collection, and plasma or serum harvested and frozen. Samples collected by outside sites were shipped to NC State University frozen and on ice via an overnight delivery service. All samples were stored at −80°C until assayed.

Drug Analysis

Serum phenobarbital and bromide concentrations were evaluated on 0 hour samples through the Clinical Pharmacology Laboratory at NC State University. Phenobarbital was measured using a commercially available fluorescence polarization immunoassay, as previously validated for dogs.[a] Bromide was measured using a modification of the previously described gold chloride assay method.[13] Gold chloride added to bromide in plasma samples produces a reaction that can be monitored colorimetrically using a spectrophotometer. Plasma samples were analyzed for LEV with high-pressure liquid chromatography using a previously described method developing in the author's (MGP) laboratory at NC State University.[11]

Pharmacokinetic Analysis

Plasma drug concentrations were plotted on linear and semilogarithmic graphs for visual analysis. Analysis of curves and pharmacokinetic modeling was conducted using a commercial pharmacokinetic program.[b] Compartmental pharmacokinetic models were considered, but did not provide consistent fits for all dogs. Therefore, the data for each animal was analyzed using a noncompartmental method which did not require compartment model assumptions. The noncompartmental model measured the area-under-the-curve (AUC) from time 0 to the last measured time point ($AUC_{0\text{-}Cn}$) using the log-linear trapezoidal method. The terminal half-life ($T_{1/2}$) was estimated from the slope of the terminal points of the curve. The peak concentration (C_{max}), trough concentration (C_{min}) and time to peak concentration (T_{max}) were determined directly from the data. Clearance was determined as per fraction absorbed (CL/F) and calculated from the equation: CL/F = dose/AUC.

Statistical Analysis

Data were analyzed for differences between treatment groups with respect to canine demographics, drug dosages, phenobarbital serum concentrations, bromide serum concentrations, and LEV pharmacokinetic parameters. Fisher's exact test was used for categorical variables, and ANOVA was utilized for continuous variables. A significance level of $P < .05$ was established for all analyses.

Results

Canine Demographics

Breeds of dogs participating in the study included Labrador retriever (n = 5), mixed breed dog (n = 3), Australian shepherd (n = 2), and one each of Golden retriever, German shepherd, Dalmatian, Saint Bernard, American Staffordshire Terrier, Irish setter, Tibetan mastiff and Wirehaired pointing Griffon. There were 5 spayed females and 13 neutered males, with a median body weight of 35.2 kg (range, 6.1–78.2 kg). Dogs were 3–14 years of age (median, 8 years) with a duration of epilepsy of 1–11 years (median, 4 years). Twelve dogs were reported to have generalized seizures, 1 was reported to have focal seizures, and 5 dogs were reported to have both generalized and focal seizures. None of the dogs were seizure free on the current treatment protocol. Average seizure frequency ranged from 1 per 12 months to 15 per month, with a median of 1 per month. There was no difference in age, weight, sex, duration of epilepsy, or average monthly seizure frequency between groups.

AED Administration

The mean daily dose of phenobarbital for dogs in the PB group was 6.3 mg/kg (SD 2.6), with a mean serum phenobarbital concentration of 25.8 μg/mL (SD 10.1). The mean daily phenobarbital dose for the dogs in the

PB–BR group was 8.6 mg/kg (SD 2.3), with a mean serum phenobarbital concentration of 23.5 μg/mL (SD 1.9). These values did not differ between groups. The mean daily bromide dose for the dogs in the BR and PB–BR groups were 40.1 mg/kg (SD 11.6) and 32.9 mg/kg (SD 12.6), respectively. Although the bromide dose did not differ between groups, the mean serum bromide concentration for the BR group (252 mg/dL, SD 58.0) was significantly different than that for the PB–BR group (161 mg/dL, SD 63.0; $P = .027$).

