

Efficiency of Levetiracetam and Gabapentin in the treatment of Epilepsy in a Cavalier King Charles Spaniel Dog with Myxomatous Mitral Valve Heart Disease, a Case Report

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Abstract

Epilepsy and seizure have a complex physiopathological background and are most common idiopathic or primary neurologic disorders in dogs. Various anticonvulsant (ACDs) and antiepileptic drugs (AEDs) are used for the management of seizures and epilepsy. The use of levetiracetam is limited in the treatment of epilepsy and is used only with expert opinion because of its undesirable side effects and its low therapeutic effect, which are not chemically related to existing AEDs. The Cavalier King Charles Spaniels (CKCSs) are predisposed to numerous inherited neurologic and cardiologic problems due to their high predisposition to genetic pool originated consanguineous diseases. The dog was 3 years old, female, CKCSs breed stud and had been suffered from epileptic seizures almost 3 months. The dog was consulted at Veterinary Faulty Clinics and myxomatous mitral valve heart disease (MMVD) was diagnosed. Phenobarbital (2.5 mg/kg BID, PO) and enalapril (0.5 mg/kg BID, PO) were prescribed for the management of epileptic seizures and medication of the MMVD. However, the dog wasn't reacted the treatment as expected and epileptic seizures were increased dramatically (~7 times per day) in addition with respiratory depression. The treatment protocol was changed to levetiracetam (15 mg/kg BID, PO). The dog was reacted well to levetiracetam treatment and epileptic seizures were disappeared with respiratory depression. Three months later a routine parasitic treatment was done with fipronil (0.067 ml/kg, spot-on). The epileptic attacks were dramatically increased and became more severe just after the fipronil treatment (~7 times per day). Thus, gabapentin (10 mg/kg, TID, PO) was decided to use together with levetiracetam (10 mg/kg BID, PO). Epileptic seizures disappeared with the use of gabapentin over again. In conclusion, the pharmacokinetics and antiepileptic effects of levetiracetam and gabapentin are not fully understood, but the combination of both drugs with a combined drug protocol may help to manage epileptic attacks without causing respiratory depression in CKCS.

Keywords: Anti-epileptic drugs, Canine, Epilepsy, Levetiracetam

1. INTRODUCTION

The Cavalier King Charles Spaniels (CKCSs) are predisposed to numerous inherited neurological and cardiological problems due to their high predisposition to genetic pool originated consanguineous diseases ¹⁻³. Mitral valvular heart disease (MMV) is one of the most common inherited disorders in CKCSs. The CKCSs have genetic mutation on the ACE-I gene. This polymorphism is related to lower ACE activity. Moreover, renal and pancreatic diseases are reported with high prevalence on post-mortem examinations 52.2% and 51.9% which have lower clinical signs at ante-mortem examinations 16.7%, 25%, respectively ⁴. Epilepsy and seizure have complex physiopathological background, and are

most common idiopathic or primary neurologic disorders in dogs ⁵⁻⁷. Various anticonvulsant (ACDs) and antiepileptic drugs (AEDs) are used for the management of seizures and epilepsy. The main goals of treatment, to eliminate epileptic events, to decrease seizure frequency and intensity, to avoid adverse effects such as long term treatment, drug-drug interactions, to decrease seizure-related mortality and morbidity, and to restore abnormal behaviour due to maintenance the life quality. Primarily preferred AEDs, were reported as effective to manage epileptic seizures have high interactions between drugs and undesirable side effects such as hepatotoxic and pancreotoxic activity on the patients ⁸. A water soluble pyrrolidone derivate levetiracetam (LEV) whose chemical structure and molecular charac-

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teristics and pharmacokinetic properties differs from other AEDs has prominent advantages as fully absorbed after oral administration, minimal protein-binding, lacked of hepatic metabolism, excreted unchanged in the urine, and short half-life⁹. Gabapentin is also safely, tolerable GABA analog second-generation antiepileptic drug which is rapidly absorbed after oral administration. The mechanism of action is not fully elucidated yet but it is not metabolized by the liver as same as levetiracetam. Hereby, gabapentin is not used the cytochrome P oxidase 450 (CYP450) isoenzyme system¹⁰. It seems more effective due to less drug interactions at management of epilepsy. Fipronil is widely used, second-generation phenylpyrazole originated antiparasitic insecticide in veterinary practice and exerted their effects by inhibition of ligand-gated chloride channels of targeted parasites. Blockage of the gamma amino butyric acid (GABA)-gated chloride channels by fipronil are caused to reduce neuronal inhibition and lead to convulsions and hyperexcitation of the central nervous system¹¹. First-line AEDs, especially phenobarbital and potassium bromide, are preferred primarily to manage the epileptic seizures in dogs by veterinarians¹². The pharmacodynamics of first line AEDs and enalapril which is used to cure symptomatic cardiac diseases are metabolized by liver enzymes especially by CYP450 pathway. However, there is not enough information about the physiopathological and pharmacological metabolic mechanisms of the levetiracetam. Additionally, no data on the interaction of levetiracetam and fipronil were found in the reference information. For that reasons, the aim of this case report is to show the successful management of epileptic seizures in a CKCS breed dog with MMVD and possible drug to drug interactions by second-generation AEDs'.

