Case Report

A Case report: Phenobarbital - responsive sialadenosis in a dog

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Abstract

A 5-year old, 1.2 kilogram, spayed female, mixed breed dog presented with vomiting, gulping, retching, excessive salivation and weight loss for 6 months. The dog had both mandibular salivary gland enlargement but was cytologically normal. Hematology blood chemistry and urinalysis were unremarkable except for neutrophilic leukocytosis and hypokalemia. Contrast study radiography found gas in the gastrointestinal (GI) tract and contrast medium left in the esophagus while abdominal ultrasonography was unremarkable. Oropharyngeal and upper GI endoscopy confirmed cervical esophageal dilatation. The dog did not respond to symptomatic treatment. Sialadenosis was diagnosed based on the clinical signs and the ruling out of other diseases with a similar presentation. Medical treatment with phenobarbital was initiated at a dosage of 1.5 mg/kg orally twice daily for 3 months. The clinical signs diminished in a few days and were completely absent within 2 weeks. The mandibular salivary glands were smaller and softened after 2 weeks of treatment. After 3 months, phenobarbital dosage was tapered (reduced) every month and withdrawn at 6 months. Seven months after treatment, the mandibular salivary gland could not be palpated and the dog gained weight and had no clinical signs. This is the first case of phenobarbital - responsive sialadenosis reported in Thailand.

Keywords: Dog, Phenobarbital, Salivary gland, Sialadenosis, Vomiting

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Introduction

The most frequent diseases affecting the salivary glands are salivary neoplasm, edema, sialadenitis, sialoceles, salivary gland infarction and sialolithiasis (Alcoverro *et al*., 2014). Sialadenosis is a rare disease in dogs. It is a bilateral, uniform, painless, non-inflammatory, non-neoplastic enlargement of the salivary glands. The mandibular salivary glands are commonly affected but the parotid or zygomatic salivary glands may be affected as well (Boydell *et al*., 2000). In humans, this is often the result of physiological hypertrophy in response to chronic stimulation or it can be secondary to autonomic neuropathies. No underlying disease can be found. The clinical signs of sialadenosis are retching or gulping, vomiting, ptyalism, lip smacking, snorting, sensitivity to gentle external palpation of the throat, inappetence and weight loss (Dagan, 2011). There are two different forms of sialadenosis. The first form is associated with an underlying esophageal disease and cytology or histopathology of the affected salivary gland reveals necrosis and metaplasia. It does not respond to treatment with phenobarbital (PB). The other form, idiopathic, displays no abnormalities except for mild hypertrophy of the salivary gland and responds rapidly to medical treatment with PB; therefore this form is called phenobarbital – responsive sialadenosis (PRS) (Boydell *et al*., 2000). Although the etiology of PRS is unclear, it has been associated with an unusual form of limbic epilepsy (Stonehewer *et al*., 2000). Limbic epilepsy is a condition of epileptic seizures that originates in/or involves the limbic system (Reid and Staba, 2014). In the veterinary field, limbic epilepsy is determined as partial epilepsy with primary or complex symptoms (Baker, 1973). The clinical signs of epilepsy are expressed as an alteration of consciousness, behavioral changes, involuntary motor activity and autonomic discharge, resulting in salivation, urination and defecation (Munana, 2013). One of the regimens for the treatment of limbic epilepsy is the use of antiepileptic drugs. PB is one of the conventional antiepileptic drugs that is effective in controlling partial epilepsy and generalized tonic – clonic seizures (Deckers *et al*., 2000). PB is still considered to be the first – line drug for the treatment of epilepsy in both dogs and cats (Munana, 2013). In the past, there have been several reports on the successful treatment of PRS which is an unusual form of limbic epilepsy using oral PB (Alcoverro *et al*., 2014; Boydell *et al*., 2000; Dagan, 2011; Nam *et al*., 2014).

The present case report describes the clinical presentations, diagnostic procedures and responses to treatment with PB in a dog who had clinical signs typical of PRS. Moreover, this is the first report on a clinical case of PRS in a dog in Thailand.

Case History and Clinical Examination

A 5-year old, spayed female, mixed breed dog weighing 1.2 kg (body condition score 2/9) was presented with vomiting, gulping, retching, excessive salivation, anorexia and weight loss (Fig. 1A). Clinical signs had been present for 6 months since she was first diagnosed with pancreatitis. Laboratory results showed neutrophilic leukocytosis and hypokalemia (Table 1).

There was some barium left in the cervical esophagus and excessive gas along the gastrointestinal (GI) tract from positive contrast radiography. No abnormality was found by abdominal ultrasonography. Fine-needle aspiration of the mandibular salivary glands revealed no evidence of neoplasia, inflammation or necrosis. The dog was admitted and treated with injectable enrofloxacin (Baytril®, Bayer, Germany) 5 mg/kg/day, amoxicillin – clavulanic acid (Synulox®, Zoetis, USA.) 20 mg/kg/day, ondansetron (Ondavell®, Indonesia) at 0.5 mg/kg every 8 hours, metoclopramide (H-paran®, LBS Laboratory, Thailand) 0.3 mg/kg every 8 hours and fluid therapy. The clinical signs of vomiting, retching, gulping and hypersalivation were not resolved after 1 week of the treatment. During hospitalization we noticed that the patient had teeth chattering with excessive salivation and retching and vomiting with an additional foamy clear content looking like saliva (Fig. 2).

