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Original article

Comparison of pharmacokinetics of intragastrically and intrarectally administered levetiracetam tablets in healthy non-epileptic dogs

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Abstract

Canine status epilepticus (CSE) is characterized by epileptic seizures that are longer than 5 min or more than one seizure with incomplete recovery. Currently, diazepam suppositories are generally prescribed for CSE. Levetiracetam (LEV) is one of the newest antiepileptic drugs currently available. This study compared the pharmacokinetics of intragastric and intrarectal administration in oral formula of LEV in four healthy beagles as a reference data when the owner administers levetiracetam to dogs by himself at home. Blood for measuring plasma LEV concentrations was collected 0, 30, 60, 90, 120, 240, 360, and 540 min after LEV administration. The time to reach the maximum plasma concentration (Tmax) was markedly shorter with intrarectal administration (45±26 min) than with intragastric administration (270±99 min). Intrarectal administration of LEV tablets could be an effective option for treating canine seizures although it might be a limit for treating CSE because the absorption rate is not fast enough.

Key words: canine status epilepticus, dogs, intragastric administration, intrarectal administration, levetiracetam, pharmacokinetics

Introduction

Epilepsy is a brain disorder characterized by chronic recurrent seizures without identifiable causes; the most common are systemic tonic-clonic seizures. It is one of the most common neurological diseases in veterinary medicine. Epileptic seizures occur in 0.5-5.7% of dogs (Peters et al. 2014). Two or more seizures with incomplete recovery of consciousness or seizures that last longer than 5 min are defined as status epilepticus (SE) (Meland and Carrera-Justiz 2018). It is necessary to suppress SE as the patient is at risk of severe complications, such as hyperthermia and brain damage (Hardy et al. 2012). The first treatment option is intravenous diazepam, and additional drugs can be added as required (Patterson 2014). At home, a diazepam suppository

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is usually used for urgent administration by the owner (Leppik and Patel 2015). Levetiracetam (LEV) is used for maintenance therapy of epilepsy but can be used for the treatment of SE that does not respond to diazepam. Previously, LEV had been administered orally (Rossetti and Bromfield 2006). Although injectable LEV has recently become available (Hardy et al. 2012), LEV might be a useful emergency treatment if it could be administered at home for canine SE (CSE) by the owner.

Therefore, we postulated that it would be useful for owners to administer LEV for canine status epilepticus (CSE) at home. This study assessed the use of intrarectal LEV tablets as an emergency treatment of CSE by measuring plasma LEV concentrations after intragastric and intrarectal administration of an oral LEV formula in healthy dogs.

Materials and Methods

Four healthy beagles (three males, one female, aged 1-8 years; weight, 8.6-21 kg) owned by the Laboratory of Veterinary Diagnostic Radiology, Faculty of Agriculture, Iwate University (Iwate, Japan) were used. This experiment was approved by the experimental animals committee of Iwate University (approval no. A201559). Before the experiment, vital signs (body temperature, heart rate, and respiration rate), complete blood counts, blood biochemistry, and neurological parameters were assessed in all dogs. The neurological examination was repeated on days 1 and 7 after the end of the experiment to assess side effects of the drug. The dogs were first given oral LEV; then, LEV was administered rectally at least 1 week later.

The experiments were done under general anesthesia. For each dog, food was withheld for at least 12 h before anesthesia, and water was withheld for at least 2 h. A catheter was placed aseptically into the cephalic vein. Each dog was premedicated with butorphanol (0.2 mg/kg) and midazolam (0.3 mg/kg). Anesthesia was induced with propofol (7 mg/kg) and maintained with isoflurane. Vital signs (heart rate, respiratory rate, oxygen saturation rate, end-tidal carbon dioxide, and blood pressure) were monitored and recorded every 10 min. The LEV tablets were powdered and dissolved in 5 ml of tap water. A catheter was attached to an endoscope and inserted to observe LEV the intragastric LEV administration. Similarly, LEV was administered intrarectally at least 1 weak later. After administration, the catheter was flushed with a small volume of tap water to ensure that none of the solution remained in the catheter. After administering LEV, the endoscope was quickly withdrawn, and the anesthesia was stopped. Before intrarectal administration, feces were removed to the furthest extent possible. LEV was administered ca. 10 cm from the anus, which was then closed by hand until the dog woke up from anesthesia. The total duration of anesthesia in all cases was ca. 30 min. After intrarectal administration of LEV, two animals were not allowed to defecate until 90 min (nDef group), whereas the other two defecated within 30 min (Def group). In the Def group, large amounts of feces were observed endoscopically before intrarectal administration.