2. CASE DESCRIPTION

The dog is a 3-year-old female, CKCS breed stud, neutered and has had epileptic seizures for about 3 months. The dog was consulted at Veterinary Faulty Clinics and myxomatous mitral valve heart disease (MMVD) was diagnosed. Diagnosis was based on the patient history, clinical symptoms and status epilepticus formation. MRI was not performed due to owner response based on the side-effects of anaesthesia requirement. Phenobarbital (2.5 mg/kg BID, PO) and enalapril (0.5 mg/kg BID, PO) were prescribed for the management of epileptic seizures and medication of the MMVD. However, the dog was not reacted the treatment as expected and epileptic seizures were increased dramatically (~7 times per day) in addition with respiratory depression. The treatment protocol was changed to levetiracetam (15 mg/kg BID, PO). The dog was reacted well to levetiracetam treatment and epileptic seizures were disappeared with respiratory depression. Three months later a routine parasitic treatment was done with fipronil (0.067 ml/kg, spot-on). The epileptic attacks were dramatically increased and became more severe just after the fipronil treatment (~7 times per day). Thus, gabapentin (10 mg/kg, TID, PO) was decided to use together with levetiracetam (10 mg/kg BID, PO). Epileptic seizures

disappeared with the use of gabapentin over again.

3. DISCUSSION

According to the American College of Veterinary Internal Medicine (ACVIM) consensus statement for seizure management in dogs based on current literature and clinical expertise; phenobarbital, bromide and imepitoin are recommended as primary and more effective monotherapeutic AEDs, than primidone, zonisamide and levetiracetam are less recommended⁸. There is a lack of knowledge about preferred AEDs by Turkish Veterinarians to the management of epilepsy in the dog. Nevertheless, in our experience first-line AEDs are widely used to control the epileptic seizures among clinicians. In this case, myxomatous mitral valve heart disease was diagnosed on an epileptic CKCS breed dog. Phenobarbital was chosen for the first decision to management of the epileptic seizures by veterinarian. Meanwhile, enalapril was preferred to alleviate the cardiac effects of MMVD.

Meurs, et al.⁴ were pioneered in the opinion of the ACE gene polymorphism in CKCSs and they previously were reported that canine ACE gene polymorphism associated with a decrease in ACE activity. According to their results, the CKCS appears to have a high prevalence of the ACE variant which reduces the levels of ACE activity. Therefore, the efficacy of an ACE-I inhibitor enalapril for the treatment of MMVD on CKCs has not been fully established.

CKCSs are brachycephalic breeds, and are predisposed to respiratory disorders related to their genetic characteristics. Summers, et al.¹³ was reported the prevalence of brachycephalic airway obstruction syndrome %16 in a total of 3624 CKCSs. Phenobarbital is a barbituric acid derivate and longest-acting barbiturate that inhibits the calcium channels, resulting in a decrease in excitatory transmitter release thus its caused to CNS and respiratory depression which may progress to Cheyne-Stokes respiration¹⁴ abnormality. The respiratory abnormality forced to reconstruct the management protocol of epileptic seizures. Hence, we decided to use the levetiracetam as a second generation AED which is widely used in human practice, lesser side effects have been reported and chemically unrelated to existing AEDs, also may be more appropriate when it is used with a combined drug protocol. Lynch, et al.¹⁵ reported that LEV's cellular target is synaptic vesicular protein SV2A. Synaptic vesicles are abundant secretor organelles of presynaptic nerve terminals which are divided into two classes based on their functions as transport and trafficking proteins. SVs are accumulated high quantities of neurotransmitters and secrete them by fusion with the presynaptic plasma membrane. One of the family members SV2A's, which is most widely distributed in the central nervous system (CNS), exact role, is still remains unclear. However, it has been proposed to be an integral membrane protein present on all synaptic vesicles. Packer, et al.¹⁶ reported that levetiracetam is a well tolerated, seizure-suppressing drug, and the success rate in 52 epileptic dogs was found %50 reduction, %15 of all the dogs were

completely free from seizures both mono- or add-on therapy. Just, 2 dogs with the levetiracetam monotherapy group were needed to add-on therapy by gabapentin after 168 days of treatment. Nevertheless, there is lack of information about why the researchers were decided to need and choose gabapentin to add-on therapy.

