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Telmisartan as an add-on treatment for dogs with refractory idiopathic epilepsy: a nonrandomized, uncontrolled, open-label clinical trial

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OBJECTIVE
To evaluate the effect on seizure frequency of add-on telmisartan treatment in dogs with refractory idiopathic epilepsy.

ANIMALS
11 client-owned dogs with idiopathic epilepsy and ≥ 2 generalized seizures/mon that were currently being treated with ≥ 2 antiepileptic drugs.

PROCEDURES
Telmisartan was administered at a dosage of 0.25 to 1 mg/kg, PO, every 12 hours for 4 to 16 months. Seizure frequencies before and during telmisartan treatment were recorded.

RESULTS
10 dogs completed the 4-month treatment protocol. One dog was excluded owing to a transient increase in serum creatinine concentration; no adverse effects of telmisartan were observed in the remaining 10 dogs. A reduction in seizure frequency greater than an estimated expected placebo effect of 30% was evident in 7 of the 10 dogs. Long-term (12 to 16 months) follow-up information was available for 6 dogs, of which 4 had a further reduction in seizure frequency. Differences in seizure frequency were not statistically significant. No significant difference was found in serum phenobarbital concentration throughout the treatment period in the 7 dogs that were tested.

CLINICAL RELEVANCE
Telmisartan has the potential to reduce seizure frequency when administered as an add-on antiepileptic drug in dogs with refractory idiopathic epilepsy. A randomized, double-blind, placebo-controlled trial is needed to determine the true efficacy of telmisartan. On the basis of our results, a sample size of 54 dogs with refractory idiopathic epilepsy would be needed.

Epilepsy is the most common chronic neurologic disease in dogs. It can be either idiopathic or acquired as a result of traumatic, ischemic, infectious, or inflammatory causes.[1–3] Despite the availability of effective antiepileptic drugs (AEDs), 20% to 30% of dogs remain refractory to treatment, and there is no cure for the disease.[4] Pathological processes associated with epilepsy, including seizures, often involve an increase in permeability of the blood-brain barrier (BBB).[5–9] It has therefore been hypothesized that vascular lesions play a key role in the pathophysiology of the disease.[5–9]

The BBB is a complex and tightly regulated structural and functional interface between the CNS and its vasculature.[5] Dysfunction of the BBB causing leakage of plasma constituents into the extracellular neuronal environment has been documented in various CNS diseases, including stroke, traumatic injuries, intracerebral hemorrhage, tumors, epilepsy, and inflammatory and neurodegenerative disorders.[6–9] Although the mechanisms underlying BBB dysfunction are only partly understood, experimental studies[6,10–14] have demonstrated that exposing the neocortex in rats to either serum albumin or transforming growth factor-β induces epileptogenesis (ie, spontaneous development of seizures and epilepsy). Albumin has been shown to bind to the transforming growth factor-β receptor ALK5 on astrocytes,[6,13] leading to a characteristic transcriptional response[14] that results in reactive astrogliosis and neuroinflammation. These responses are followed by changes in the extracellular matrix,[15] reduced inhibition of

γ-aminobutyric acid, and generation of new excitatory synapses.[16,17] Conversely, suppression of transforming growth factor-β signaling in the presence of albumin blocks the neuroinflammatory response and prevents epilepsy.[13,14]

Using dynamic contrast-enhanced MRI, we previously demonstrated clinically relevant BBB dysfunction in 21% and 71% of dogs with naturally occurring epilepsy when the whole brain or the piriform lobe, respectively, was analyzed.[17] BBB leakage was associated with glial activation and neuroinflammation in a subset of dogs in which a neuropathological examination was performed.[17] These findings were similar to those described for rodents in which the brain was exposed to albumin and for resected tissues from human patients with epilepsy[6,7,18] and suggest that the disrupted BBB may be a novel target for treatment.[13,19] Losartan, an angiotensin II receptor blocker, has been shown to block transforming growth factor-β signaling and prevent development of epilepsy induced by BBB dysfunction.[13] Similarly, losartan has been shown to decrease seizure severity or enhance the efficacy of AEDs in 2 models of epilepsy involving rodents.[20,21] Telmisartan is a related angiotensin II receptor blocker that is often used for the treatment of hypertension in dogs and has been similarly reported to suppress transforming growth factor-β signaling.[22] Although no data are available regarding the dosage of telmisartan needed to induce an antiepileptic effect in dogs, a previous study[23] found that it was safe when administered at dosages ranging from 0.3 to 3 mg/kg/d.

