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Studies on comparative efficacy of phenobarbitone sodium, phenytoin and potassium bromide in the treatment of epilepsy in dogs

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Abstract
Successful management of epilepsy requires knowledge of the pharmacologic properties of available antiepileptic medications, regular patient evaluations to assess response to therapy and monitor for adverse effects. A one year study on epileptic dogs presented to the Teaching Veterinary Clinical Complex, College of Veterinary Science and Animal Husbandry, Mhow was conducted to asses the comparative efficacy of drugs such as Phenobarbitone sodium, Phenytoin and Potassium bromide in the treatment of epilepsy in dogs on the 0th day of presentation. The efficacy of three drugs were evaluated on the basis of improvement in clinical signs and reduction in occurrence of seizures. Comparing the results of these drugs it was revealed that Phenobarbitone sodium is highly efficacious followed by potassium bromide and followed by Phenytoin.

Keywords: drug efficacy, epileptic seizures, phenobarbitone

Introduction
An epileptic seizure is "a transient occurrence of signs due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher *et al*., 2005) [4]. Canine epilepsy can result from structural, metabolic, genetic, or unknown causes. Focal motar and generalised are the clinical manifestations of seizures in dogs similar to those observed in humans. Phenobarbital is one of the first-choice anticonvulsant drugs in dogs because of its efficacy, convenient dosing regimen, reasonable time required to achieve steady-state concentrations, low cost and relative safety (Masucci, 2016) [5] and Potassium bromide (Kbr) is the oldest and, chemically, the simplest of the anticonvulsant drugs which became popular as a second anticonvulsant drug in dogs (Dowling, 1994) [3]. Phenytoin (PHT) is considered a first or second choice in the treatment of status epilepticus that is refractory to benzodiazepines (Andersen, 1992) [1]. The aim of the present study is to asses the comparative efficacy of above three drugs in treating epileptic dogs at the 0th day of presentation.

Material and Methods
A total of 2144 dogs of 30 different breeds presented to the T.V.C.C College of Veterinary Science and Animal Husbandry, Mhow, (MP) were observed during the one year study period (from march 2017 to feb. 2018) and among them 19 reported cases of epileptic condition with clinical signs like seizures, severe muscular tremor, convulsions etc were taken for the study. The haematobiochemical parameters like haemoglobin, packed cell volume (PCV), total leukocyte count (TLC), differential leukocyte count (DLC), alanine transaminase (ALT) and serum creatinine were performed on the 0thday using automated machines Abacus- 380 and minichem 100 (with Erba Mannheim kit) for haematological and biochemical studies respectively. Two ml of blood were collected in EDTA vials for haematological study and three ml of blood were collected in test tubes followed by serum seperation by centrifugation after clotting for biochemical study. The study was conducted on 18 dogs suffering from epilepsy. The dogs were divided into three groups, having six dogs in each. The data were subjected to analysis of variance employing Completely Randomized Design.

Plan of work

G Groups	No. of dogs	Treatment regimen
1.	06	Treated with Phenobarbitone sodium@ 5mg/kg BW I/V for 3 months
2.	06	Treated with Phenytoin @ 15mg/kg BW b.i.d. orally for 3 months
3.	06	Treated with potassium bromide @ 25mg/kg orally in divided doses for 3 months

Result and Discussion

Table 1: Value of Mean ±SE Haemoglobin (g/dl) of dogs of different groups

Days	Groups		
	I	II	III
0	16.03±1.17^{a}	16.05±0.99^{a}	15.91±1.68^{a}
7	15.35±0.56^{a}	15.13±1.10^{a}	15.53±1.58^{a}
14	15.16±0.35^{a}	16.63±1.49^{a}	15.12±1.25^{a}
28	15.06±0.83^{a}	16.61±1.06^{a}	14.95±0.99^{a}
45	14.31±0.61^{a}	16.71±1.01^{a}	13.48±1.05^{a}

Table 2: Value of Mean ±SE Packed cell volume (%) of dogs of different groups

Days	Groups		
	I	II	III
0	46.70±3.07^{a}	46.95 ± 1.73^{a}	48.87 ± 5.55^{a}
7	46.17±0.94^{a}	46.25 ± 1.79^{a}	46.52 ± 2.89^{a}
14	45.87±0.63^{a}	52.01 ± 4.33^{a}	44.66 ± 1.89^{a}
28	44.45±1.21^{a}	47.91 ± 2.09^{a}	44.21 ± 1.76^{a}
45	43.35±1.19^{a}	47.77 ± 1.32^{a}	41.84 ± 1.54^{a}

