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< Case Report >

Phenobarbital and zonisamide treatment of a cat with epilepsy of unknown cause

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Abstract

A Korean domestic short hair (1-year-old, male) presented with 2 to 3 weeks of seizures, aggressive behavior, vomiting, anorexia, and lethargy. The frequency of seizure had gradually increased from once a week to once every 3 hours. Physical and neurologic examination, diagnostic screening tests, including complete blood count (CBC), serum chemistry, electrolyte, coagulation test, X-ray, ultrasonography, and urinalysis were performed. Feline Leukemia Virus (FeLV), Feline Immunodeficiency Virus (FIV) and Toxoplasma spp. All tested negative, but the Feline Corona Virus (FCoV) kit revealed a positive result. To determine the exact diagnosis, magnetic resonance imaging (MRI) was performed but yielded no specific findings. The patient was then diagnosed with idiopathic epilepsy and treatment of phenobarbital was initiated. A month's treatment with phenobarbital proved ineffective as symptoms worsened. Zonisamide was then selected as an additional anticonvulsant. After adding zonisamide, symptoms improved, and seizures abated for 15 months. This is the first case report in South Korea describing the use of phenobarbital and zonisamide in the treatment of a cat with idiopathic epilepsy.

Key words : Feline, Idiopathic epilepsy, Magnetic resonance imaging (MRI), Phenobarbital, Zonisamide

INTRODUCTION

Epilepsy is a chronic neurologic disease that causes recurrent seizures and has an intracranial etiology. Thus, extracranial disorders related to metabolic conditions (e.g., hypocalcemia and hypoglycemia) or toxins (e.g., organophosphate and ethylene glycol) may induce seizure activity but are not considered epilepsy even if the repetitive seizures occur over time (Christopher, 2013). According to the recent suggestions of the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), epilepsy can be classified into three groups, genetic epilepsy, structural epilepsy, and epilepsy of unknown cause (Berg et al, 2010). Genetic epilepsy is a direct result of a known or strongly suspected genetic defect or defects in which seizures are the core sign of the disorder (Christopher, 2013). Until now, only one study has identified a familial spontaneous epileptic cat strain (Kuwabara et al, 2010). Structural epilepsy is defined as epilepsy caused by any cortical, subcortical, or thalamic structural lesion evident with magnetic resonance imaging (MRI) or histopathology (Wahle et al, 2014). Structural lesion that is too subtle to be detected by current diagnostic technologies or genetic disorder that is not yet revealed may be included in this category (Christopher, 2013). Initiation of antiepileptic treatment is usually recommended when an identifiable structural lesion is present, more than one cluster seizures have occurred, seizure is seen within 6 weeks of last seizure activity, or status epilepticus has occurred (Bailey and Dewey, 2009; Pakozdy et al, 2014). With several antiepileptic drugs being used in veterinary practice, phenobarbital is the typically used drug of choice. Based on its efficacy, relative safety,

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reasonable dosing frequency (q12h) and low cost, phenobarbital is considered as a first-line treatment. For initial therapy, a dose of 2.5～3 mg/kg PO q12h is recommended with the dosage adjustment based on drug levels, efficacy and adverse effects (Plumb, 2015). Adverse effects include sedation, ataxia, polyuria (PU), polydipsia (PD), polyphagia (PP), leukopenia, thrombocytopenia, skin eruptions, and coagulopathy (Pakozdy et al, 2014). In contrast to dogs, hepatotoxicosis has not been reported in cats as a complication of phenobarbital. Zonisamide, once-daily administration of a 5～10 mg/kg dose, is another drug that can be used in cats with epilepsy (Bailey and Dewey, 2009). There is a single report describing the pharmacokinetics of zonisamide in cats, with maximum concentrations achieved approximately 4 hours after oral administration and an elimination half-life of approximately 33 hours (Muñana, 2013). Although the toxicity of zonisamide is comparatively low in cats, half of the cats that were administered 20 mg/kg/day daily experienced adverse effects such as anorexia, diarrhea, vomiting, somnolence and locomotor ataxia (Hasegawa et al, 2008). This is the first case report describing phenobarbital and zonisamide for the treatment of idiopathic epilepsy in a cat in South Korea.

