Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy

Curtis W. Dewey, DVM, MS, DACVIM, DACVS; Sofia Cerda-Gonzalez, DVM, DACVIM; Jonathan M. Levine, DVM, DACVIM; Britton L. Badgley; Julie M. Ducoté, DVM, DACVIM; Gena M. Silver, DVM, DACVIM; Jocelyn J. Cooper, DVM; Rebecca A. Packer, DVM, MS, DACVIM; James A. Lavely, DVM, DACVIM

Objective—To assess tolerability and short-term efficacy of oral administration of pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with poorly controlled suspected idiopathic epilepsy.

Design—Open-label, noncomparative clinical trial.

Animals—11 client-owned dogs suspected of having idiopathic epilepsy that was inadequately controlled with phenobarbital, potassium bromide, or a combination of these 2 drugs.

Procedures—Dogs were treated with pregabalin (3 to 4 mg/kg [1.4 to 1.8 mg/lb], PO, q 8 h) for 3 months. Number of generalized seizures in the 3 months before and after initiation of pregabalin treatment was recorded. Number of responders (≥50% reduction in seizure frequency) was recorded, and seizure frequency before and after initiation of pregabalin treatment was compared by use of a nonparametric Wilcoxon signed rank test.

Results—Seizures were significantly reduced (mean, 57%; median, 50%) after pregabalin administration in the 9 dogs that completed the study; 7 were considered responders with mean and median seizure reductions of 64% and 58%, respectively. Adverse effects for pregabalin were reported in 10 dogs. Mean and median plasma pregabalin concentrations for all dogs were 6.4 and 7.8 µg/mL, respectively.

Conclusions and Clinical Relevance—Pregabalin may hold promise as a safe and effective adjunct anticonvulsant drug for epileptic dogs poorly controlled with the standard drugs phenobarbital or potassium bromide. Adverse effects of pregabalin appeared to be mild. Additional studies with larger numbers of dogs and longer follow-up intervals are warranted. (J Am Vet Med Assoc 2009;235:1442–1449)

Idiopathic epilepsy is a common and challenging problem in dogs, with estimates that 25% to 30% of these patients are poorly controlled when treated with the standard anticonvulsant drugs phenobarbital and potassium bromide. In addition to the adverse emotional and financial effects that seizure activity has on dog owners, there is evidence that poorly controlled seizure activity in epileptic dogs administered standard treatments has a substantial negative impact on patient lifespan. Despite the addition of several new anticonvulsant drugs for use in dogs during the past 10 to 15 years, there is still a paucity of safe and effective alter-native anticonvulsant drugs for epileptic dogs that are poorly controlled by administration of phenobarbital, potassium bromide, or a combination of these 2 drugs.

Pregabalin (S-[-])-3-isobutyl GABA) is a newly introduced GABA analogue that is structurally similar to gabapentin. The main mechanism of action for pregab-
al is believed to involve interaction with the \( \alpha_\delta \) subunit of neuronal voltage-gated calcium channels. Both gabapentin and pregabalin are believed to exert their positive clinical effects primarily through this mechanism, with pregabalin having an increased binding affinity for the \( \alpha_\delta \) subunit. Binding of a drug to the \( \alpha_\delta \) subunit site leads to a decrease in intracellular calcium ion influx; this in turn results in a subsequent reduction in release of excitatory neurotransmitters (eg, glutamate, norepinephrine, or substance P) into the synaptic cleft. Pregabalin is considered the successor to (ie, next generation of) gabapentin. Pregabalin also has a higher oral bioavailability and longer elimination \( t_{1/2} \) in humans, compared with those for gabapentin. In addition, pregabalin is suspected to be a more potent anticonvulsant and antinociceptive agent than gabapentin on the basis of experimental studies in rodents and clinical trials in humans.

To our knowledge, there is no available literature regarding the clinical use of pregabalin in dogs, although there is evidence supporting the efficacy of gabapentin in this species as an anticonvulsant drug.

