Successful Long-term Management of Pharmacoresistant Idiopathic Epilepsy in a French Bulldog

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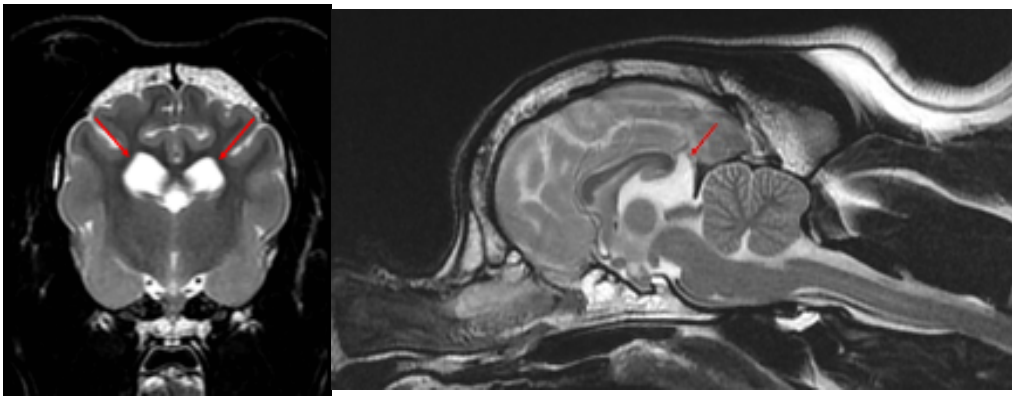
ABSTRACT

A 2-year-old French bulldog was presented with cluster seizures. Based on the examination results, the dog was diagnosed with idiopathic epilepsy. He was administered several antiepileptic drugs for 1 year. However, he continuously experienced cluster seizures within 1 week after withdrawing phenobarbital or decreasing its dosage to half (4 mg/kg once daily), although other antiepileptic drugs were used, and serum drug levels reached therapeutic levels. After changing the phenobarbital dosage to 2 mg/kg twice a day, the patient did not present with additional seizures for at least 3 months; however, the dog presented clinical signs when 4 mg/kg phenobarbital was administered once daily. Furthermore, several antiepileptic drugs were discontinued, and the seizures were finally successfully controlled through a combination of potassium bromide and the decreased phenobarbital dosage. We found that the refractory seizures responded only to phenobarbital and were finally adequately managed by adjusting the frequency and dosage of phenobarbital and add-on antiepileptic drugs. Our findings suggest that seizures could be affected by the administration frequency, rather than the total administered dose, of phenobarbital. Therefore, this case report can be helpful for clinicians considering a therapeutic strategy for drug-resistant epilepsy.

Epilepsy is a common neurologic disease in small animals (3, 4, 7, 11). The incidence of epilepsy in dogs has been reported to be approximately 0.6-5% (4, 7) Epilepsy is defined as chronic multiple

Figure 1. *T2-weighted transverse (A) and sagittal (B) images on magnetic resonance imaging scan. (A) Mild dilation of the lateral ventricles (ventricular height to brain height = 0.20) (arrow). (B) Mild dilation of the quadrigeminal cistern without compression of the cerebrum and cerebellum (arrow).*



seizures, usually more than two seizures in a month (14). Idiopathic epilepsy is defined as recurring seizures with no defined structural or metabolic causes (14). Approximately 38% to 77% of dogs with idiopathic epilepsy present cluster seizures, which refer to two or more seizures occurring within 24 hours (10). They can be used as a prognostic factor reflecting the remission rate and survival time (9). The frequency of cluster seizures in dogs with idiopathic epilepsy is negatively correlated with the remission rate and survival time [10).

Therefore, choosing proper anticonvulsants for reducing the seizure frequency is very important in canine patients with idiopathic epilepsy. Since seizures are usually well-controlled by therapy, patients with idiopathic epilepsy have a good prognosis(13). Patients with idiopathic epilepsy have been reported to have long survival times of approximately 11.8 years or even to their expected life span with treatment(13). Antiepileptic drugs (AEDs) have been used for epilepsy management by reducing the seizure frequency by at least 50% and avoiding drug-induced adverse effects.(3). Phenobarbital and potassium bromide (KBr) are the first-choice drugs for dogs with epilepsy (3). Phenobarbital is effective as a monotherapeutic agent in 60 to 80% of dogs with epilepsy (3, 120. Adding KBr to an existing phenobarbital regimen has been reported to improve seizure control in 50% of dogs. Further, it could decrease or discontinue the phenobarbital dosage (3). However, refractory seizures that are unresponsive to these medications can be controlled by adding levetiracetam or zonisamide (2, 3).

This report presents a dog with refractory seizures that initially only responded to phenobarbital despite administration of add-on therapy including KBr, levetiracetam, and zonisamide. In our patient, the seizures were successfully controlled by adjusting the administration frequency of phenobarbital in combination with KBr, which allowed the phenobarbital dosage to be finally reduced without seizure recurrence. Therefore, this case report aims to help clinicians to establish a therapeutic plan for pharmacoresistant idiopathic epilepsy.