Blood was collected from the cephalic vein before (0 minutes) and at 30, 60, 90, 120, 240, 360 and 540 min after LEV administration. First, 1 ml of blood was aspirated with a syringe before the collection, and 2 ml of blood was collected using a different syringe for measuring plasma LEV concentration. The collected blood was quickly centrifuged (3,500 × g, 8 min, 20°C) and stored in a freezer at −80°C. The plasma LEV concentration was measured by an external commercial laboratory using liquid chromatography-tandem mass spectrometry at 1-2 days after sample collection.

Means±standard error of the mean were calculated for the following parameters: time to reach maximum plasma concentration (Tmax), maximum concentration (Cmax), and area under the curve from administration to 540 min (AUC).

Results

The mean Tmax for intrarectal and intragastric administration was 45±26 and 270±99 min, respectively (Table 1). Intrarectal administration produced a substantially faster response than intragastric administration did, although no statistical difference due to the number size. On the other hand, Cmax and AUC of intrarectal and intragastric administration were 33.5±3.9 μg/mL, 11,968±1,076 min · μg/mL and 23.1±13.2 μg/mL, 6,947±4,023 min · μg/mL, respectively. In contrast to Tmax, Cmax and AUC of intragastric administration were higher than those found after intrarectal administration.

Figure 1 shows the mean blood LEV concentrations in the dogs upon intragastric administration of LEV and changes in blood LEV concentrations after LEV was administered intrarectally. In case of dividing dDef group (black circles) and Def group (white circles) within intrarectal administration results, high Cmax and AUC values were observed in the nDef group, and these values were similar to those recorded after intragastric administration of LEV (each average was 35.7 μg/mL and 10,955 min · μg/mL versus 33.5±3.9 μg/mL and 11,968±1,076 min · μg/mL). By contrast, values in the Def group were lower than those recorded after intragastric administration of LEV (10.6 μg/mL and 2,940 min · μg/mL).

No neurological abnormalities were determined be-

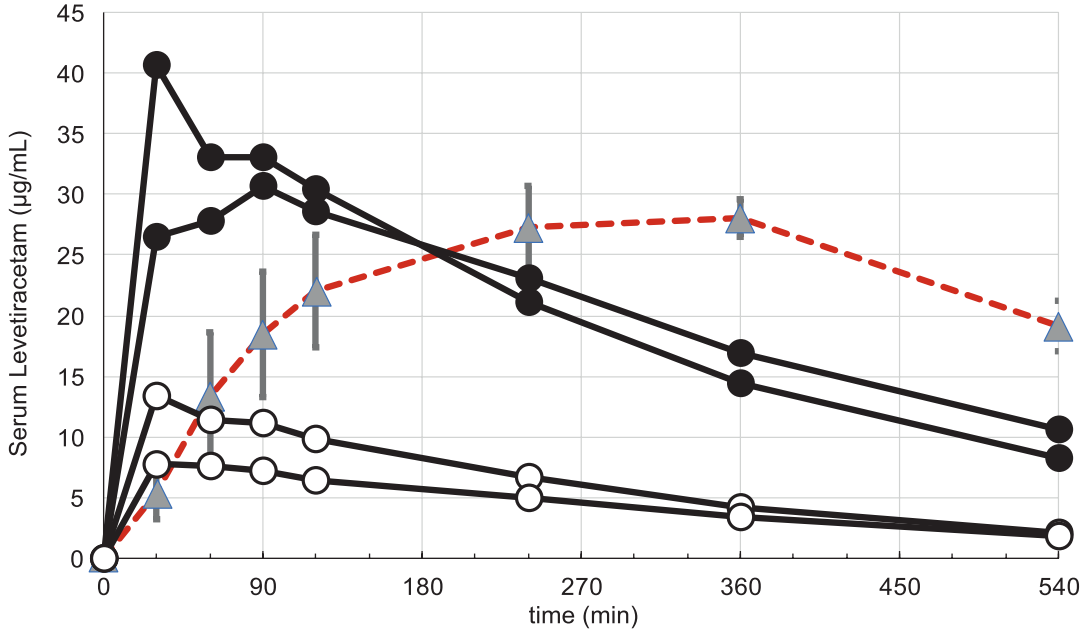

Fig. 1. Plasma levetiracetam concentrations (µg/dl) in four dogs at the time of blood collection after intrarectal (black or white circles and solid line) and intragastric (triangles and dotted lines) drug administration (vertical bars represent standard errors). The dogs of intrarectal administration group were classified into individuals having defecation within 30 minutes after drug administration (white circles) and individuals having no defecation (black circles).

