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Open-label clinical trial of rectally administered levetiracetam as supplemental treatment in dogs with cluster seizures

Giulia Cagnotti[1] | Rosangela Odore[1] | Iride Bertone[1] | Cristiano Corona[2] | Elena Dappiano[1] | Giulia Gardini[1] | Barbara Iulini[2] | Claudio Bellino[1] | Antonio D'Angelo[1]

[1]Department of Veterinary Science, University of Turin, Turin, Italy

[2]Istituto Zooprofilattico del Piemonte Liguria e Valle d'Aosta, Turin, Italy

Correspondence
Giulia Cagnotti, Department of Veterinary Science, University of Turin, Largo Paolo Braccini 2, 10095, Grugliasco, Turin, Italy.
Email: giulia.cagnotti@unito.it

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Abstract

Background: Treatment options for at-home management of cluster seizures (CS) and status epilepticus (SE) are limited. The pharmacokinetics of levetiracetam (LEV) after rectal administration in both healthy and epileptic dogs has been investigated recently.

Hypothesis/Objectives: To investigate the clinical efficacy of rectally administered LEV in preventing additional seizures in dogs presented for CS and SE. We hypothesized that rectal administration of LEV in addition to a standard treatment protocol would provide better control of seizure activity as compared with the standard treatment protocol alone.

Animals: Fifty-seven client-owned dogs with CS or SE.

Methods: Prospective open-label clinical trial. Patients included in the study were assigned to receive either a standard treatment protocol comprising IV/rectal diazepam and IV phenobarbital q8h (control group) or a standard treatment protocol in association with a single dose of 40 mg/kg LEV rectally (rectal LEV group). Dogs that experienced no additional seizures were defined as responders, whereas those that showed additional seizure activity were classified as nonresponders.

Results: Twenty-one dogs were assigned to the rectal LEV group, and 36 to control group. Given the small number of cases of SE, statistical analysis was performed only on patients with CS. The response rate was 94% in the rectal LEV group and 48% in the control group ($P < .001$).

Conclusions and Clinical Importance: Rectally administered LEV combined with a standard treatment protocol provided good control of seizure activity in patients with CS. The validity of these results should be confirmed in a double-blinded, placebo-controlled clinical trial.

KEYWORDS

dogs, epilepsy, neurology, therapy

Abbreviations: AEM, antiepileptic medication; CS, cluster seizures; IVETF, International Veterinary Epilepsy Task Force; LEV, levetiracetam; PB, phenobarbital; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy; VTH, Veterinary Teaching Hospital.

1 | INTRODUCTION

Medical literature provides evidence for progressive loss of efficacy of benzodiazepines during prolonged seizure activity because of a functional alteration of gamma aminobutyric acid-A receptors that are internalized into the cells.[1] This limitation has prompted investigation of other treatment options for the emergency management of these neurological conditions. Furthermore, in both human and veterinary medicine, treatment guidelines for cluster seizures (CS) and status epilepticus (SE) must balance the need for seizure control with the risk of dangerous adverse effects (eg, cardiorespiratory depression) associated with antiepileptic medication (AEM) administration.[1,2] To enhance the anticonvulsant action of AEMs and decrease the occurrence of adverse effects, the concept of early polytherapy recently has been introduced in human medicine.[3] Although the literature on early combined polytherapy is still limited, it is hypothesized that AEMs with different molecular mechanisms of action can be combined together so as to enhance their anticonvulsant properties.[4]

Because of its different mechanism of action, its favorable pharmacokinetics, and favorable safety profile, levetiracetam (LEV) has been investigated as a candidate for early combined polytherapy in human medicine. In particular, 2 experimental studies on mice and human patients have provided evidence of synergy between LEV and diazepam.[5,6] Levetiracetam use also has gradually increased in recent years in veterinary medicine as long-term monotherapy or pulse treatment given IV or PO in CS patients.[7,8] The latter treatment strategy has been proposed to avoid the induction of LEV tolerance as reported in both mice and dogs.[9,10]

The PO route can be easily employed by owners at home. However, the postictal phase in epileptic patients can impair swallowing ability, preventing use of the PO route because of aspiration risk, thus delaying the initiation of treatment. For this reason, we evaluated another route of administration of LEV in epileptic patients.