CASE PRESENTATION

A 2-year-old female French bulldog weighing 15 kg was admitted to the Konkuk University Veterinary Medicine Teaching Hospital with a 1-year history of intermittent cluster seizures. Prior to admission, the dog had been treated with phenobarbital (4 mg/kg twice a day orally) and levetiracetam (20 mg/kg thrice a day orally) for 1 year. The dog had neither been exposed to toxin nor traumatized. All vaccinations had been completed. The results of physical examina-

tion, complete blood count, serum chemistry profile, radiography, and ultrasonography were unremarkable except for hyperechoic sludges in the urinary bladder. Neurological examination indicated that the mental status, cranial nerve reflexes, spinal reflexes, and postural reactions were within normal limits. Based on these findings, extracranial causes were excluded.

Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis were performed to identify intracranial lesions. MRI images showed no significant compression and edema in the cerebrum and cerebellum, although the bilateral lateral ventricles and quadrigeminal cistern were mildly dilated (Fig. 1). Incidentally, we detected fluid in the bilateral tympanic cavity but not in the external ear canals. Cytologic CSF analysis showed no remarkable findings except for blood contamination during CSF centesis. Based on the MRI and CSF analysis findings, the patient was diagnosed with idiopathic epilepsy.

Although the seizures did not continue after applying pharmacological treatment, there was a need to adjust the anticonvulsant drugs since the patient was on long-term high doses of phenobarbital and levetiracetam. Initially, we added zonisamide (Donga Pharm., Republic of Korea; 10 mg/kg twice a day orally) and KBr (Duksan Pure Chemicals, Republic of Korea, 40 mg/kg once a day orally) to the existing treatment regimen before reducing the phenobarbital dosage (Table 1). After attaining the KBr therapeutic level (1.2 mg/ml; reference range, 1.0-3.0 mg/ml), we tried to decrease the phenobarbital dosage by half (4 mg/kg once a day) to reduce the risk of hepatopathy from long-term phenobarbital use (Table 1 and 2). However, whenever we tried to reduce the phenobarbital dosage, the cluster seizures recurred within 1 week. Consequently, phenobarbital was increased to the previous dosage (4 mg/kg twice a day orally) and the serum chemistry profile was monitored for potential side effects of phenobarbital.

Approximately 3 months after the first visit, the serum levels of KBr and zonisamide were monitored again. Since the serum level of zonisamide was 7.60 ug/ml, which was below the therapeutic level (reference range, 10-40 ug/ml), the zonisamide dosage was increased to 15 mg/kg twice a

Table 1. *Dosage of antiepileptic drugs and seizure episodes (*) according to time flow*

	Week 0	Week 6	Week 7*	Week 8	Week 9*	Week 10	Week 11	Week 12	Week 17	Week 20	Week 22
Phenobarbital (mg/kg)	4 BID	4 BID	4 SID	4 BID	4 SID	4 SID	4 BID	4 BID	4 BID	4 BID	2 BID
Potassium bromide (mg/kg)	40 SID	40 SID	40 SID	40 SID	40 SID	40 SID	40 SID	40 SID	28 BID	28 BID	40 SID
Levetiracetam (mg/kg)	20 TID	20 TID	20 TID	20 TID	20 TID	20 TID	20 TID	20 TID	20 TID	20 TID	-
Zonisamide (mg/kg)	10 BID	10 BID	10 BID	10 BID	10 BID	10 BID	10 BID	10 BID	15 BID	15 BID	-

**Seizure episode*
SID, once daily; BID, twice a day; TID, three times a day.

Table 2. *Serum level of antiepileptic drugs (bromide, phenobarbital, and zonisamide)*

	Week 2	Week 7	Week 12	Week 20	therapeutic range
Bromide	0.3 mg/ml	1.2 mg/ml	1.2 mg/ml	1.3 mg/ml	1.0-3.0 mg/ml
Phenobarbital	ND	ND	25.3 ug/ml	ND	15-35 ug/ml
Zonisamide	ND	ND	7.60 ug/ml	46.40 ug/ml	10-40 ug/ml

ND, not done.

day. Moreover, the KBr dosage was increased to 28 mg/kg twice a day based on the formula of adjusting the KBr concentration according to its clearance and bioavailability due to its low therapeutic serum level (1.2 mg/ml; reference range, 1.0-3.0 mg/ml) (11).

Approximately 1 month after increasing the KBr and zonisamide dosage, the serum level of zonisamide exceeded the therapeutic level (46.40 ug/ml; reference range, 10-40 ug/ml). Therefore, the zonisamide dosage should have been decreased to 12.5 mg/kg twice a day since phenobarbital could increase the clearance of zonisamide by approximately 50% (11) and we planned to ultimately decrease the phenobarbital dosage after stabilizing the serum levels of the anticonvulsant drugs to within the therapeutic range.