Bharathraj, et al.¹¹ reported the interaction between fipronil and status epilepticus; the blockage of the GABA-gated chloride channels by fipronil reduces neuronal inhibition and leads to convulsions and hyperexcitation of the central nervous system. Fipronil has also been previously reported to trigger hyperexcitability such as tremor, convulsions, seizures and death¹². Even if, fipronil is noncompetitively bound GABA_A-gated chloride channels thereby blocking the inhibitory action of GABA_A in the CNS, the return of the epileptic seizures, after well managed levetiracetam therapy which also act on voltage- or ligand-gated ion channels involved in synaptic transmission¹⁷, could be mediated by unexplained drug-drug interactions in our case.

Govendir, et al.¹⁸ reported that gabapentin treatment as an adjunctive agent to phenobarbital and/or potassium bromide increased the interictal period and shortened the post-seizure recovery and in some dogs seizures were terminated while in others there was an increase in interictal period. Platt, et al.¹⁹ treated 11 dogs with refractory idiopathic epilepsy, they concluded that after 3 months gabapentin therapy lead to reduction in the number of seizures %50 and it should be considered as an adjunctive anticonvulsant treatment. Therefore we decided to add-on therapy with gabapentin to manage the epileptic seizures after fipronil treatment. Up to now, we were not encountering new attack and still continue applying the gabapentin as an add-on therapy protocol.

4. CONCLUSION

In conclusion, new generation AEDs were reported to have lesser side effects based on the pharmacokinetic data which is indicated that levetiracetam not using the cytochrome P450 liver metabolic pathway. In addition to this advantageous metabolic activity, it may be effective in controlling routine epileptic seizures of CKCSs without causing respiratory depression. Fipronil, phenylpyrazole origin and other antiparasitic drugs should be used very carefully and under veterinary consultant supervision due to their side effects especially in epileptic dogs. Finally, gabapentin could be a good option for the alternative add-on therapy to control epileptic seizures in CKCSs.

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Selçuk Duman

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Osman Kola

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Mersin University

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Vedat Taşdemir

Mechanical Prog
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Yasemin Coşkun

Biological Science
Süleyman Demirel University

Zekine Pündük

Medicine
Balıkesir University

Zülküf Kaya

Civil Engineering
Erciyes University

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Invited Speakers

Invited Speaker	University/Country	Title of oral presentation(s)
1.  Mamatimin Abbas	CNRS, Université de Bordeaux, Lab. IMS, UMR 5218, 33607, Pessac, France	<i>Thin film transistors: from vacuum deposition to solution processing</i>
2.  Mokhtaria Dehar	Laboratory of Macromolecular Physical Chemistry, Department of Chemistry, University of Oran1 Ahmed Ben Bella, BP 1524 EL-M'Naouer, Oran 31100, Algeria	<i>Synthesis of crosslinked polymers of poly [p- and m- (N-vinylbenzylidene)] derivative of 1,2,4-triazole and their antimicrobial activity studies</i>
3.  Mahmoud Mirzaei	Isfahan University of Medical Sciences, Isfahan, Iran	<i>In Silico Science and Engineering Insights</i>
4.  Roxana Bugoi	Horia Hulubei National Institute for Nuclear Physics and Engineering, 30 Reactorului Street, Magurele 077125, Romania	<i>Archaeometric Studies on Roman Glass Finds from Romania</i>
5.  Moulkheir Ayat	Moulay Tahar University, Department of Chemistry, Faculty of Sciences, BP138 City, Nasr Saida 20000, Algeria	<i>Synthesis of block Copolymers consists on Vinylidene Chloride and alpha- MethylStyrene by Cationic Polymerization using an Acid Exchanged Montmorillonite Clay as Heterogeneous Catalyst (Algerian MMT)</i>
6.  Mohammed Ouikhalfan	Cadi Ayyad University, Faculty of Sciences and Techniques, Department of Applied Physics, Marrakesh, Morocco	<i>Thermal properties of TiO₂ enhanced Myristic Acid as a phase change material</i> <i>Thermal properties of ZnO enhanced polyethylene glycol (PEG) as a phase change material</i> <i>Review on thermal conductivity enhancement of form-stable phase change materials (FSPCMs)</i>