The pharmacokinetics of LEV after rectal administration in both healthy and epileptic dogs recently has been investigated. These studies indicated that administration of 40 mg/kg per rectum achieved the minimum target concentration of 5 μg/mL 10 and 30 minutes after the administration in healthy and affected dogs, respectively.[11,12]

Our aim was to investigate the clinical efficacy of rectally administered LEV in preventing additional seizures when administered to dogs presented for CS and SE. We hypothesized that administration of LEV rectally in addition to a standard treatment protocol would provide better control of seizure activity as compared with the standard treatment protocol alone.

2 | MATERIALS AND METHODS

The study was approved by the Bioethics Committee of the University of Turin (protocol #9834, dated February 25, 2016). Written informed consent was obtained from the dog owners before enrollment in this open-label clinical trial.

2.1 | Dogs

Dogs referred to the Veterinary Teaching Hospital (VTH) of the Department of Veterinary Science, Turin, between September 2016 and May 2018 for CS or SE of any type were eligible for inclusion in the study. No age, breed, or sex limitations were applied. If the dogs were referred to the VTH for CS or SE multiple times during the study period, only the first hospitalization was considered for the purpose of the study. Status epilepticus and CS were defined according to the definitions of the International Veterinary Epilepsy Task Force (IVETF) consensus report.[13]

Minimum database blood tests, including CBC, serum biochemistry profile, serum electrolyte concentrations, blood ammonia concentration, and preprandial and postprandial bile acid concentrations were performed. All dogs underwent neurological examination by a board-certified neurologist (A.D.) or a neurology resident (G.C.) under the supervision of the board-certified neurologist. Dogs were excluded if already under treatment with LEV for long-term seizure control or if further diagnostic tests indicated reactive seizures.

A diagnosis of idiopathic epilepsy was made according to the IVETF consensus report,[14] whereas a diagnosis of structural epilepsy was suspected when reactive causes of seizures were excluded, along with signalment, history, and an abnormal interictal neurological examination. Magnetic resonance imaging results, cerebrospinal fluid analysis results or both were included if available but were not required for the diagnosis of structural epilepsy.

Eight dogs included in the present study had been enrolled in a previous study evaluating the pharmacokinetics of LEV administered per rectum in dogs with CS and SE.[12]

2.2 | Study design

At the time of presentation to the VTH, a standard care protocol comprising rectal/IV diazepam (at a dosage of 1-2 mg/kg if the patient was seizuring at presentation) followed by IV phenobarbital (PB; 4-5 mg/kg q8h) was administered to each dog. After administration of these medications, the patients were selected to receive either a single dose of rectal LEV at a dosage of 40 mg/kg in association with PB q8h (rectal LEV group) or no other medications except for PB q8h (control group). No proper randomization of patients between the 2 study groups was performed because the dog owner, through written informed consent, made the final decision for assigning the dog to the rectal LEV group or control group.

The LEV suspension employed was created and administered as previously reported.[12] The dogs were monitored for additional seizures for the first 24 hours after admission and until discharge. Dogs that experienced no additional seizures in the first 24 hours were defined as responders, whereas those that showed additional seizure activity and therefore required other AEMs in the first 24 hours were classified as nonresponders.

2.3 | Statistical analysis

Statistical analysis was performed using commercially available software (R 3.5.2—R Core Team, 2018). Data were analyzed for normality using the Shapiro-Wilk test and were found to be nonparametric. Numerical data (age and body weight) were tested using the Wilcoxon rank sum test; categorical data (sex, reason for presentation, and seizure etiology) were tested using the test for equality of proportions or Chi-square test, where appropriate. A comparison between the number of responders versus nonresponders between the 2 groups was carried out using Fisher's 2-tailed exact test. In addition, a comparison between the number of responders versus nonresponders in relation to the etiology (idiopathic versus suspected or confirmed structural epilepsy) of seizure activity was performed using Fisher's 2-tailed exact test. Results were considered statistically significant at a significance level of $P < .05$.