CASE

A 1-year-old intact male Korean Domestic Shorthair was referred after having 3 weeks of seizures, aggressive behavior, vomiting, anorexia, and lethargy. The frequency of seizure had gradually increased from once a week to once every 3 hours with duration of 20 to 30 seconds. Physical and neurologic examinations showed no abnormalities. Diagnostic screening tests including complete blood count (CBC), serum biochemistry, electrolyte, kit, radiography, ultrasonography, prothrombin time (PT), activated partial thromboplastin time (aPTT) and urinalysis were performed. CBC showed increase in WBC (23.6×10^{12}/L (reference range, $5.5\sim19.5\times10^{12}$/L)) with grade 4 toxic change (Giantism) and decrease in platelets (118×10^{9}/L (reference range, $300\sim800\times10^{9}$/L). Serum biochemistry revealed decreased blood urea nitrogen (BUN) (10 mg/dL [reference range, 16～33 mg/dL]) and lipase (15 U/L [reference range, 40～500 U/L]). Albumin (3.1 g/dL [reference range, 2.2～3.9 g/dL]) and globulin (3.5 g/dL [reference range, 2.8～4.8 g/dL]) were normal value indicating albumin: globulin ratio (A:G ratio) of 0.88 (Table 1). A diagnostic kit, including feline leukemia virus diagnostic (FeLV) and Feline immunodeficiency virus (FIV), was negative, but the kit for the Feline corona virus (FCoV) revealed a positive result. Serum was sent to the referral laboratory for the toxoplasma split titer (Immunoglobulin G [IgG] and immunoglobulin M [IgM]) by enzyme linked immunosorbent assay (ELISA), but was also negative. Abdominal ultrasound scan revealed, enlargement of multiple mesenteric lymph nodes, with a largest size being 2×2. There was no peritoneal fluid nor was there peritonitis. There was a delay in both PT (24.3 [reference range, 15～22 sec]) and aPTT (＞200 [reference range, 65～119 sec]). Urinalysis revealed positive RBC (2+), protein (3+) and WBC (3+) with the pH of 8. The urine specific gravity (USG) was measured by urinometer resulting hypersthenuria (＞1.060). On urinary cytology, a number of struvites were seen. For the exact diagnosis, magnetic resonance imaging (MRI) was performed. However, the MRI did not show any specific feature, leading to a diagnosis of idiopathic epilepsy. After the diagnosis, treatment with phenobarbital (2.5 mg/kg PO q12h) was selected for the first-line of therapy. On day 14, patient's appetite recovered and the frequency of seizure decreased to once daily. The same medication was given and further monitoring was planned.

On day 30, the frequency and duration of seizure had deteriorated (1～2 times daily with the duration of 1～2 minutes) and the behavior became more aggressive. The A:G ratio was 0.82 and radiographic examination showed no specific findings. Due to a worsening in clinical symptoms, a higher dose of phenobarbital (3 mg/kg PO q12h) and zonisamide (7.5 mg/kg PO q12h), as an additional anticonvulsant, was prescribed until day 183. During this period, the frequency of seizure significantly decreased and the aggressive behavior disappeared. Seizure occurred only one time at day 109 and other clinical signs including anorexia and vomiting gradually improved. On day 184, considering the owner's finan-

Table 1. Changes of complete blood count and serum biochemistry parameters of the patient

	Reference	Day 0	Day 65	Day 184
WBC	5.5～19.5×10^{12}/L	23.6	16.7	17.4
RBC	5～10 ×10^{12}/L	9.14	8.29	10.9
Hct	24～45%	39.8	36.9	48.6
Hb	8～15 g/dl	12.9	12.4	16.3
THR	300～800×10^{9} /L	118	140	179
Albumin	2.2～3.9 g/dL	3.1	3	3.4
Globulin	2.8～4.8 g/dL	3.5	3.7	2.2
T-protein	5.2～8.2 g/dL	6.6	6.7	5.6
Amylase	500～1400 U/L	725		781
T-Chol	62～191 mg/dL	140		148
Creatinine	0.6～1.6 mg/dL	1.1		1.4
Glucose	85～130 mg/dL	112		105
BUN	16～33 mg/dL	10		27
Phosphorus	4.5～10.4 mg/dL	8.0		6.2
Lipase	40～500 U/L	15		13
CK	0～394 U/L	63		
AST	12～46 U/L	19		39
ALT	28～106 U/L	28		197
ALP	14～111 U/L	86		100
GGT	0～4 U/L	0		0
Na	150～165 mEq/L	157.2	153.9	155.3
K	3.7～5.9 mEq/L	4.45	3.85	4.13
Cl	115～126 mEq/L	116.5	119.3	117.7

cial situation and reduced clinical symptoms, both anti-epileptic drugs were withdrawn.