Overall, the responder rate of refractory epileptic dogs treated with gabapentin as an adjunct drug in 2 clinical reports was approximately 41% to 55%. In one of these reports, there was a significant overall reduction in seizures by use of gabapentin, whereas in the other report, gabapentin use did not result in a significant overall reduction in seizures. The elimination \( t_{1/2} \) of gabapentin in dogs is 3 to 4 hours. In a study in which investigators evaluated the pharmacokinetics of administration of a single dose of pregabalin to clinically normal dogs, the mean elimination \( t_{1/2} \) of pregabalin was approximately 7 hours. In addition, the mean time that the plasma concentration of pregabalin remained within or greater than the lower limit of the reported therapeutic range in humans (2.8 \( \mu \)g/mL) was approximately 11 hours. Those authors theorized that pregabalin, a potentially more potent anticonvulsant drug with a longer elimination \( t_{1/2} \) than its predecessor gabapentin, would be an effective adjunct treatment in most poorly controlled epileptic dogs. The purpose of the study reported here was to evaluate the short-term efficacy and tolerability of pregabalin as an adjunct orally administered anticonvulsant treatment in dogs with suspected idiopathic epilepsy poorly controlled by administration of phenobarbital, potassium bromide, or a combination of these 2 drugs.

Materials and Methods

**Study design**—The study was conducted as an open-label, noncomparative clinical trial (ie, owners and investigators were not blinded as to treatments administered to each dog, and the drug was not compared against a placebo or another drug). The study was approved by the Institutional Animal Care and Use and Committees at Cornell University, Texas A&M University, and Purdue University. Owners of all dogs enrolled in the study provided written consent.

**Animals**—Dogs were eligible for inclusion in the study when they satisfied the criteria for idiopathic epilepsy and were considered poorly controlled with standard treatment (phenobarbital, potassium bromide, or a combination of the 2 drugs) for this condition. Criteria for a diagnosis of suspected idiopathic epilepsy included onset of generalized seizure activity between 1 and 5 years of age; clinically normal neurologic status during the interictal period; and results of hematologic and biochemical analyses (ie, a CBC and blood biochemical analysis) within the respective reference ranges (except for those abnormalities attributable to administration of phenobarbital, potassium bromide, or a combination of these 2 drugs). The determination of poorly controlled seizure activity was based on dogs having a mean of \( \geq 2 \) seizures/mo despite steady-state plasma concentrations of phenobarbital, potassium bromide, or both that were within established therapeutic ranges for these drugs. The therapeutic range used in the study for phenobarbital was 15 to 45 \( \mu \)g/mL. The therapeutic range used in the study for potassium bromide was 0.9 to 3.0 mg/mL when a patient was receiving potassium bromide alone and 0.8 to 2.4 mg/mL when a patient was receiving both phenobarbital and potassium bromide. Owners were required to have maintained accurate seizure logs to record seizure frequency for their dogs to be eligible for study inclusion. It was required that each had a minimum seizure history recorded for 3 months with steady-state concentrations of phenobarbital, potassium bromide, or both prior to entering the study, with at least 6 total seizures during that time period. Seizures occurring during a cluster event were counted as individual seizures. Additional information recorded included breed, age, sex, body weight, duration of seizure history, and results of pertinent diagnostic tests (eg, computed tomography, magnetic resonance imaging, or analysis of CSF).

**Pregabalin treatment**—A dose of pregabalin (3 to 4 mg/kg [1.4 to 1.8 mg/lb], PO, q 8 h) was administered to each dog, for a period of 3 months. This dose range was chosen on the basis of a pharmacokinetic study of oral administration of pregabalin to clinically normal dogs. The first 2 dogs were administered an initial dose of 4 mg/kg, but they became excessively sedate. Thus, all subsequent dogs were administered pregabalin at a rate of 3 mg/kg (0.9 mg/lb), PO, q 8 h; the dose was increased by 1 mg/kg (0.45 mg/lb) each week until the dogs reached the maximum tolerated dose of 3 or 4 mg/kg, PO, q 8 h. Data collection during the 3-month period after initiation of pregabalin treatment began at the time the maximum tolerated dose was attained. Owners were instructed that they should not alter the phenobarbital or potassium bromide doses during the 3-month study period.

