MANAGEMENT OF CANINE EPILEPSY REFRACTORY TO COMMON MEDICATION

Debaki Ghosh and Sarmista Debbarman[1]
Department of Surgery, [1]Dept. of Clinical Vety. Medicine, Faculty of Veterinary and Animal Sciences.
West Bengal University of Animal & Fishery sciences, Kolkata-37
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Introduction

Epilepsy is a neurological disorder characterized by recurrent seizures .The seizures may be the consequences of trauma, toxin, brain tumor, infection and "idiopathic". Seizures are of two categories: generalized (grand mal) or partial (focal). Generalized seizures clinically appear with involuntary jerking or twitching movements of all four limbs with loss of consciousness. Partial seizures may involve one limb, side of the body, or face which may progress to generalized seizures. The most common treatment of canine epilepsy is by administration of phenobarbiturate. But many times the dogs are found to be refractory to phenobarbiturate (Thomas, 2010). The article is a study on management of canine epilepsy refractory and intolerable to phenobarbiturate.

Materials and Methods

Twelve adult (Avg.4Yr) dogs of either sex of different breeds suffering from grand mal seizure for avg. duration of 8 yrs. on phenobarbiturate medication but showing relapse of symptoms at least weekly intervals were considered as refractory to treatment and included in this study. Some of these dogs were with hepatobilliary dysfunction due to long term medication with phenobarbiturate as indicated by elevated liver function test (LFT) profile viz. alkaline phosphatase (ALP), alanine trans aminase (ALT) , aspertate trans aminase (AST) and total bilirubin (Muller, 2009). The animals were divided randomly into two equal groups (Gr. A and B) and treated with Potassium bromide alone and in combination with Levetiracetam respectively.

Phenobarbiturate was withdrawn tapering the dose in 7 days and concomitantly potassium bromide was administered orally @150mg/kg divided in two halves as a loading dose for 5 day followed by @30mg/kg as maintenance in two divided doses in one group alone and in another group in combination with Levetiracetam @ 30mg/kg orally in two divided doses. The dogs irrespective of groups were observed for any remarkable clinical signs like recurrence of seizure, behavioral abnormalities, state of appetite, pattern of urination , postural abnormalities and condition of visible mucous membrane. The dogs were monitored for different clinical and haemato-biochemical parameters in pre and intra-therapeutic period to assess overall wellbeing and effectiveness of the drug to control the epilepsy for duration of 6 months.

Results and Discussion

Epilepsy cannot be cured, but can usually be controlled with anticonvulsant drugs. Dogs diagnosed with idiopathic epilepsy may require treatment for lifetime, and sometimes with more than one drug. Administration of antiepileptic drug does not necessarily guarantee that a dog will be entirely seizure free and relapse of the episode once in two months for duration of less than four minute even is considered to be controlled seizure (Podell, 2012). Phenobarbiturate, the most widely prescribed medicine for treating seizure in dog is 60- 80

% effective. It causes CNS depression nonselectively by increasing action of GABA and inhibiting release of glutamate from the nerve ending. But many dogs are found to be refractive to Phenobarbiturate for epilepsy (Thomas, 2000). Phenobarbiturate also causes different degrees of hepatopathy making it unsuitable for continuing the therapy (Muller, 2009). The epileptic dogs refractive as well as intolerable to phenobarbiturate, showing generalized seizure at least once in a week for duration of few seconds to minutes were incorporated in this study. Some animals before starting the medications with the specific protocol in group A or B showed symptoms of anorexia, distended abdomen , physically palpable liver as well as hepatomegaly on USG. The marked haemato-biochemical alteration in the pre treatment period (Table 1 and 2) were also indicative of significant adverse effect of long term phenobarbiturate treatment in different dogs. Induced hepatopathy by phenobarbiturate on long term administration has been reported by many workers in dog which were also noticed in present study and evidenced by elevated ALP, ALT, AST and total bilirubin (Muller, 2009; Gaskill and Cribb, 2000).