Given this background, we believe that telmisartan may be a useful adjunctive antiepileptic treatment in dogs. Specifically, the objective of the study reported here was to evaluate the effect on seizure frequency of add-on telmisartan treatment in dogs with refractory idiopathic epilepsy.

Materials and Methods

Ethical considerations

The study protocol was approved by the Koret School of Veterinary Medicine Animal Care and Use Committee (reference No., KSVM-TH/26_2016). Owners of all dogs included in the study provided signed informed consent prior to enrollment in the study.

Study design

The study was designed as a non-randomized, prospective, open-label clinical trial without a control group. The study was conducted at the Koret School of Veterinary Medicine Teaching Hospital. Owners and attending clinicians were not blinded to the intervention. Owing to the novelty of telmisartan treatment for this indication, no pilot data were available with which to perform a power analysis or sample size calculation. Therefore, sample size was not predetermined for this study. A key objective was to provide these data for future studies.

Animals

Dogs treated at the Koret School of Veterinary Medicine Teaching Hospital because of idiopathic epilepsy were evaluated for the study. Dogs were eligible for inclusion in the study if they met the tier II confidence level for a diagnosis of idiopathic epilepsy, as recommended by the International Veterinary Epilepsy Task Force,[24] with the exception that analysis of serum bile acid concentrations was not designated as an inclusion criteria. In addition, results of an MRI, CSF analysis, CBC, serum biochemical analyses, and urinalysis performed at the time of diagnosis (0 to > 1 year prior to the present study) had to have been normal. Finally, dogs had to have had a history of recurrent seizures for ≥ 1 year and a detailed and complete record of seizure frequency with ≥ 2 seizures/mo for at least 3 consecutive months during which the dog was appropriately treated with ≥ 2 conventional AEDs. For this study, we did not adhere to the inclusion criteria defined for pharmacoresistance by the International Veterinary Epilepsy Task Force because some dog owners were on the verge of euthanizing their dogs and were reluctant to pay for the additional testing needed to evaluate pretreatment AED concentrations.

On admission, all dogs underwent physical and neurologic examinations by a board-certified veterinary neurologist as well as serum biochemical testing and a CBC. Dogs were excluded if a cause of the seizures was identifiable (eg, a brain neoplasm or trauma); if they had concomitant disease such as liver, kidney, or heart disease; or if they had undergone surgery in the month before enrollment in the study. Breed, sex, and age were recorded during the enrollment appointment. Owners were asked to sign a consent form indicating their understanding that telmisartan was being used in an extralabel manner and that possible adverse effects of the drug included low blood pressure and increased serum creatinine concentration. Blood pressure and serum creatinine concentration were measured in all dogs and dogs with a median arterial blood pressure < 70 mm Hg or a serum creatinine concentration > 1.3 mg/dL were excluded.

Categorization of seizure control

The primary goal was that dogs would be seizure free, which was defined as an interictal interval of at least 3 months and > 3 times the longest pretreatment interictal interval. The secondary goal was a ≥ 30% reduction in seizure frequency.[25]

Telmisartan treatment

Telmisartan was given at an initial dosage of 0.25 mg/kg, PO, every 12 hours for the first week. The dosage was then increased to 0.5 mg/kg, PO, every 12 hours and to 1 mg/kg, PO, every 12 hours if serum creatinine concentration was unchanged. Serum creatinine concentration and blood pressure were checked during weekly visits to the Koret School of Veterinary Medicine Teaching Hospital for the first 3 weeks and then monthly by the referring veterinarian. Owners were asked to record details of all seizure episodes including date, time, duration, and possible inciting events. No changes to the antiepileptic treatment regimen were made other

than the addition of telmisartan. Adverse effects that required discontinuation of the treatment were a serum creatinine concentration > 1.3 mg/dL, a mean arterial blood pressure < 70 mm Hg, or any other unexpected adverse effects. Owners were asked to report any unexpected change in their dog's appetite, activity level, or general behavior.

Four months after the initiation of treatment, complete neurologic and physical examinations were performed during a follow-up visit to the Koret School of Veterinary Medicine Teaching Hospital, and seizure records were collected. Owners of dogs that achieved either of the study goals who elected to continue telmisartan treatment were instructed to monitor renal function once a month with their local veterinarian. These dogs were reevaluated after 12 or 16 months of treatment, and the additional data on seizure frequency were recorded and analyzed. Owners of dogs that failed to achieve the primary or secondary study goal were advised to stop telmisartan treatment.