Although had not yet observed adverse effects such as hepatotoxicity, we recommended trying to reduce the phenobarbital dosage again for long-term management. With the owner's consent, we gradually decreased the phenobarbital dosage (2 mg/kg twice a day orally) and stopped all other add-on treatments except KBr (40 mg/kg once per day orally). Although the phenobarbital dosage was the same as before (4 mg/kg/day), the seizures have not recurred up to now, which is at least for 3 months after reducing the AEDs dosage. Further, she has regularly undergone routine checkups and biochemistry analysis, including hepatic panel, have not revealed remarkable findings.

DISCUSSION

Overall, 88% of dogs with idiopathic epilepsy respond well to AEDs (13). Phenobarbital is a very effective seizure control agent in small animals (5, 11, 12). Phenobarbital treatment has shown seizure control in 90% and 80% of cats and dogs with idiopathic epilepsy, respectively (5, 13). Long-term use of phenobarbital has shown seizure control in 53% of dogs with epilepsy (13). Despite its effectiveness in controlling seizures, long-term use of phenobarbital has potentially life-threatening adverse effects such as immune-mediated anemia, thrombocytopenia, and neutropenia (11). Specifically, drug-induced hepatotoxicity is the most critical adverse effect (1, 3, 5, 6, 11). Therefore, other AEDs with less life-threatening adverse effects have been suggested as alternatives to phenobarbital.

KBr is generally well tolerated and its most common side effects are polydipsia, polyphagia, and mild ataxia (3, 11). It can also be used in conjunction with phenobarbital and its reported success rate of seizure control is up to 90% (13). Further, adjunct KBr treatment can allow reduction of the phenobarbital dosage (3).

Levetiracetam is one of the add-on AEDs used in small animals to control refractory seizures with phenobarbital (3, 5, 11). An approximate 77% reduction in seizure frequency was observed in dogs with pharmacoresistant epilepsy to phenobarbital and KBr after add-on levetiracetam therapy (15). Long-term use of levetiracetam is extremely safe with only mild side effects (3, 11). Even dogs with levetiracetam overdose of up to 1200 mg/kg/day were reported to only show salivation, vomiting, and unsteady gait (3).

Zonisamide also has little side effects such as mild sedation, vomiting, and

generalized ataxia with a study reporting their prevalence to be only 10% (2, 11). The seizure frequency in dogs undergoing zonisamide therapy has been reported to decrease by approximately 80% (3).

Our canine patient continually experienced cluster seizures after the withdrawal or decrease of the phenobarbital dosage to half (4 mg/kg once daily), even with use of other AEDs and the drug serum levels reaching therapeutic levels. However, since adding phenobarbital to the pre-existing treatment, the patient has not shown additional seizures. Interestingly, the administration frequency of phenobarbital seemed to affect the manifestation of cluster seizures even though the administered total phenobarbital dosage was the same (4 mg/kg/day). Our canine patient has not presented with additional seizures after reducing the phenobarbital dosage to 2 mg/kg twice a day even though she had presented clinical signs when the phenobarbital dosage was decreased to 4 mg/kg once daily. This result implies that clinicians should not only consider not only total phenobarbital dosage but also the administration frequency when decreasing the phenobarbital dosage.

In veterinary medicine, imepitoin was recently approved as a therapeutic agent of idiopathic epilepsy in Europe (12). Imepitoin administration has similar effectiveness as phenobarbital in managing generalized seizures, and is more effective in the dogs with seizures occurring more than once per month but with less adverse effects (4, 8, 11). The adverse effects of imepitoin are mild and transient (4, 11). Only 29% of dogs showed excitability, sedation, polyphagia, generalized tremors, and gastrointestinal interruptions with these side effects disappearing within 10 days (4). Although imepitoin has still not been imported to the Republic of Korea, we consider it as an additional treatment. Since imepitoin controls cluster seizures and refractory epilepsy with mild side effects with long-term use, it can be a therapeutic option in cases showing refractory seizures after withdrawing phenobarbital.

In conclusion, most patients with idiopathic epilepsy respond well to AEDs. However, our canine patient presented with pharmacoresistant epilepsy that only responded to phenobarbital and did not show satisfactory results with add-on antiepileptic drugs. To reduce the adverse effects of long-term phenobarbital use, KBr could be added to the therapeutic regimen and after attaining the serum therapeutic levels, the phenobarbital dosage could be decreased. Interestingly, the clinical condition of our canine patient differed according to the frequency of administration. Therefore, even with an equal total dosage of phenobarbital, the administration frequency can affect the management of seizures. Further, our case revealed that pharmacoresistant epilepsy can be properly managed properly with the combination of KBr and a minimum phenobarbital dosage for a long-term period. Therefore, this case report can be helpful to clinicians for estimating the long-term prognosis of refractory epilepsy and to develop a therapeutic plan for drug-resistant epilepsy.

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