After pregabalin administration at the highest tolerated dose for a minimum of 1 week, a blood sample was collected for determination of trough plasma pregabalin concentration. The trough blood samples were collected just before administration of the subsequent scheduled dose of pregabalin. Plasma was harvested within 2 hours after collection. Plasma samples were shipped overnight to a commercial laboratory where pregabalin concentrations were measured via HPLC by use of a modification of a method described elsewhere.
Follow-up monitoring—Safety of and tolerability for pregabalin were ascertained by monitoring dogs for adverse effects at follow-up examinations conducted by 1 or more of the authors and via telephone conversations with owners and referring veterinarians. Adverse effects attributable to pregabalin administration were recorded. In addition, a CBC, blood biochemical analysis, and urinalysis were performed monthly during pregabalin treatment.

Statistical analysis—Success for each dog was defined as a minimum reduction in seizure frequency of 50% (ie, a responder) when comparing the 3-month period after initiation of pregabalin treatment with the 3-month period preceding pregabalin treatment. Seizure frequency was compared between the 3-month periods before and after initiation of pregabalin treatment by use of a nonparametric Wilcoxon signed rank test for paired data. A Mann-Whitney U test was also used to compare seizure reduction between dogs with therapeutic plasma concentrations of 1 drug (phenobarbital or potassium bromide) and dogs with therapeutic plasma concentrations of both of those drugs prior to initiation of pregabalin treatment. Number of seizures per cluster event was recorded before and after initiation of pregabalin administration in the 7 dogs with cluster seizure activity that completed the study. The number of seizures per cluster event was recorded before and after initiation of pregabalin treatment. For each dog, the mean number of seizures per cluster for all cluster events in the 3-month period before initiation of pregabalin treatment was calculated and compared with the mean number of seizures per cluster for all cluster events in the 3-month period after initiation of pregabalin treatment by use of a nonparametric Wilcoxon signed rank test for paired data. All statistical analyses were conducted with a commercially available program; and significance for all analyses was set at values of P < 0.05.

Results

Eleven dogs met the criteria for inclusion in the study. Five dogs were enrolled at Cornell University, 2 were enrolled at Texas A&M University, and 1 was enrolled at each of the remaining 4 participating centers. Breeds represented included the Giant Schnauzer (n = 2), Australian Shepherd (2), Boxer (1), Rat Terrier (1), German Shepherd Dog (1), German Shepherd Dog crossbred dog (1), English Setter (1), Golden Retriever (1), and Jack Russell Terrier (1). There were 4 neutered males, 2 sexually intact males, and 5 spayed females. Age of the dogs ranged from 1.8 to 7 years (mean, 4.8 years; median, 4.4 years). Duration of seizure history was 5 months to 6 years (mean, 2.3 years; median, 2 years). Body weight ranged from 8 to 42 kg (17.6 to 92.4 lb), with a mean of 29.5 kg (65 lb) and a median of 32 kg (70.4 lb). Five dogs had brain imaging (computed tomography in 1 dog and magnetic resonance imaging in 4 dogs) and CSF evaluation performed; no abnormalities were identified.

Eight of the 11 dogs were receiving both phenobarbital and potassium bromide. 2 dogs were receiving only phenobarbital, and 1 dog was receiving only potassium bromide. All dogs had plasma concentrations of at least 1 drug (phenobarbital or potassium bromide) within the therapeutic range. Plasma concentrations of phenobarbital ranged from 19.8 to 40.0 µg/mL (mean, 27.7 µg/mL; median, 27.1 µg/mL). Plasma concentrations of potassium bromide ranged from 0.2 to 2.81 mg/mL (mean, 1.6 mg/mL; median, 1.9 mg/mL). Three dogs had plasma concentrations of potassium bromide less than the therapeutic range, but all had plasma concentrations of phenobarbital within the therapeutic range.