3 | RESULTS

Sixty-six dogs were referred because of CS and SE to the VTH between September 2016 and May 2018. Nine of 66 patients were excluded from the study. Four patients were excluded because further investigations led to a diagnosis of reactive seizures, 4 because they were already being treated with LEV for long-term seizure control, and 1 patient because the episodes possibly related to seizure activity were witnessed only by the owner and no proper evidence of epileptic seizures could be obtained, respectively.

In total, 57 patients were included in the study: 21 dogs were assigned to the rectal LEV group and received 40 mg/kg of LEV per rectum in addition to the standard protocol, and 36 were assigned to the control group and received only the standard care protocol. Table 1 presents signalment and patient characteristics. There were no statistically significant differences in median age, sex, body weight, reason for presentation, and seizure etiology between the LEV and the control group.

A diagnosis of idiopathic epilepsy (Tier I or II confidence level using the IVETF consensus report) was present in 16 patients in the control group (44%) and in 12 patients in the rectal LEV group (57%). A structural etiology was suspected or confirmed in 20 patients (56%) in the control group and in 9 (43%) in the rectal LEV group. Table 1 presents details on the definitive diagnoses.

Given the small number of patients admitted with SE in both groups, statistical analysis was performed taking into consideration only patients affected by CS. Fisher's 2-tailed exact test showed a statistically significant difference ($P < .001$) between the 2 groups: the response rate was 94% (17/18) in the rectal LEV group and 48% (15/31) in the control group.

Fisher's 2-tailed exact test showed no statistically significant differences between the response rate of patients affected by idiopathic and those with suspected or confirmed structural epilepsy ($P = 1$). When the test was performed on each group separately, no statistically significant differences were found (rectal LEV group, $P = .48$; control group, $P = 1$).

TABLE 1 Information on patients included in the study for each study group. No statistically significant differences were found between the 2 study groups in age, sex, body weight, reason for presentation, and seizure etiology. The smallest *P* value obtain was .08 (sex)

	Rectal LEV group	Control group
Breed	Mixbreed (8/21), French Bulldog (3/21), Boxer (2/21), Corso Dog (2/21), German Shepherd (2/21), Bloodhound (1/21), Dachshund (1/21), Pyrenean Mountain Dog (1/21), Argentine Mastiff (1/21)	Mixbreed (14/36), Border Collie (3/36), Pinscher (2/36), Yorkshire Terrier (2/36), American Staffordshire (1/36), Bernese Mountain Dog (1/36), Breton (1/36), Cavalier King Charles Spaniel (1/36), Chihuahua (1/36), Dogue de Bordeaux (1/36), English Bulldog (1/36), German Shepherd (1/36), Golden Retriever (1/36), Labrador Retriever (1/36), Maltese (1/36), Poodle (1/36), Pug (1/36), Siberian Husky (1/36), Spitz (1/36)
Age	Median 75 (range, 49-113 months)	Median 68 (range, 31.5-93 months)
Sex	12 males (57%), 5 females (24%), 3 males neutered (14%), 1 female neutered (5%)	20 males (55%), 10 females (28%), 6 females neutered (17%)
Body weight	Median 24 (range, 16-28.7 kg)	Median 16 (range, 7.15-27.8 kg)
Epilepsy etiology	10 dogs Tier I idiopathic epilepsy, 2 dogs Tier II idiopathic epilepsy, 3 dogs intracranial neoplasia, 1 dog hemorrhagic stroke, 5 dogs suspected undefined structural epilepsy	9 dogs Tier I idiopathic epilepsy, 7 dogs Tier II idiopathic epilepsy, 2 dogs undefined degenerative disease, 2 dogs meningoencephalitis of unknown origin, 1 dog hydrocephalus, 1 dog intracranial neoplasia, 16 dogs suspected undefined structural epilepsy
Long-term AEMs	PB (5/21), PB and KBr (3/21), Imepitoin (1/21), none (12/21)	PB (10/36), PB and KBr (4/36), none (22/36)
Presentation	Generalized SE (3/21), CS (18/21)	Generalized SE (5/36), CS (31/36)