Table 3: Value of Mean ±SE Total leucocyte count (thousand/cu.mm) of dogs of different groups

Days	Groups		
	I	II	III
0	12.4 ± 1.33^{ab}	13.87 ± 0.73^{a}	14.17 ± 1.45^{a}
7	13.15 ± 1.16^{a}	12.26 ±0.98^{ab}	12.26 ±0.91^{ab}
14	11.79 ±0.72^{ab}	10.39 ±0.42^{bc}	11.05 ±0.56^{bc}
28	10.35 ±0.53^{bc}	10.84 ±0.50^{bc}	9.30 ± 0.46^{cd}
45	8.41 ± 0.48^{c}	9.66 ± 0.53^{c}	8.16 ± 0.68^{d}

Means having different superscripts within column differ significantly (P<0.05).

Table 4: Value of Mean ±SE Differential leucocyte count (thousand/cu.mm) of dogs of different groups

DLC (%)	Group	Days				
Neutrophil		0th	7th	14th	28th	45th
	I	77.16±3.02^{a}	75.66±3.14^{a}	63.66±3.07^{b}	67±2.28^{b}	67±2.28^{b}
	II	78.33±2.33^{a}	75±2.16^{ab}	66.5±1.96^{cd}	69.66±1.58^{bc}	60.83±2.65^{d}
	III	66.83±5.04^{a}	70.33±0.8^{a}	65.66±0.91^{a}	64.16±2^{ab}	58.83±1.57^{b}
	IV	70.16±1.27^{a}	69±1.36^{a}	68.33±1.47^{a}	68.33±1.4^{a}	68.33±1.64^{a}
Lymphocyte	I	20.16±2.61^{b}	20.16±2.45^{b}	32.83±3^{a}	30.5±2.32^{a}	35.83±2.22^{a}
	II	19±1.63^{d}	21±1.93^{cd}	31.5±1.56^{ab}	27.1±1.92^{b}	36±1.69^{a}
	III	27.5±5.35^{c}	25.33±0.66^{c}	31±1.39^{bc}	34.33±1.52^{ab}	38.83±1.74^{a}
	IV	25.16±1.57^{a}	26.16±1.19^{a}	26.16±1.19^{a}	25.66±2.04^{a}	27.83±0.70^{a}
Monocyte	I	0.83±0.65^{a}	2.33±0.61^{a}	2.33±0.42^{a}	1±0.36^{a}	1.5±0.76^{a}
	II	1±0.44^{a}	2±0.68^{a}	1.16±0.40^{a}	1.33±0.33^{a}	1.5±0.84^{a}
	III	3±0.57^{a}	2±0.57^{a}	1.16±0.30^{a}	0.33±0.33^{a}	0.66±0.33^{a}
	IV	2.66±0.49^{a}	2.16±0.65^{a}	2.66±0.71^{a}	2.66±0.76^{a}	1.5±0.42^{a}
Eosinophil	I	1.83±1.041^{a}	1.83±0.47^{a}	1.16±0.79^{a}	1.33±0.61^{a}	0.5±0.22^{a}
	II	1.66±0.84^{a}	2±0.44^{a}	0.66±0.33^{a}	1.83±0.47^{a}	1.5±0.42^{a}
	III	2.5±0.42^{a}	2.16±0.47^{a}	2±0.81^{a}	0.66±0.36^{a}	1.5±0.22^{a}
	IV	1.66±0.55^{a}	2.66±5.84^{a}	2.66±0.61^{a}	2.83±0.70^{a}	1.66±0.61^{a}
Basophil	I	0.16±0.16^{a}	0±0^{a}	0.16±0.16^{a}	0.16±0.16^{a}	0±0^{a}
	II	0±0^{a}	0±0^{a}	0.16±0.16^{a}	0±0^{a}	0.33±0.21^{a}
	III	0.16±0.16^{a}	0.16±0.16^{a}	0.16±0.16^{a}	0.16±0.16^{a}	0.16±0.16^{a}
	IV	0±0^{a}	0±0^{a}	0.33±0.21^{a}	0.33±0.21^{a}	0.33±0.21^{a}