Levetiracetam immediate-release formulation was administered at 8-hour intervals in 17 dogs and every 12 hours in 1 dog. The dog receiving LEV at 12-hour intervals was in the PB–BR group. The mean LEV dose for the entire study population was 26.4 mg/kg (SD 9.3). Dogs in the PB group had a mean LEV dose of 33.1 mg/kg (SD 10.1) compared to a mean dose of 23.2 mg/kg (SD 5.0) and 22.9 mg/kg (SD 9.4) for the BR and PB–BR groups, respectively. The differences in dose between groups were not statistically significant. Nonetheless, to account for any potential effect of the difference in the pharmacokinetic analysis, LEV concentrations were normalized to the mean study dose of 26.4 mg/kg, and pharmacokinetic parameters calculated on the adjusted concentrations.

Pharmacokinetic Analysis

Normalized plasma concentrations and pharmacokinetic parameters for LEV in the 3 groups of dogs are shown in Table 1 and Figure 1. Compared to the BR group, both the PB and the PB–BR groups had significantly lower C_{min}, C_{max}, $T_{1/2}$, and $AUC_{0\text{-}Cn}$, and higher CL/F. Compared to the BR group, the PB group had a decrease in C_{max} of 49%, a decrease in $T_{1/2}$ of 35%, and an increase in CL/F of 160%. Similarly, the magnitude of the difference in C_{max}, $T_{1/2}$ and CL/F for the PB–BR group compared to the BR group were 63%, 49%, and 275%, respectively. No difference in any of the pharmacokinetic parameters was noted when comparing the PB and PB–BR groups.

Discussion

The findings from this study demonstrate that the pharmacokinetics of LEV in dogs with epilepsy are altered by concurrent administration of AEDs. Dogs in the PB and PB–BR groups had lower LEV plasma concentrations and had more rapid oral clearance of LEV when compared to dogs in the BR group, indicating that the coadministration of phenobarbital alters the metabolism of LEV. In contrast, no significant differences were identified in any of the pharmacokinetic parameters between the PB and the PB–BR groups, suggesting that bromide administration does not have an effect on LEV disposition.

Canine demographics as well as drug dosages and serum drug concentrations did not differ between groups of dogs in this study, with the exception of serum bromide concentrations. Dogs in the BR group had higher serum bromide concentrations than dogs in the PB–BR group, despite being on similar dosages of bromide. This could be attributed to differences in diet between the groups, as changes in dietary chloride content alter the disposition of bromide in dogs.[14] Dietary analysis would be necessary to confirm this supposition, which was not possible within this study. However, the difference in bromide concentrations is not believed to impact the study findings, as bromide does not appear to affect the pharmacokinetics of LEV.

In healthy dogs, a single oral dose of LEV before and after a 21-day course of oral phenobarbital administered every 12 hours resulted in a significant decrease in C_{max} and $T_{1/2}$, and a significant increase in CL/F compared with values obtained when LEV was administered alone.[12] Thus, this study identifies similar pharmacokinetic alterations in a group of dogs with naturally occurring epilepsy being chronically treated with LEV and phenobarbital.

Based on its pharmacologic properties, LEV is expected to have a low potential for drug interactions.[2] LEV is minimally bound to plasma proteins, and undergoes primarily renal elimination, with a large portion of the drug excreted unchanged in the urine. Induction or inhibition of hepatic drug metabolism represents the

Table 1. Dose normalized pharmacokinetic parameters (mean ± SD) for epileptic dogs administered LEV and phenobarbital (PB group), LEV and bromide (BR group), and LEV, phenobarbital and bromide in combination (PB–BR group).

Parameter	Units	BR Group	PB Group	PB–BR Group	*P* Value[a]	*P* Value[b]	*P* Value[c]
T_{max}	hours	2.17 ± 1.47	2.17 ± 1.47	2.33 ± 1.37	1.0	.84	.84
C_{max}	μg/mL	73.4 ± 24.0	37.5 ± 13.7	26.5 ± 8.96	.0021	<.001	.27
C_{min}	μg/mL	33.5 ± 16.8	5.52 ± 4.71	3.06 ± 3.32	<.001	<.001	.68
$T_{1/2}$	hours	4.99 ± 1.41	3.24 ± 1.42	2.52 ± 0.640	.024	.0031	.33
$AUC_{0\text{-}Cn}$	h*μg/mL	329 ± 114	140 ± 64.7	98.7 ± 42.2	<.001	<.001	.39
CL/F	mL/h/kg	71.8 ± 22.1	187 ± 81.9	269 ± 127	.039	.0015	.13

Noncompartmental method, with AUC calculated using trapezoidal method.