Abbreviations: CS, cluster seizures; KBr, Potassium Bromide; LEV, levetiracetam; PB, phenobarbital; SE, Status epilepticus; AEMs, antiepileptic medications.

4 | DISCUSSION

Our study provides preliminary evidence for the efficacy of rectally administered LEV when combined with a standard treatment protocol in preventing the onset of additional epileptic seizures in dogs with CS. Given the promising results of previous pharmacokinetics studies,[11,12] we evaluated the potential beneficial effect of rectally administered LEV combined with other AEMs in controlling seizure activity in dogs with CS. Our results show that dogs with CS treated using rectally administered LEV in addition to a standard treatment protocol consisting of diazepam and PB experienced substantially better control of seizures as compared with a control group of patients treated with AEMs using the standard treatment protocol alone. These results suggest that rectal administration could represent a viable alternative to PO administration of AEMs and therefore extend treatment options for the at-home management of these neurological emergencies before referral to a specialized veterinary clinic or hospital.

The lack of a placebo-controlled group of patients is the main limitation of our study. Of note, however, is that a reduction in placebo exposure recently has been advocated in human medicine. The sudden unexpected death in epilepsy (SUDEP) rate has been reported to be higher among placebo-treated participants of add-on treatment epilepsy trials in human medicine, suggesting that adding effective AEMs instead of placebo in epilepsy trials can decrease the risk of death of epileptic patients.[15]

Death during or immediately after seizure activity has been documented in epileptic dogs as well, suggesting that the concept of SUDEP also can be extended to veterinary patients.[16] The add-on administration of AEMs to a standard antiepileptic regimen therefore seems a valuable alternative to a placebo-controlled trial, even if the latter study design still represents the gold standard for treatment investigations.

In our study, allocation to the 2 groups was based on the dog owners' final decisions for their dogs to receive or not receive rectally administered LEV, and thus the lack of randomization is another study limitation. The decision to perform post hoc analysis only on the patients affected by CS was based on the few cases of SE enrolled in both study groups. However, the results obtained for this specific patient category were as promising as those obtained for both conditions, confirming the potentially beneficial effect of rectally administered LEV in addition to a standard treatment protocol.

Several patients were already being treated for long-term seizures with PB and potassium bromide. Unfortunately, information on serum concentrations of AEMs was not available or up-to-date for all patients included, and for this reason it was not taken into account in the final analysis of the study results. It is therefore impossible to evaluate the influence of these medications on patient outcome.

It has been hypothesized that dogs with structural epilepsy have a higher risk of death and presumably less control of seizure activity despite treatment with AEMs.[17-19] We found no statistically significant difference in response rate between dogs affected with idiopathic epilepsy (Tier I or II confidence level of the IVETF consensus report) and those with presumptive or confirmed structural epilepsy. However, the final diagnosis of structural epilepsy could not be established in all patients and, for this reason, the conclusions must be considered with caution.

In conclusion, based on our study data, rectally administered LEV combined with a standard treatment protocol seems to provide good control of seizure activity in patients with CS. Because of the low number of cases of SE included in our study, this assumption cannot be extended to SE, and further investigations are warranted.

The validity of our results should be confirmed in a double-blinded placebo-controlled clinical trial.

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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.

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

The study was approved by the Bioethics Committee of the University of Turin (protocol #9834 dated February 25, 2016).

HUMAN ETHICS APPROVAL DECLARATION

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

ORCID

Giulia Cagnotti https://orcid.org/0000-0003-1287-6723

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