Statistical analysis

All statistical analyses were conducted with a commercially available software program (MatLab software; Mathworks Inc). Data were summarized as median and range. A paired, 2-sided, nonparametric Wilcoxon signed-rank test was used to compare seizure frequencies before and during treatment. Pretreatment seizure frequency was calculated for the 3 months before the initiation of telmisartan administration. Posttreatment seizure frequency was calculated for the first 4 months of telmisartan administration and, for dogs that received long-term treatment, for the following follow-up treatment from month 4 to month 12 or 16. To take into consideration a possible placebo effect, which was estimated as a 30% reduction in seizure frequency,[26] the pretreatment seizure frequency of each dog was reduced by 30% prior to comparison with the seizure frequencies after 4 months or after 12 or 16 months of telmisartan treatment. For all analyses, values of $P < 0.05$ were considered significant.

Results

Animals

Eleven dogs met the inclusion criteria, including 5 mixed-breed dogs, and 1 each of the following breeds: French Bulldog, Poodle, Cane Corso, German Shepherd Dog, Boxer, and Labrador Retriever. One dog, a 2.5-year-old Poodle, was excluded from the study owing to a transient increase in serum creatinine concentration to 1.54 mg/dL (reference range, 0.5 to 1.3 mg/dL) 2 weeks after initiation of telmisartan treatment. In this dog, serum creatinine concentration returned to reference limits when telmisartan administration was stopped. Of the 10 dogs that completed the first 4-month treatment period, 6 were castrated males, 2 were spayed females, and 2 were sexually intact males **(Supplementary Table S1)**. Median age was 5.5 years (range, 3 to 10 years), and median body weight was 30.5 kg (range, 11 to 42 kg).

Median duration of idiopathic epilepsy prior to enrollment in the study was 4 years (range, 1.5 to 6 years). Two dogs with cluster generalized tonic-clonic seizures (3 to 12 seizures/event) had 1 and 0.4 seizure events/mo and were hospitalized during seizure events. The typical pattern for the remaining 8 dogs was single generalized tonic-clonic seizures, with pretreatment seizure frequency ranging from 3.5 to 15.5 seizure events/mo. All 10 dogs were routinely receiving phenobarbital in combination with 1 to 3 additional AEDs for at least 3 months prior to study enrollment. Plasma phenobarbital concentration prior to the study was within the therapeutic range (ie, 15 to 40 µg/mL) in 9 of the 10 dogs that completed the study (median, 28.1 µg/mL; range, 19.8 to 39.5 µg/mL). Pretreatment serum creatinine concentration ranged from 0.78 to 1.15 mg/dL (reference range, 0.5 to 1.3 mg/dL). One dog had a mean systolic and diastolic blood pressures of 185 and 95 mm Hg, respectively, on 3 consecutive measurements on the same day. The dog was still included in the study, and blood pressures were 114 and 70 mm Hg, respectively, when the dog was reevaluated 1 week later. In this dog, idiopathic epilepsy had been diagnosed 2 years earlier, and the dog had been routinely monitored prior to inclusion in the study. Therefore, high blood pressure was not considered the primary cause of the epilepsy. Adverse effects associated with AED administration were reported by most owners before the initiation of telmisartan treatment and included polydipsia, polyphagia, polyuria, weakness, and general fatigue. Blood pressure and serum creatinine concentration the week after treatment initiation were within reference limits in all 10 dogs. Therefore, the telmisartan dosage was increased to 0.5 mg/kg, PO, every 12 hours. Similarly, blood pressure and serum creatinine concentration were within reference limits 2 weeks after treatment initiation in all 10 dogs, and the telmisartan dosage was further increased to 1 mg/kg, PO, every 12 hours for the remainder of the study. In 4 dogs, telmisartan administration was discontinued after 4 months. Four dogs received telmisartan for 12 months, and 2 dogs received telmisartan for 16 months.

One dog with cluster seizures achieved the primary goal of being seizure free after 4 months of telmisartan treatment, and 7 of the 10 dogs (the 2 with cluster seizures and 5 with single generalized seizures) achieved the secondary goal of a ≥ 30% reduction in seizure frequency. During the first 4 months of telmisartan treatment, median seizure frequency for all 10 dogs was reduced by 62.5% from 5.5 seizure events/mo (range, 0.4 to 15.5 seizure events/mo) to 2.37 seizure events/mon (range, 0 to 12 seizure events/mo; $P = 0.0045$; **Figure 1**).