Table 5: Value of Mean ±SE ALT (IU/L) of dogs of different groups

Days	Groups		
	I	II	III
0	29.21±3.26^{a}	43.58±5.50^{a}	42.81±9.22^{a}
7	33.81±1.36^{a}	32.63±4.51^{a}	32.6±6.17^{a}
14	29.11±3.21^{a}	32.66±5.48^{a}	37.75±7.04^{a}
28	35.45±5.89^{a}	32.65±5.26^{a}	37 95±6.16^{a}
45	31±5.61^{a}	30.05±3.46^{a}	31.82±6.88^{a}

Table 6: Value of Mean ±SE Serum Creatinine (mg/dl) of dogs of different groups

Days	Groups		
	I	II	III
0	1.27±0.31^{a}	1.26±0.77^{a}	1.23±0.08^{a}
7	1.13±0.13^{a}	1.18±0.13^{a}	1.53±0.19^{a}
14	1.13±0.10^{a}	1.36±0.14^{a}	1.08±0.09^{a}
28	1.18±0.09^{a}	1.25±0.18^{a}	1.24±0.12^{a}
45	1.41±0.14^{a}	1.13±0.14^{a}	0.86±0.13^{a}

Table 16: Comparative efficacy of drug based on the improvement in the clinical signs

Parameters	Group I					Group II					Group III				
	0	7	14	28	45	0	7	14	28	45	0	7	14	28	45
Severity	+++	+	+	-	-	+++	++	++	+	+	+++	++	+	+	-
Average Frequency/day	4	1	1	-	-	3	3	2	2	1	3	2	1	1	-
Average Duration (minute)	3	1	1	-	-	2	1	1	1	1	2	1	40s	1	-
No of dogs showed recovery under treatment	0	5	5	6	6	0	0	1	1	1	0	3	3	3	4

+++ - Strong

++ - Moderate

+ - Mild

The dogs under study were observed for the improvement in clinical signs and reduction in occurrence of seizures on the 0th, 7th, 14th, 28th and 45th day of medication along with blood collection for hematobiochemical studies. The parameters specifically noticed were the severity of the seizure, frequency of the seizure and duration followed by the reduction in occurrence of seizure. In group I after the medication it was noticed that 5 out of 6 animals showed reduction in seizure occurrence to a remarkable level by 7th day. The severity was reduced from strong seizures to mild seizures within 7th day of medication and no seizure were reported in 5 animals up to 45th day and the remaining one showed improvement in condition by 28th day of medication. The average frequency of the seizures reduced to once from 4 times before the medication. And the average duration was reduced up to 33.33% as it is reduced to 1min from the 3 min duration noticed before medication. A 100% recovery in seizure was observed in group 1 by the 45th day under medication.

In the second group it was noticed that 1 out of 6 showed improvement in the reduction of seizure from the 14th day of medication. The average severity was reduced to moderate by the 7th day and later to mild from 28th day with an average frequency reduction from 3 times to 2 times, and the average duration was also had a reduction of 1 min from the 2 min noticed before medication. A 16.66% recovery was only noticed in the group 2 by the 45th day under treatment.

In the third group it was observed that 3 out of 6 showed improvement by 7th day followed by 4 out of 6 by the 45th day of medication. The average severity of the seizures were first reduced to moderate level at 7th day and later to mild form by the 14th day of medication. Average frequency reduced to 2 times by the 7th day and later to once by 28th days of medication than the 3 times occurrence before medication. Average duration was also reduced from 3 min to 1 min by the 28th day of medication. A 66.66% recovery from seizure occurrence was thus observed in group 3 by the 45th day under treatment.

Comparing the results of seizure reduction and improvement in the clinical signs it was revealed that Phenobarbitone sodium is highly efficacious followed by potassium bromide followed by Phenytoin.

Summary

The study was conducted to know the Comparative drug efficacy of Phenobarbitone sodium, Phenytoin and Potassium bromide in the treatment of epilepsy in dogs on 0, 7, 14, 28 and 45days.Comparing the results of seizure reduction and improvement in the clinical signs, Phenobarbitone sodium turned out to be the highly efficacious drug and Phenytoin being the lowest.

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