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Idiopathic refractory epileptic dogs: Levetiracetam or gabapentin add-on to phenobarbital therapy

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Abstract
The most common epilepsy in small animal practice is idiopathic epilepsies. Phenobarbital (Pb) is used as first line of therapy by many practitioners. Clinical cases were considered refractory when they had epilepsies inspite of adequate serum therapeutic Pb level. The purpose of the study was to identify the right add-on between Levetiracetam and Gabapentin which suits as Pb add-on therapy. The total refractory epileptic clinical case in the study period was 36. They had the mean serum Pb level of 26.52±3.63µg/ml. The parameters studied were number of epileptic episodes, duration of epilepsy, interictal periods, mentation of treated animals, neuro-behaviour and notifiable side effects. Based on the data it was found that there was a highly significant reduction in the number of epileptic episodes in Gabapentin added group when compare to Levetiracetam group. There was a significant reduction in duration of epilepsy and interictal periods in Gabapentin added group when compare to Levetiracetam addition. The other parameter varied without any significance. It was concluded from our study that Gabapentin add-on therapy was more effective in reducing the frequency and duration of epilepsies and increasing the inter-ictal periods of animals with refractory epilepsies having adequate serum therapeutic Pb level.

Keywords: Idiopathic, epileptic, dogs, gabapentin, phenobarbital

1. Introduction
Seizures are the most common neurologic conditions encountered in small animal practice with an estimated prevalence in a non-referral population of 0.5% to 5% [1]. Clinical disorder that is characterized by recurrent seizures of any cause is called as epilepsy [2]. Among the various types of epilepsies, iIdiopathic epilepsy (IE) is the most common cause in dogs [3]. Preferred therapy for IE includes administration of a single antiepileptic drug rather than a combination of drugs. This is to avoid drug-drug interactions, increased cost, the need to monitor and interpret serum concentrations of multiple drugs, more complicated dosing schedules and provides a simpler regimen that may improve compliance [4, 3, 2].

The first-line drug for the treatment of idiopathic epilepsy is Phenobarbital by many practitioners, based on its efficacy, low cost, ease of administration, relative safety, greater data from veterinary studies compared to other drugs and reasonable time required to achieve steady-state concentrations [3, 5]. Phenobarbital is effective in 60% to 80% of dogs with idiopathic epilepsy if plasma concentrations are maintained within the therapeutic range of 20 mg/mL to 45 mg/mL [6, 2]. It has been estimated that up to 30% of dogs have refractory epilepsy and do not attain satisfactory seizure control with conventional Phenobarbital therapy [7]. If the single agent does not adequately control seizures at optimal dosages, then a second drug should be added [2].

Levetiracetam possesses a favorable pharmacokinetic profile in dogs including high bioavailability, limited hepatic metabolism, minimal effect on the disposition of other antiepileptic drugs and a high therapeutic index with respect to its use as an add-on antiepileptic medication [8]. This drug is often used as add-on treatment and the effect has not been fully evaluated in dogs [9]. Gabapentin is well absorbed after oral administration in dogs with maximum blood concentrations achieved within 2 hours. Administration of Gabapentin at 10 mg/kg every 8 h resulted in a significant decrease in the number of seizures per week and the number of days per week with any generalized seizures refractory to Phenobarbital and potassium bromide [10]. Studies have already evaluated the use of Gabapentin as add-on therapy in dogs with refractory epileps [2].

The aim of the study was to find the right add-on in Phenobarbital refractory cases in animals with serum therapeutic Phenobarbital range.

Further in the refractory cases the aim is to achieve a 100% increase in interictal time period, or a 50% decrease in seizure frequency, without drug toxicity.

2. Materials and Methods

2.1 Location of study

The study was conducted at the outpatient unit of Madras Veterinary college clinics, Southern India. The dogs with the history of epilepsy were identified based on the history and clinical examination. These cases were further confirmed as idiopathic epilepsy based on the absence of inflammatory cells in Cerebrospinal fluid analysis and imaging techniques. These idiopathic epilepsy cases were treated with Phenobarbital at therapeutic doses @ 2-4 mg/kg initially. These cases were regularly treated over a period from minimum 3 months to even one and half year. These cases were monitored by serum Phenobarbital level after 30 days of initiation of therapy. The samples were analysed by using commercial laboratories (Lister metropolis, Chennai) through spectrophotometric ally after serum separation at -20°c. In all these cases the samples were collected in morning hours from fasted animals. Those dogs which are not within the therapeutic range (15-40 µg/dl) of serum Phenobarbital level were excluded from this study. Further the dose rate of Phenobarbital was increased in some cases even upto 6 mg/kg until the serum level increase to 35 µg/dl. All these animals were monitored for blood counts and serum hepatic enzymes every six months. From these, those dogs which are refractory to Phenobarbital therapy were randomly chosen for this study. The sick and ailing animals were identified by their institutional case number.

2.2 Therapeutic study

The study was carried out for about a period of three years. The age of first incidence of idiopathic epilepsy was recorded carefully. These dogs were randomly divided in to two groups. Group I was administered with Levetiracetam @ 20mg/kg, tid as add-on therapy. Group II was administered with Gabapentin @ 15 mg/kg, tid as add-on therapy. Owners were encouraged to record the frequency of epileptic episodes and other parameters along with video recording. The parameters studied were incidence of epilepsy, duration of epilepsy, interictal period, side effects, mentation of animal and neuro-behavior of that animal with owner. Owners were encouraged to record the outcome of therapy.