Owners of 5 of 6 dogs receiving phenobarbital or potassium bromide alone or that had subtherapeutic plasma concentrations of 1 of the 2 drugs when administered in combination reported various degrees of adverse effects associated with drug treatment prior to entry into the study. The owner of 1 of these 2 dogs had attempted to add potassium bromide to phenobarbital treatment in the past but considered the adverse effects (restlessness and pacing) to be intolerable. Four dogs all had typical adverse effects of phenobarbital or potassium bromide treatment (eg, polyphagia, polydipsia, polyuria, and pelvic limb ataxia); owners of 2 of these dogs reported that prior attempts to increase the dose of potassium bromide had caused unacceptable degrees of these adverse effects (these dogs were subsequently withdrawn from the study), whereas owners of the other 2 of these dogs preferred to attempt pregabalin treatment rather than to increase the adverse effects already evident by adding (1 dog) or increasing the dose of (1 dog) potassium bromide. One dog receiving a combination of phenobarbital and potassium bromide had a plasma concentration of potassium bromide in the low end of the therapeutic range; however, the owner of this dog reported that prior attempts to increase the phenobarbital or potassium bromide dosage were not tolerated.

Nine of the 11 dogs had cluster seizures as their typical pattern. Nine dogs achieved a final dose of 4 mg/kg, and the other 2 dogs achieved a final dose of 3 mg/kg. The 2 aforementioned dogs were withdrawn from the study at 38 days at the request of the owners. These owners withdrew their dogs because of a combination of perceived lack of efficacy and the degree of adverse effects. One of the owners also had failed to adhere to the study protocol. Both of the dogs that were withdrawn prematurely were considered drug failures. These dogs were subsequently euthanatized because of uncontrolled seizure activity.

Seizures were reduced after pregabalin administration in the remaining 9 dogs (Figure 1). Seizure reduction ranged from 23% to 83% (mean, 57%; median, 50%). Seizure frequency before pregabalin treatment for these dogs ranged from 2 to 6.3 seizures/mo (mean, 4.2 seizures/mo; median, 4.3 seizures/mo), whereas seizure frequency for the 3-month period after initiation of pregabalin treatment ranged from 0.7 to 3.3 seizures/mo (mean, 1.8 seizures/mo; median, 1.7 seizures/mo). This represented a significant (P = 0.005) reduction in seizure frequency for these dogs. Seven of these 9 dogs were responders, with a mean seizure reduction of 64% (median, 58%).

Number of seizures per cluster event was recorded for the 3-month periods before and after initiation of pregabalin administration in the 7 dogs with cluster
Adverse effects attributed to pregabalin treatment were reported in 10 dogs, which consisted most notably of sedation and ataxia. One dog had no adverse effects attributed to pregabalin treatment. In those 10 dogs, owners recorded that the adverse effects were apparent or exaggerated (eg, worsening of preexisting ataxia) after adding pregabalin to the treatment regimen. Six dogs had evidence of sedation (3 were described mild and 3 were described as severe by the owners). One of the dogs with severe sedation was started at a dose of 4 mg/kg, PO, every 8 hours, and the sedation became less apparent when the dose was reduced to 2 mg/kg, PO, every 8 hours. Five of the dogs with sedation also had some degree of ataxia. Four other dogs had ataxia but without sedation. In the 9 dogs that had ataxia, 5 were described as mild and 4 were considered severe. One owner reported that his dog had several episodes of apparent dizziness and weakness once the 4 mg/kg dose was achieved. In all dogs, the adverse effects appeared to persist unabated for the 3-month evaluation period; however, adverse effects alone were not considered sufficiently severe to discontinue pregabalin treatment in any of the dogs.