Five dogs that achieved the secondary goal and 1 dog whose owner elected to remain in the study continued treatment for an additional 8 or 12 months. For these 6 dogs, median seizure frequency was reduced by 75% from 5.5 seizure events/mo (range, 0.4 to 8 seizure events/mo) to 0.37 seizure events/mo (range, 0.1 to 7 seizure events/mo; $P = 0.15$; Figure 1). One of these dogs relapsed after the 12-month follow-up examination while still receiving telmisartan and again had seizures at the pretreatment frequency.

When correcting for the placebo effect, median seizure frequency was not significantly reduced after 4 months of telmisartan treatment or after 12 or 16

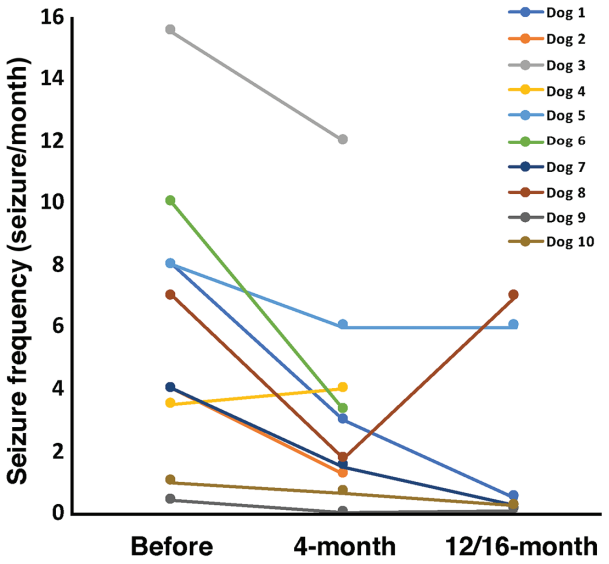

Figure 1—Seizure frequency (seizure events/mo) in 10 dogs with refractory idiopathic epilepsy (ie, ≥ 2 generalized seizures/mo) treated with telmisartan as an add-on to their current antiepileptic drug regimen. Seizure frequency was calculated as the mean frequency during the 3 months before telmisartan administration (Before), during the initial 4 months of telmisartan administration (4-month), and from month 4 to month 12 or 16 of treatment for dogs (n = 6) that received telmisartan long-term (12/16-month).

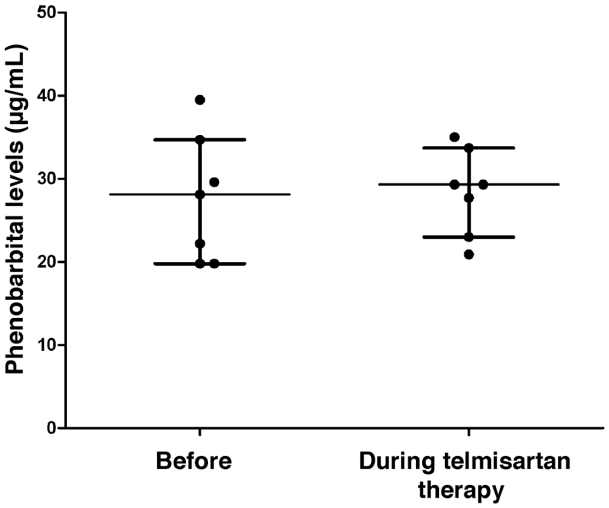

Figure 2—Scatterplots of serum phenobarbital concentrations in 7 of the dogs in Figure 1 before and during telmisartan treatment. In each plot, the center horizontal line represents the median, and the whiskers represent the 95% CI for the data. Concentrations did not differ significantly between time points.

months of treatment. However, 4 of the 6 dogs that were treated for 12 or 16 months achieved the secondary goal of a ≥ 30% reduction in seizure frequency.

Median serum phenobarbital concentration did not significantly change in the 7 dogs that had pre- and posttreatment concentrations measured **(Figure 2)**. Serum phenobarbital concentration was not measured in the remaining dogs owing to financial limitations.