2.3. Statistical analysis

The number of frequencies and interictal period differ from individual to individual majority of the parameters under this study were qualitative in nature. Hence χ^2 value with Yate's correction was applied to this study. 9123506310

3. Results

The total refractory epileptic case in the study period was 36. These cases were initially treated with Phenobarbital for about minimum period on 3 months at therapeutic doses. The mean age of incidence of idiopathic first epilepsy in our study is 4.2 ± 1.8 years. The serum Phenobarbital level was estimated through commercial laboratories. The mean serum Phenobarbital in these cases was 26.52±3.63µg/ml. One animal in our study had high serum Phenobarbital value 39.67 µg/ml but however the liver enzymes in those animals were within range and there was no notable other. The mean serum Phenobarbital level in Levetiracetam and Gabapentin treated groups were 20.39 ± 2.86 µg/ml and 29.59±3.87 µg/ml respectively. The add-on therapy was added to period of 10 days until the serum steady state reached and then the therapeutic response was recorded properly.

Table 1: Different parameters and their significance with Gabapentin treated groups when compare to Levetiracetam group

S. No.	Parameters	χ^2 Value with Yate's correction	P value
1.	Incidence/number of epilepsy	16.041**	0.002 (P≤0.01)
2.	Duration of epilepsy	11.389*	0.02 (P≤0.05)
3.	Interictal period	6.979*	0.03 (P≤0.05)
4.	Mentation of animals	1.923	0.38 (P≥0.05)
5.	Neuro-behaviour	1.345	0.85 (P≥0.05)
6.	Side effects	2.138	0.34 (P≥0.05)

There was a highly significant reduction in the number of epilepsy when add-ons were added. Between the groups Gabapentin showed better reduction in number of epilepsy than Levetiracetam. There was a significant reduction in duration of epilepsy and interictal periods when compare to Levetiracetam group. The other parameters varied without any significance. In both the add-on drugs there were no notifiable side effects by the owners.

4. Discussion

Seizures are often traumatic for owners, it is important for the practitioner to understand when to initiate anti-epileptic drug therapy and be comfortable with client education regarding seizures [11]. The idiopathic epilepsy onset of age in our study was 4.2 ± 1.8 years. Most dogs with idiopathic epilepsy suffer their first seizure between 6 months and 5 years of age, although seizures occasionally start before 6 months or as late as 10 years of age [16]. The aim of the study was using AEDs for seizure control is to achieve a 100% increase in interictal time period, or a 50% decrease in seizure frequency, without drug toxicity. Approximately 20 to 50% of epileptic dogs treated with PB alone continue to have unacceptable seizure activity, become refractory to this medication [6]. Phenobarbital (PB) is well absorbed after oral administration in dogs, with a reported bioavailability of approximately 90%. Measurement of trough serum PB concentrations is helpful in determining the need for more frequent dosing in epileptic dogs with poor seizure control [5]. The most efficacious and safe therapeutic range reported for dogs is 15–35 63µg/dl /mL although efficacy can be seen at lower concentrations [11]. The serum PB level in all the refractory cases was within the therapeutic range despite one animal with 39.67 µg/ml. However there was no signs of PB side effects in that animal. Phenobarbital may cause blood dyscrasias and hepatotoxicity, which can be fatal [12]. None of the refractory case in our study had blood dyscrasia. The dose rate was increased in 6 animals even upto 6mg/kg to reach the maximum serum therapeutic Phenobarbital level in dogs. If seizures are not controlled, the initial dose should be increased by approximately 25% until serum Phenobarbital concentrations

reach 30 mg/mL or intolerable side effects develop [2]. PB is an auto inducer of hepatic microsomal enzymes (p450 system), which can progressively reduce the elimination half-life with chronic dosing, known as metabolic tolerance over time [6]. The reason to increase in therapeutic dose is as stated above. A drug should not be considered to have failed until maximum dosage or therapeutic serum concentrations have been attained, or unacceptable side effects occur [2]. Levetiracetam and Gabapentin were chosen as add-ons in our study because not many studies are available as monotherapy to dogs. Other drugs like Zonisamide and Potassium bromide were not used because of the cost and/or unavailability in Indian market. The difficulties felt by many pet owners in Levetiracetam and Gabapentin therapies was frequent dosing i.e. tid dosing. Since, both the drugs have rapid metabolism and short half-life 4-8 hours [6] and 3 to 4 hours [3] respectively. From our study it was found that Gabapentin had reduced the incidence, duration of epilepsy and significantly increased the interictal period in refractory epilepsies. The reason for this might be the elimination half-life for Levetiracetam is shortened to about 1.7 hours in dogs taking Phenobarbital [13]. Further, PB is believed to induce the oxidative metabolism of levetiracetam in extra hepatic tissues [7]. Gabapentin improves seizure control when added to Phenobarbital and/or bromide [14, 10]. Further the combination effect of Gabapentin with Pb has not been studied properly. In both the add-on therapies there was not much side effects as reported by owners. Levetiracetam is well tolerated with mild, transient sedation and decreased appetite being uncommon side effects in iodiopathic epileptic cats [15]. The common side of Gabapentin includes sedation and ataxia [2].

From this study it was concluded that Gabapentin add-on therapy was more effective in reducing the frequency and duration of epilepsies and increasing the inter-ictal periods of animals with refractory epilepsies having therapeutic serum Phenobarbital level.

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