Six dogs had mild increases in liver enzyme activities during the 3-month period after initiation of pregabalin treatment. Four dogs had increases in serum alkaline phosphatase activity (139, 337, 123, and 744 U/L, respectively; reference range, 12 to 122 U/L). Two of these dogs had an increase in serum alkaline phosphatase activity (218 and 361 U/L, respectively) prior to initiation of pregabalin treatment. Both dogs were receiving phenobarbital. Two dogs with increases in alanine aminotransferase activity before pregabalin treatment had further increases in activity of this enzyme after initiation of pregabalin treatment (160 and 309 U/L, respectively; reference range, 25 to 106 U/L). However, these values decreased in both dogs during a subsequent follow-up examination conducted at the end of the 3-month study period (66 and 177 U/L, respectively).

Plasma concentrations of pregabalin were measured via HPLC for all dogs at various times during the study (between 30 and 90 days after initiation of pregabalin treatment). Two dogs had plasma concentrations of pregabalin (2.0 and 2.6 µg/mL, respectively) less than the range considered therapeutic for humans (2.8 to 8.2 µg/mL), but the remaining 9 dogs had concentrations within the therapeutic range. Trough serum concentra-
Concentrations of pregabalin for all dogs ranged from 2.0 to 11.0 µg/mL (mean, 6.4 µg/mL; median, 7.3 µg/mL).

Discussion

Conducting clinical drug trials, such as the one reported here, is fraught with a number of inherent difficulties. These difficulties include the use of multiple definitions of refractory epilepsy, variable measures of drug success or failure in the literature, and variations among potential trial participants with regard to pretrial drug regimens. Although we restricted entry into our study to dogs receiving standard anticonvulsant drugs (eg, phenobarbital, potassium bromide, or both), with plasma concentrations for at least 1 drug within the therapeutic range, our resulting patient population remained variable with regard to the specific drugs administered and the plasma concentrations of these drugs. More specifically, our group of dogs consisted of a number of treatment subgroups, including those with phenobarbital at therapeutic concentrations (n = 2 dogs), phenobarbital at therapeutic concentrations and potassium bromide at subtherapeutic concentrations (3), phenobarbital at therapeutic concentrations and potassium bromide at low therapeutic concentrations (1), phenobarbital at therapeutic concentrations and potassium bromide at mid to high therapeutic concentrations (4), and potassium bromide alone at therapeutic concentrations (1). Our criteria for patient entry were similar to those used in 2 other studies14,15 but were less stringent than those used in most of the similar studies15,16,22 in dogs. In those studies,14,15,22 entry was restricted to patients with therapeutic drug concentrations of both phenobarbital and potassium bromide.

Ideally, new drugs for treatment of dogs with epilepsy should be evaluated in a randomized, double-blind, placebo-controlled manner. Similar to findings in humans, there could be a placebo effect in open-label epilepsy trials of dogs that would lead to an exaggerated estimate of efficacy for the drug being investigated.23 The authors believe that a placebo-controlled study would be ethical to apply to dogs with focal (partial-onset) seizures, as has been done in human medicine, but such a study may represent an ethical dilemma when applied to dogs with severe generalized epilepsy characteristic of the participants in the study reported here. In addition, in the authors’ experience, owners of dogs with poorly controlled epilepsy are often reluctant to participate in a trial evaluating an unproven drug such as pregabalin. When given the choice between a placebo and a drug with no evidence of efficacy, it is likely that many dog owners would choose not to enroll their pets in such a study. Verifying the plasma concentrations of pregabalin in all dogs was important to fairly evaluate the drug and to begin to establish the therapeutic range for pregabalin in dogs. It would have been more pertinent to have a canine-specific (ie, validated in canine plasma) HPLC assay for measuring plasma concentrations of pregabalin in this study; however, multiple attempts by the authors to procure pure drug standard from the manufacturer to establish such an assay were unsuccessful.