The last recheck of the patient was 473 days after the diagnosis. The patient had had no seizure activity since day 109. That is approximately a year in total, with other clinical symptoms being minimal.

DISCUSSION

Various sources of veterinary literature have used the term “idiopathic epilepsy” to refer to a chronic neurologic condition characterized by recurrent seizures with no definable underlying cause (Christopher, 2013). In canine and human epilepsy, the term “idiopathic” has been used to explain epilepsy that is thought to be of genetic etiology (Wahle et al, 2014). However, until now, only one study has identified a familial spontaneous epileptic cat strain (Kuwabara et al, 2010). To avoid confusion in terms, this case report used the term “cause unknown” instead of “idiopathic”. Several cases report the prevalence of epilepsy, cause unknown, ranging from 22 to 54% in epileptic cats (Rusbridge, 2005; Schriefl et al, 2008; Pákozdy et al, 2010; Wahle et al, 2014). The broad range of the prevalence may be due to different standards of classification or of cases with provisional diagnosis without advanced diagnostics such as MRI and histopathology. The age of cats with epilepsy of unknown cause tended to be younger than those with structural brain lesions with a mean age of 3.5 years in two publications (Bailey and Dewey, 2009; Pákozdy et al, 2010).

In order to rule out other causes of seizure, various examinations should be performed. This may include history taking, physical examination, neurologic examination, blood examination, urinalysis, cerebrospinal fluid (CSF) analysis, and MRI. In addition, serology testing to rule out FeLV, FIV, feline infectious peritonitis (FIP), and toxoplasmosis may be required (Pakozdy, 2014). To meet the criteria of the unknown epilepsy, the examinations above should have no abnormalities related to the clinical symptoms of seizure. The examinations listed above did not show specific abnormality that is thought to be related to epileptic activity. Neurologic

examinations including observation (e.g. mental status, behavior, and gait), postural reaction (e.g. proprioceptive positioning and hopping), spinal reflexes (e.g. withdrawal, extensor carpi radialis, and patellar), and cranial nerves (e.g. oculovestibular, menace, and papillary light reflex [PLR]) were normal. However, a normal neurologic examination result does not rule out brain disease (Pakozdy et al, 2014; Bailey and Dewey, 2009). In one documented case of 81 cats with recurrent seizures, neurologic examination was normal in all but 3 cats showing decreased menace response (n=3) and abnormal postural reactions (n=2) (Wahle et al, 2014). The patient was examined FCoV kit but was revealed positive. However, serologic analysis of antibodies to coronavirus does not confirm FIP (Little, 2012). Serum biochemistry, A:G ratio was 0.88 at day 0 and 0.82 at day 30. Considering the overall results of examinations normal serum total protein, 6.7 (reference range, 5.2～8.2), A:G ratio and absence of ocular or other organic lesion, FIP was not likely to be the diagnosis. Finally, ruling out structural epilepsy by MRI, the patient was diagnosed “Epilepsy of unknown causes”.

Phenobarbital is frequently used as the drug of choice for cats with epilepsy (Pakozdy et al, 2013). However, depending on the situation, other anticonvulsants such as levetiracetam, zonisamide, gabapentin, intravenous diazepam can be used, alone or in combination. When the patient did not show improvement in symptoms after phenobarbital was given, we selected zonisamide as additional antiepileptic drug. One source had reported using zonisamide in 2 cats refractory to phenobarbital of which discontinuance was made following signs of anorexia in one cat and a very good response showing dramatic reduction in seizure frequency was seen in another cat (Bailey and Dewey, 2009). As phenobarbital can increase the clearance of zonisamide in dogs, when adding it to a dog already receiving phenobarbital, a higher dose of the drug (10 mg/kg PO q12h) may be administered (Plumb, 2015). Due to the lack of data related to the two drugs in cats from the relative case, we used zonisamide at a dose of 7.5 mg/kg PO q12h higher than the recommended dose in cats (5～10 mg/kg PO q24h). Contrary to the poor response when using phenobarbital alone, the patient showed significant improvement of symptoms related seizure after adding zonisamide.

Generally, an antiepileptic drug is considered effective if the seizure frequency is reduced by 50% or more (Bailey and Dewey, 2009; Pakozdy, 2013). In this case, frequency of seizure activity of 1～2 times a day significantly reduced to once in 79 days with seizure-free period of 364 days until the last recheck.

In conclusion, this study shows that using phenobarbital with zonisamide presented good response in a cat with epilepsy of an unknown cause for the first time. Further study is needed to determine the most effective dose of zonisamide to use in cats already receiving phenobarbital.

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