The withdrawal / discontinuation of phenobarbiturate in the animals of both groups were decided due to either refractiveness or adverse effect of the drug. The withdrawal of phenobarbiturate was done in 7 days with concomitant loading dose of potassium bromide in all animals irrespective of groups. Administration of potassium bromide in dog was found to be cumbersome as the drug is hardly available commercially. Within first week of study in both the groups no dogs showed any remarkable improvement in term of seizure episode but subsequently they were observed free from epileptic fits. During the six months of study , the interval occurrence and duration of the episode of fits were 82.73±2.57 days ; 2.01± 0.34 sec and 127.15± 1.62 days ;1.85±0.12 sec in group A and B respectively. The symptoms of ataxia, drowsiness, polydipsia, polyurea and increased hunger were noticed in two dogs of either group on second weeks of study which disappeared subsequently. The distension, tenderness of abdomen, symptoms of vomition and anorexia observed in some dogs before the study subsided in the animals of both groups might be due to the adverse effect of phenobarbiturate on long term use The antiepileptic effect of potassium bromide is thought to be the result of bromide's generalized effect on neuronal excitability and activity. Bromide ions compete with the chloride ions transport across cell membrane resulting in membrane hyperpolarisation there by raising seizure threshold and limiting the spread of epileptic discharge (Rossmeisl and Inzana, 2009). Bromide is renally eliminated and does not undergo hepatic metabolism, thus useful in dogs with liver disease. All the haemato-biochemical data returned to the normal reference level within short duration of study indicative of tolerance of potassium bromide alone and in combination with Levetiracetam in hepato-compromised epileptic dogs. The elevated serum amylase and lipase though were observed in both groups but were within the reference range indicating that the prescribe d drug did not induce any remarkable pancreatopathy. The administration of potassium bromide has been reported to induce ataxia, sedation, polyurea and polydipsia, pancreatitis and other pancreatopathy (Rossmeisl and Inzana, 2009). In the present study no evidences either clinically or haemato-biochemically were suggestive of such adverse effect of potassium bromide during the six months of study. Levetiracetam a pyrrolidine-based anticonvulsant has an unknown mechanism of action. It has been used as an adjunct antiepileptic drug for dogs and cats and is occasionally used as mono therapy (Trepanier *et al.*2007). In dogs, it has excellent oral

bioavailability, does not appear to undergo hepatic metabolism, is primarily excreted unchanged in the urine thus making it an ideal antiepileptic drug in hepatic compromised patient. (Gambardella *et al*. 2008).

Table.1: Serum biochemical values at different intervals in pre and intra- treatment periods