T_{max}, time of peak plasma concentration; C_{max}, peak plasma concentration; C_{min}, trough plasma concentration during sampling period; $T_{1/2}$, terminal half-life; $AUC_{0\text{-}Cn}$, area-under-the-curve from time zero to last sampling point; CL/F, oral clearance.

Statistical analyses were performed using ANOVA; [a]comparison between BR and PB groups, [b]comparison between BR and PB–BR groups, [c]comparison between PB and PB–BR groups.

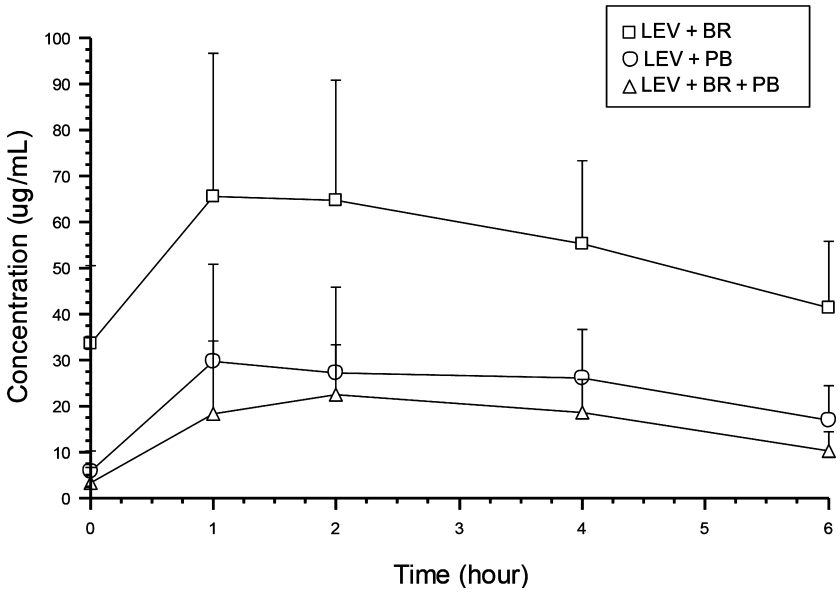

Fig 1. Mean plasma levetiracetam concentrations in dogs with epilepsy being concurrently treated with phenobarbital (PB group), bromide (BR group), or phenobarbital and bromide in combination (PB–BR group). Error bars represent SD.

majority of AED interactions recognized in clinical settings.[15] In dogs, 89% of LEV is excreted in the urine, with approximately 50% excreted unchanged.[7,8] The remaining drug is metabolized through hydrolysis and to a lesser extent, oxidation. Hydrolysis is mediated by the nonspecific esterase enzyme system, which has a broad tissue distribution including the blood, liver, kidney, lung, brain and intestine. The metabolism of LEV is not dependent of the hepatic cytochrome P450 system.[16] However, studies in rats have demonstrated that the oxidation of LEV can be induced by phenobarbital.[7] Rats pretreated with phenobarbital had a significant increase in the urinary excretion of LEV metabolites resulting from oxidation of the parent compound compared to rats pretreated with saline. Furthermore, the oxidative pathways appear to play a larger role in LEV metabolism in dogs compared to rats.[7] Consequently, it seems possible that phenobarbital induced oxidation accounts for the altered disposition of LEV demonstrated in this study; induction of oxidative enzymes could lead to increased LEV metabolism, resulting in increased clearance of the drug.[12] Further evaluation of the effect of phenobarbital on LEV metabolism in these dogs would require measurement of urinary drug metabolites, which was beyond the scope of this study.