Although clinical usefulness is suggested by the findings of this clinical trial, there are several caveats to consider when drawing conclusions of drug efficacy as well as the extent of such efficacy from these results. Although patient entry was limited to those receiving standard drugs (ie, phenobarbital, potassium bromide, or both) in an effort to have the group as uniform as possible, the patient population that was evaluated was still disparate. In addition to 3 dogs that received only 1 anticonvulsant medication, there was a fairly broad range of plasma drug concentrations in the dogs, especially for potassium bromide, with 3 dogs having plasma concentrations of potassium bromide that were less than the therapeutic range. Some of the dogs may have achieved better control had the plasma concentration of phenobarbital or potassium bromide (or both) been increased. Although such optimization of plasma drug concentrations is a matter of clinician preference, it is possible that the lack of such optimization in the clinical trial reported here resulted in a nonuniform population of dogs in terms of likely degree of achievable seizure control. Four dogs were identified that had plasma concentrations of phenobarbital well within the therapeutic range as well as plasma concentrations of potassium bromide at the upper end of the therapeutic range. Two of these dogs with the most optimized plasma drug concentrations had an apparently positive response to pregabalin treatment (seizure reduction of 50% and 77%, respectively). The other 2 dogs included 1 dog that had the lowest seizure reduction (23%) of the dogs that concluded the study and 1 dog that had a dramatic increase in seizure frequency (139%) before being withdrawn from the study prematurely. This somewhat all-or-nothing response to anticonvulsant drug intervention in dogs with refractory epilepsy is a phenomenon that the authors have observed over the years and one that has been recognized in other clinical trials.14,15,20 Although based on a small subgroup of dogs, this finding is important clinically because it suggests that pregabalin may be beneficial for some epileptic dogs but will likely fail in others. In particular, the 4 dogs in this study with high plasma concentrations of both phenobarbital and potassium bromide may represent a subpopulation of dogs least likely to benefit from treatment with an additional drug such as pregabalin.

Despite the limitations of this study, analysis of the results of our clinical trial suggested that pregabalin may be an effective adjunct drug for dogs with idiopathic epilepsy that are poorly controlled with standard (eg, phenobarbital or potassium bromide) treatment. Analysis of the results also suggested that the extent of seizure reduction will likely be higher in dogs that do not have plasma concentrations of both phenobarbital and potassium bromide in the high end of the therapeutic ranges.

Cluster seizure activity is widely regarded among veterinarians to be particularly difficult to control in dogs.1,2 The significant reduction in seizure frequency, despite the fact that 9 of the 11 dogs in this clinical trial typically had cluster seizures before initiation of pregabalin treatment, further supports that pregabalin holds promise as an effective adjunct drug for treatment of dogs with epilepsy. The tendency is for individual seizures within a cluster period to be more accurately counted prospectively (period after initiation
of pregabalin treatment), compared with the counts for the seizure logs recorded by the owners (period before pregabalin treatment). This phenomenon was apparent during this study, and it has been the authors’ experience in other anticonvulsant clinical trials. Therefore, it is more likely that the seizure frequency after initiation of treatment would be artificially inflated, rather than being artificially decreased. The 9 dogs that completed the clinical trial had a significant reduction in seizure frequency (mean reduction, 37%) for the 3-month period after initiation of pregabalin treatment, regardless of factors that may have unfairly predisposed to drug failure (such as a preponderance of dogs with cluster seizures and underestimation of seizure frequency in the period before pregabalin treatment). Also, the number of seizures per cluster event was significantly reduced in the period after initiation of pregabalin treatment for the 7 dogs that had cluster seizure activity. In addition to the significant decrease in seizure frequency in the 9 dogs that completed the study, 7 of the 11 dogs that entered the study were considered treatment successes (ie, responders).