Discussion

Results of the present study suggested that telmisartan may potentially reduce seizure frequency when administered as an add-on AED in dogs with refractory idiopathic epilepsy. However, our study was underpowered to answer the research question when adhering strictly to International Veterinary Epilepsy Task Force guidelines and, in particular, to the International Veterinary Epilepsy Task Force's definition of pharmacoresistance. An appropriately powered, randomized, double-blind, placebo-controlled trial is needed to determine the true efficacy of telmisartan. On the basis of our results, we can state that a sample size of 54 dogs (27 in each group) with refractory idiopathic epilepsy would be needed.

Telmisartan is routinely used to treat proteinuria and hypertension in dogs and has minimal adverse effects in dogs with normal blood pressure.[27,28] This was supported by our results, as we did not identify clinically relevant decreases in blood pressure during the course of the study. Because < 3% of telmisartan is metabolized by glucuronidation in the liver and > 97% is eliminated unchanged via the bile and feces,[29–31] we anticipated minimal interactions with other AEDs. Indeed, in the 7 dogs tested, posttreatment serum phenobarbital concentrations were not significantly different from pretreatment concentrations.

The potential benefit of telmisartan as an adjunctive treatment in dogs with idiopathic epilepsy is supported by studies[19,30] demonstrating an association between BBB dysfunction, activation of transforming growth factor-β signaling, and epileptogenesis. Furthermore, BBB dysfunction was demonstrated in 21% of dogs with idiopathic epilepsy with dynamic contrast-enhanced MRI,[18] and this dysfunction could potentially account for the poor response to common AEDs in some dogs with idiopathic epilepsy, included dogs in the present study. Unfortunately, dynamic MRI for detection of BBB dysfunction was not available for dogs in the present study, and we could not test whether response to telmisartan treatment was associated with the extent of BBB dysfunction. We also cannot say, therefore, whether any positive effects of telmisartan were associated with repair of the BBB or were a result of direct effects on the neural network. It is possible that the positive effects of telmisartan were due to its neuroprotective features, which have been demonstrated previously,[32–35] or were a result of increases in blood concentrations of an AED other than phenobarbital, such as potassium bromide, imepitoin, or levetiracetam. On the basis of our results, after correcting for a possible placebo effect, 4 of 10 dogs with idiopathic epilepsy and ≥ 2 generalized seizures/mo may respond to telmisartan treatment when given at the described dosage in conjunction with conventional AEDs.

For dogs in the present study, telmisartan was the third or the fourth AED that was administered. Subjectively, we did not identify any association between the other AEDs given and the response to telmisartan, but a larger group of dogs is needed to answer this question. As mentioned, we could not determine whether

telmisartan exerts its antiepileptic effect by increasing the concentrations of other AEDs. However, behavioral changes such as lethargy or sedation, which are common effects of increased AED blood concentrations, were not reported by any of the owners when telmisartan was administered. Moreover, owners of 6 of the 10 dogs included in the study elected to continue treating their dogs with telmisartan beyond the initial 4-month study period on the basis of its efficacy and lack of noticeable adverse effects. Quality of life was not assessed in this study but should be assessed in future studies to evaluate the effect of the drug on the wellbeing of dogs and their owners. One of these dogs was later reported to relapse to its pretreatment seizure frequency while still receiving telmisartan. Because no other drug was found to be effective for this dog, the owner had elected to continue with telmisartan treatment for 12 months.

Another mechanism by which telmisartan may potentially exert its antiepileptic activity is through its effects on maintaining and increasing regional cerebral blood flow.[36] Telmisartan has been shown to affect the renin-angiotensin system in the CNS by blocking the angiotensin II type 1 receptor[37,38] or by increasing the production of nitric oxide in endothelial cells, causing blood vessel relaxation and preserving cerebral blood flow in animals with experimentally induced brain insult.[39,40]

The dosage used in the present study was based on results of a previous study that analyzed the effect of telmisartan on renal function.[23] It is possible that a higher dosage of telmisartan would be more efficacious in reducing seizure frequency. Future studies should examine the proposed mechanisms whereby telmisartan reduces the frequency of epileptic seizures, test the hypothesis that imaging of BBB function could serve as a prognostic and pharmacologic biomarker for the therapeutic effect of telmisartan, and measure serum concentrations of all AEDs administered during telmisartan treatment. In addition to evaluating the efficacy of telmisartan as an add-on AED, these studies may help identify specific subsets of dogs that are more likely to benefit from the addition of this drug.

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Supplementary Materials

The supplementary table is available at the journal website: avmajournals.avma.org