The effect of co-administration of enzyme inducing AEDS such as phenobarbital, primidone, carbamazepine, and phenytoin to enhance the elimination of LEV is well documented in humans with epilepsy.[17–21] Much of this data have been derived from therapeutic drug monitoring databases. A prospective study evaluated the disposition of a single oral dose of LEV in humans with epilepsy receiving treatment with enzyme inducing AEDs compared to a control group of patients either not receiving pharmacological treatment or receiving AEDs not considered to be enzyme inducers.[22] The group of patients administered enzyme inducing AEDs had a significant increase in LEV CL/F of approximately 25% compared to controls. Furthermore, the amount of drug metabolized in relation to the amount excreted unchanged in the urine was 40% higher in the enzyme-inducing group compared to controls, although the main metabolite of LEV that results from hydrolytic pathways was not different between the two groups. These findings lend support to the hypothesis that enzyme inducing AEDs enhance the clearance of LEV by increasing the formation of secondary metabolites.

The mean minimum LEV plasma concentrations obtained in the PB and PB–BR groups were 5.52 μg/mL and 3.06 μg/mL, respectively, compared to 33.5 μg/mL for the BR group. There is no information available on a therapeutic range for LEV concentrations in dogs, although the human reference range of 5–40 μg/mL is frequently extrapolated for use in veterinary patients. If one assumes that a minimum plasma concentration of 5 μg/mL is needed to achieve seizure control in dogs, it is apparent that both the PB and PB–BR groups had values either at or below this minimum desired concentration. Hence, the standard recommended oral dosage of 20 mg/kg every 8 hours might not be sufficient to maintain blood concentrations within the proposed reference range when LEV is administered concurrently with phenobarbital. However, although there was no difference in the monthly seizure frequency between the groups of dogs, data on seizure frequency before starting AEDs were not collected, and therefore conclusions regarding seizure control cannot be made.

The nature of this study results in a few inherent limitations. To encourage study participation, both the duration of sampling and the number of samples obtained from each dog were kept to a minimum.

Sampling points were carefully selected based on previous pharmacokinetics studies, but the study by intention was not devised to provide terminal sampling points extending through 3–5 half lives. This resulting pharmacokinetic analysis yielded relatively large values for percent of the AUC extrapolated to infinity that ranged from 27.5 to 46.4%. For this reason, $AUC_{0\text{-}Cn}$ was reported in this study rather than the more commonly utilized $AUC_{0\text{-}\infty}$. Terminal half-life is calculated from the slope of the plasma concentration versus time curve, and will also have some inaccuracy in its estimation because of the sparse terminal sampling points. In addition, since the study was not designed with the administration of an accompanying IV dose, the plasma concentrations measured only represent the fraction (F) of the oral dose that reached the systemic circulation, and the true value of systemic clearance (CL) is not known. Finally, drug dosages were not standardized for the study, a shortcoming inherent to population pharmacokinetic studies that aim to evaluate drug disposition in the clinical setting as opposed to administering a drug to participants for research purposes. However, for the pharmacokinetic analysis of plasma LEV, the concentrations were normalized to the average dose administered.

In conclusion, this study demonstrated a pharmacokinetic interaction between LEV and phenobarbital in epileptic dogs that resulted in lower LEV plasma concentrations and more rapid LEV clearance. These results should be taken into consideration when utilizing LEV as add-on treatment in dogs with epilepsy. A clinically relevant pharmacokinetic interaction has been defined as "one that, because of its mechanism and magnitude, will occur in the majority of patients and will require a dose adjustment so as to avoid an adverse outcome (eg, seizure breakthrough or exacerbation of side effect)".[15] Although the interaction appears to occur predictably in dogs comedicated with LEV and phenobarbital, its clinical relevance has not been established. Nonetheless, the findings suggest that therapeutic drug monitoring is warranted when LEV is used as add-on treatment with phenobarbital. In addition, an increase in LEV dosage accompanied by regular monitoring of LEV serum concentrations in the individual dog might lead to improved therapeutic efficacy. Further study is needed to determine the reference range for LEV in dogs with epilepsy, and to develop specific recommendations for LEV dosage adjustments in dogs concurrently being administered phenobarbital.

Footnotes

[a] IMMULITE 1000 Immunoassay System Phenobarbital Assay. Siemens Healthcare Diagnostics, Inc, Tarrytown, NY

[b] Phoenix WinNonlin, Pharsight, Certara Corporation, St. Louis, MO

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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