The assessment of what constitutes acceptable seizure control in epileptic dogs is somewhat contentious and may differ between veterinarians and dog owners. Although it has been suggested\(^{1,24}\) that a seizure frequency of 1 seizure/mo represents acceptable control, there is evidence\(^{13,24}\) that owners of epileptic dogs consider 1 seizure/3 mo to be acceptable. Even with the value of 1 seizure/mo, it is important to mention that only 4 of the dogs in the study reported here achieved this degree of seizure control. Of these 4 dogs, only 1 of 2 dogs that had plasma concentrations of phenobarbital well within the therapeutic range as well as plasma concentrations of potassium bromide at the upper end of the therapeutic range (optimized standardized drug treatment) achieved a seizure frequency of 1 seizure/mo. In contrast, 3 of the 4 dogs that achieved a seizure frequency of ≤1 seizure/mo after initiation of pregabalin treatment were not receiving a combination of phenobarbital and potassium bromide and did not have therapeutic plasma concentrations of both drugs. These findings reinforce the concept that the dogs in our study with plasma concentrations of both phenobarbital and potassium bromide within the respective therapeutic ranges likely represented a subgroup that was more difficult to treat than those with only 1 drug within the therapeutic range.

One potential concern regarding drug efficacy that was not addressed in this study is that of the so-called honeymoon effect. This phenomenon describes an initial positive response to a drug intervention that is subsequently lost over time in some patients. This loss of efficacy over time may be attributable to several factors, including development of drug tolerance and kindling with subsequent recruitment of more neurons into the seizure focus. There are 2 open-label, noncomparative studies\(^{21,22}\) in dogs in which it was suspected that a subset of patients had a honeymoon effect. Because the follow-up monitoring for the clinical trial reported here was limited to a 3-month period, it is currently unknown whether the use of pregabalin in dogs will be associated with a honeymoon effect.

When evaluating an adjunct drug for adverse effects in a clinical trial, it can be challenging to ascertain those adverse effects attributable to the drug being evaluated and those effects attributable to concurrently administered drugs. In all 10 dogs in which adverse effects were reported, the owners indicated that these effects developed after the addition of pregabalin to the treatment regimen. In addition, these adverse effects appeared to be constant for the entire 3-month evaluation period. It is clear from our data that sedation and ataxia should be expected adverse effects of pregabalin treatment, which are similar to the effects reported for the drug’s predecessor, gabapentin. On the basis of our experience with pregabalin, we recommend that dogs initially receive a low dose (ie, 2 mg/kg, PO, q 8 to 12 h) and increase the dose by 1 mg/kg each week until the target dose is attained.

The importance of the mild increase in liver enzyme activities detected in the 6 dogs during pregabalin treatment is unknown. One of the dogs with a transient increase in alanine aminotransferase activity during the pregabalin treatment period was receiving only potassium bromide before the addition of pregabalin. In humans, there is negligible hepatic metabolism of pregabalin, with the drug being primarily (approx 98%) excreted as unchanged drug in the urine.\(^{11,13}\) Gabapentin is also primarily excreted via the kidneys in humans, with virtually no hepatic metabolism of the drug; in contrast, approximately 30% to 40% of orally administered gabapentin undergoes hepatic metabolism in dogs.\(^{23,26}\) The extent of hepatic metabolism of pregabalin in dogs is currently unknown, but it is reasonable to expect that the drug may undergo some hepatic metabolism because it is closely chemically related to gabapentin. In addition, although there is no known interaction between pregabalin and phenobarbital in humans, it is unknown whether such an interaction exists in dogs. In the future, it may be worthwhile to serially monitor plasma concentrations of phenobarbital to ascertain whether pregabalin affects these values. Until more information is available concerning the metabolism and the effect of pregabalin on the liver in dogs, it is advisable to monitor liver enzymes in these patients on a regular basis.

The dog euthanatized because of severe pancreatitis at the end of the pregabalin treatment was considered to have developed this disorder because of ingesting garbage. Although we do not believe that this was an adverse effect of pregabalin administration, it is important to emphasize the limited size of the study population and the need to be vigilant in the future for potential links between a new drug and apparently nonrelated adverse effects. There has been an association detected between potassium bromide use and development of pancreatitis in dogs, especially in dogs concurrently receiving phenobarbital.\(^{27}\) More recently, it has been suggested\(^{28}\) that administration of phenobarbital alone may also predispose dogs to developing pancreatitis, which would be in addition to administration of potassium bromide or a phenobarbital–potassium bromide combination. The dog that developed pancreatitis in our clinical trial was receiving both phenobarbital and potassium bromide. The possibility that either of these
Two dogs in our study were withdrawn prematurely; primarily because of a perceived lack of efficacy combined with adverse effects of the drug. In humans, up to approximately one-third of study participants in pregabalin clinical trials\textsuperscript{13,16} withdrew prematurely because of adverse drug effects (eg, somnolence, dizziness, or headache).