Table 1. The time to reach the maximum levetiracetam (LEV) concentration (Tmax), maximum plasma concentration of LEV (Cmax), and area under the curve from administration to 540 min (AUC) following intragastric and intrarectal administration of LEV (40 mg/kg) in four beagles. Data are presented as the mean±standard error of the mean (SE)

	intragastric	intrarectal
Tmax (min)	270±99	45±26
Cmax (µg/mL)	33.5±3.9	23.1±13.2
AUC0-540 min (min · µg/mL)	11.968±1.076	6.947±4.023

fore or on days 1 and 7 after LEV administration, although immediately after awakening from anesthesia, all dogs exhibited mild depression or decreased postural reaction due to the effects of anesthesia.

Discussion

LEV is an antiepileptic drug with a new, effective mechanism of action. Misra et al. (2012) reported that LEV could control SE in 76.3% of humans. Diazepam and phenobarbital suppositories are currently used to treat dogs with epileptic episodes that occur at home. However, other options are needed when these drugs do not have a sufficiently strong effect on the seizures (Blades and Rossmeisl 2017). Therefore, we considered intrarectal administration of a LEV oral preparation dissolved in water as a method for treating CSE at home. We found that with intrarectal administration of LEV, sufficient blood concentrations were attained under certain conditions.

The Tmax after intrarectal administration of LEV was much shorter than that after intragastric administration, and a similar plasma LEV concentration was obtained within 30 min of administration in all dogs. By contrast, a longer time was required to increase the plasma LEV concentration with intragastric administration. Therefore, intrarectal LEV can be used as an emergency treatment to increase plasma LEV concentrations quickly. It can also be used easily by the owner to treat CSE. However, although a dog owner can easily administer LEV intrarectally to treat CSE, the treatment is considered insufficient because the mean Tmax is 45 min; thus, this method can only be used to treat seizure clusters.

Some LEV is metabolized by cytochrome P450 enzymes in the liver, but most of the LEV is excreted unchanged in the urine (Tulloch et al. 2012). When administered intrarectally, the absorbed drug enters the vena cava without passing through the liver and then goes directly into the systemic circulation. Because LEV exhibits almost no first-pass effect due to the liver with intrarectal administration, it has a bioavailability of almost 100% (Moore et al. 2011). By contrast, intragastric LEV, i.e. with oral medication, is mainly absorbed

in the small intestine, from where it passes through the liver before entering the systemic circulation. This is why intrarectal LEV is rapidly absorbed and the plasma concentration rises quickly.

Plasma LEV levels did not increase markedly in two individuals (Def group) after intrarectal administration, probably because the LEV solution administered intrarectally was excreted with feces soon after administration. As the tap water used for dissolving the LEV likely leaked out, an appropriate solution volume should be used in each individual for clinical implementation.

Levetiracetam has a wide range of efficacy, and the dose range for treating human SE is 12-46 μg/ml (Yang et al. 2002, Perrenoud et al. 2018) or 5-30 μg/ml (Rossetti and Bromfield 2006). However, the therapeutic dose range for dogs is unknown. In this study, plasma concentrations in the nDef group reached 10 μg/ml ca. 10 min after administration, whereas those in the Def group reached 5 μg/ml within 30 min. Therefore, assuming that the LEV therapeutic dose in dogs with SE is 5-46 μg/ml, which is similar to that in human SE, intrarectal administration should increase the plasma concentrations to an effective level.

After intrarectal administration in the nDef group, Cmax and AUC were near to those recorded after intragastric administration, whereas Def group values were only one third of those observed after intragastric administration. These results suggest that if solution leakage does not occur, intrarectal administration has the same therapeutic effect as intragastric administration. Thus, intrarectal administration is a viable option for delivering LEV.

The limitations of this study are the small number of samples, the use of normal dogs, and the effects of anesthesia. However, the similarity of the plasma LEV concentration curves in the two dogs administered LEV intrarectally suggests that the results obtained are reasonable despite the small number of cases. Moreover, although the effect on CSE was not investigated, with the plasma LEV concentrations attained, a therapeutic effect can be expected (Packer et al. 2015). As anesthesia had the same effect on each dog, the actual clinical effects may have been underestimated in this study (Patterson et al. 2008).

In this study, we compared the plasma LEV concentrations after intragastric and intrarectal administration of an oral LEV formula, in the context of using these two methods as emergency treatment for dogs with CSE. The results indicate that intrarectal LEV administration is convenient but insufficient for CSE treatment due to a long Tmax. Nevertheless, intrarectal LEV administration may be a viable emergency option for dogs with seizure clusters.

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