Group		A(n=6)					B(n=6)				
Days		**0**	**15**	**30**	**90**	**180**	**0**	**15**	**30**	**90**	**180**
Kidney function	BUN **mg/dL**	24.04 ±0.05	23.72 ±0.06	24.11 ±0.05	23.24 ±0.02	23.53 ±0.06	22.22 ±0.07	20.7 ±0.1	21.22 ±0.05	20.89 ±0.02	21.25 ±0.04
	SC **mg/dL**	1.21 ±0.02	1.14 ±0.04	1.21 ±0.04	1.16 ±0.02	1.04 ±0.03	0.98 ±0.02	0.98 ±0.07	1.04 ±0.03	0.98 ±0.04	0.91 ±0.06
Liver function	ALT **u/L**	86.03* ±0.04	61.07 ±0.02	42.08 ±0.07	38.03 ±0.04	36.03 ±0.01	79.03* ±0.04	52.22 ±0.08	45.03 ±0.12	37.23 ±0.17	32.03 ±0.14
	AST **u/L**	70.03* ±0.11	54.07 ±0.18	37.05 ±0.07	34.03 ±0.19	31.07 ±0.21	67.03* ±0.21	53.04 ±0.24	35.08 ±0.27	33.03 ±0.21	32.03 ±0.29
	ALP **u/L**	259.5* ±0.22	171.6 ±0.28	123.1 ±0.32	120.6 ±0.29	117.6 ±0.42	234.6* ±0.08	164.6 ±0.31	142.1 ±0.51	128.6 ±0.29	121.3 ±0.42
	TB **mg/dl**	0.91* ±0.07	0.81 ±0.02	0.73 ±0.07	0.61 ±0.01	0.55 ±0.31	0.86* ±0.31	0.72 ±0.02	0.70 ±0.27	0.64 ±0.07	0.57 ±0.23
Electrolytes	Ca **mmol/L**	10.22 ±0.06	10.31 ±0.02	10.2 ±0.12	9.27 ±0.06	9.93 ±0.21	11.2 ±0.20	10.11 ±0.16	10.28 ±0.02	9.542 ±0.08	10.02 ±0.15
	Na **meq/L**	149.00 ±0.61	148.95 ±0.77	150.01 ±0.05	149.86 ±0.11	147.79 ±0.95	153.01 ±0.25	149.96 ±0.13	151.43 ±0.76	150.31 ±0.25	148.86 ±0.98
	K **meq/L**	5.22 ±0.18	5.12 ±0.25	4.92 ±0.16	5.07 ±0.12	5.29 ±0.21	4.88 ±0.19	5.12 ±0.22	5.02 ±0.20	4.94 ±0.11	4.92 ±0.17
	Chloride **mmol/L**	121.54 ±0.02	125.13 ±0.62	120.51 ±0.12	119.54 ±0.02	121.06 ±0.62	119.01 ±0.07	120.33 ±0.11	120.54 ±0.72	119.77 ±0.12	121.15 ±0.09
Lipid profile	Trigly **mg/dL**	282.45 ±0.31	291.70 ±0.87	278.33 ±0.97	298.73 ±0.76	282.09 ±0.37	282.71 ±0.53	279.02 ±0.31	290.73 ±0.91	282.79 ±0.11	285.51 ±0.35
	Cholest **mg/dL**	324.39 ±0.48	342.01 ±0.48	329.99 ±0.48	371.39 ±0.48	312.02 ±0.98	365.39 ±0.54	344.19 ±0.44	329.30 ±0.77	324.39 ±0.31	319.06 ±0.27
Pancreas function	Serum amylase **u/L**	374.62 ±0.97	381.77 ±0.77	389.62 ±0.43	392.12 ±0.55	392.97 ±0.64	347.99 ±0.66	370.62 ±0.90	377.99 ±0.37	384.62 ±0.54	381.95 ±0.97
	Lipase **u/L**	268.96 ±0.29	277.55 ±0.31	281.96 ±0.38	280.12 ±0.20	288.54 ±0.25	248.99 ±0.59	260.16 ±0.26	268.94 ±0.25	274.96 ±0.29	284.44 ±0.33
	Glucose ® **mg/dL**	102.46 ±0.25	111.06 ±0.21	112.32 ±0.15	113.46 ±0.26	117.46 ±0.15	98.46 ±0.11	109.96 ±0.25	112.99 ±0.75	116.46 ±0.25	111.01 ±0.21

Table no.2: Haematological values at different intervals in pre and intra- treatment periods

Groups	Days	HB(g/dl)	PCV (%)	TEC(x10^6/µl)	TLC(/µl)	ESR(mm/h)
A (n=6)	0	10.13±0.36	48±0.09	7.9±0.08	15700±2.02	5.26 ±0.30
	15	12.86±0.44	41±0.04	8.2±0.12	15000±1.99	4.20 ±0.31
	30	13.55±0.15	44±0.19	7.8±0.07	15451±2.22	3.26 ±0.44
	90	13.46±0.76	36±0.12	7.4±0.11	15700±1.12	3.68 ±0.37
	180	13.02±0.81	35±0.09	8.0±0.02	15070±3.22	4.26 ±0.01
B (n=6)	0	10.02±0.56	45±0.08	7.7±0.22	15200±4.22	3.24 ±0.31
	15	12.86±0.05	40±0.11	7.8±0.67	15771±2.76	3.86 ±0.62
	30	13.73±0.37	36±0.09	7.7±0.02	15000±2.22	3.26 ±0.39

	90	13.99±0.54	38±0.06	8.2±0.07	15841±2.00	3.75 ±0.38
	180	13.86±0.68	33±0.32	8.0±0.22	15892±4.22	3.26 ±0.31

Summery and Conclusion

The epileptic dogs mostly treated with phenobarbiturate are often found refractory and intolerable to phenobarbiturate. Such dogs may be treated effectively with potassium bromide alone or in combination with Levetiracetam. Withdrawal of phenobarbiturate in refractory cases and administration of potassium bromide in loading dose should be done concomitantly for better effect. To minimize the adverse effect of potassium bromide regular monitoring of clinical and haemato-biochemical parameters are essential to assess the therapy. Combination of phenobarbiturate and Levetiracetam not only controlled the epilepsy effectively but also reduced the seizure episode in term of frequency and duration in most of the dogs. The adverse reactions so far recorded in the study in the both groups were of similar and transient and probably independent on medication.

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