Owners of 8 of the 11 dogs in the clinical trial reported here were interested in continuing the pregabalin treatment beyond the 3-month study period on the basis of perceived efficacy and lack of severe adverse effects. One of these dogs was later euthanized because of pancreatitis; the treatment in 2 other dogs was changed to less expensive drugs (gabapentin or zonisamide) because of cost concerns for the pregabalin. The 3 other dogs continued to receive pregabalin treatment.

The dosing regimen chosen for this clinical trial was based on pharmacokinetic data from a study\textsuperscript{17} in clinically normal dogs administered a single dose of pregabalin. In that pharmacokinetic study,\textsuperscript{16} the mean time for which the plasma concentration of pregabalin of the dogs remained higher than 2.8 \(\mu\)g/mL (the presumed lower limit of therapeutic efficacy) was nearly 11 hours (range, 7 to 14 hours). On the basis of these data, it was assumed that although a 12-hour interval between doses may be appropriate in many cases, some dogs may not maintain plasma concentrations of pregabalin within the therapeutic range between dose administrations with this interval. Dogs in this study were maintained on an 8-hour administration interval to maximize the likelihood of maintaining plasma concentrations of pregabalin in all dogs for all time periods within the reported therapeutic range for humans. It is possible that with chronic administration of pregabalin in dogs and attendant drug accumulation, a 12-hour administration interval will also be effective in this species.

In this clinical trial, the mean and median trough plasma concentrations of pregabalin (6.4 and 7.3 \(\mu\)g/mL, respectively) were much higher than the lower limit of therapeutic efficacy reported for humans. In fact, most of the dogs had trough plasma concentrations of pregabalin considerably higher than this lower limit. It is important to mention that the 2 dogs with trough concentrations less than the lower limit were in the responder group. This finding may be attributable to a period of decreased seizure frequency that was unrelated to pregabalin administration because seizure frequency in epileptics does wax and wane in some patients. Alternatively, this may suggest that the lower limit of the pregabalin therapeutic range in dogs may be < 2.8 \(\mu\)g/mL.

A 12-hour administration interval would be more convenient for owners and might potentially decrease the number and severity of adverse effects. In 1 clinical trial\textsuperscript{13} in which investigators evaluated 12-hour versus 8-hour administration intervals for pregabalin in humans with focal (partial-onset) seizures, reductions in seizure frequency (compared with results for a placebo) were higher in the 8-hour administration group (49% responder rate) than in the 12-hour administration group (43% responder rate); however, the difference between these 2 groups was not significant. The therapeutic range for pregabalin efficacy in dogs and whether a 12-hour administration interval is appropriate for this drug in epileptic dogs are questions that will require further clinical evaluation of pregabalin administration to dogs with refractory idiopathic epilepsy.

Results of the study reported here support the use of pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of both in epileptic dogs poorly responsive to these standard drugs. In addition to significantly reducing seizure frequency in most of the dogs that were administered pregabalin, the adverse effects associated with pregabalin administration were typically mild and similar to those reported after administration of gabapentin. Treatment efficacy in this study was greater than that reported for dogs treated with gabapentin.\textsuperscript{13,15} Further investigation into pregabalin use in dogs with refractory epilepsy is warranted, as determined on the basis of the results of this clinical trial. In particular, a randomized, double-blinded study with a more uniform patient population and long-term evaluation of pregabalin efficacy or inefficacy would yield important clinical information regarding this potentially useful new drug.

References