Oropharyngeal examination and upper GI endoscopy were done under general anesthesia. Dilatation of the cervical esophagus was found. Pyridostigmine (Pyrimine®, SPS, Thailand) at a dosage of 1 mg/kg, Mosapride (Gasmotin®, Sumitomo Dainippon Pharma, Thailand) at a dosage of 0.5 mg/kg and Dimenhydrinate (Dramamine®, OLIC, Japan) at a dosage of 2 mg/kg orally every 8 hours were added to the treatment. The dog was also fed small meals and put in an elevated position with the forelimbs higher than the hindlimbs held for at least 15 minutes. Unfortunately, the dog showed no response to medical treatment.

Treatment and Discussion

A therapeutic trial with phenobarbital at a dosage of 1.5 mg/kg orally twice daily was initiated to confirm PRS. The clinical signs of vomiting, retching, gulping and hypersalivation decreased dramatically in a few days and disappeared in 2 weeks. The mandibular salivary glands became soften and decreased in size after 2 weeks. The serum PB level was 6.4 µg/ml. The dog had no abnormal clinical signs (Fig. 1B). Hair regrowth and a decrease in the size of the mandibular salivary glands were detected. At 6 weeks of the treatment, her body weight was 2.7 kg with a body condition score of 5/9 and she looked bright, alert and active (Fig. 1C). The serum PB level at 4 and 6 months of the treatment were 7.3 µg/ml and less than 0.5 µg/ml, respectively. The mandibular salivary gland became smaller and could not be palpated at 6 months. The body weight was 3.4 kg with a body condition score 6/9 (Fig. 1D).

PRS is a rare disease in dogs. It is characterized by normal cytological and/or histopathological features of enlarged salivary glands with no evidence of specific disease. Definitive diagnosis includes typical clinical signs such as vomiting, nausea, hypersalivation, enlargement of the salivary glands and lack of substantial microscopic lesions and the exclusion of other related diseases causing similar clinical signs (Nam *et al*., 2014). In this case, the dog had vomiting,

retching, gulping and hypersalivation for 6 months. Bilateral enlargement of the mandibular salivary glands was found during physical examination. The laboratory results showed leukocytosis from chronic disease and hypokalemia which is caused mainly by hypersalivation because potassium concentration in canine saliva is 3-7 times higher than serum concentration (Gilor *et al*., 2010). In our report, the dog had clinical history of chronic disease and leukocytosis for at least 6 months. Due to rational combination antimicrobial therapy may be the most effective action taken to enhance antimicrobial efficacy for chronic or serious infection, enrofloxacin combined with amoxicillin – clavulanic acid was prescribed in the dog. Fluoroquinolones (e.g., enrofloxacin) are often combined with beta – lactams (e.g., amoxicillin – clavulanic acid), metronidazole, or clindamycin to target both gram – positive and gram – negative infections (Boothe, 2012). However, the dog did not respond to symptomatic treatment due to the underlying cause still existing. Diagnosis and treatment in this case was the same as previous studies (Alcoverro *et al*., 2014; Dagan, 2011; Nam *et al*., 2014; Stonehewer *et al*., 2000; Terry, 2010) which were based on clinical signs, ruling out systemic etiologies involving vomiting and hypersalivation, absence of pathologic change in the salivary glands, insufficient response to conventional therapy and a rapid response to PB.

Figure 1 Clinical presentation of the dog, before treatment (A), 2 weeks (B), 6 weeks (C) and 6 months (D) after PB treatment

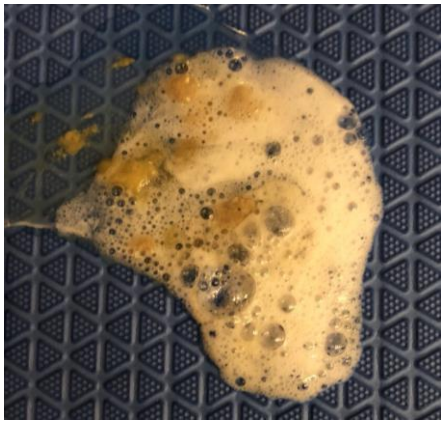

Figure 2 Character of vomitus

On a follow - up examination, 2 weeks after initiating treatment with PB, the dog showed a complete resolution of the clinical signs which was the same result as in the study of Dagan (2011). The size of the mandibular salivary glands after 6 weeks of treatment decreased but was still bigger than normal. The previous case report of Nam *et al*. (2014) found that the mandibular salivary glands were of normal size at 3 months after treatment.

The pathogenesis of PRS and the reason why it responds to PB are not well understood. There is no evidence in the literature that PB has a direct effect on saliva production or esophageal motility (Alcoverro *et al*., 2014). The hypertrophic salivary gland is not necessarily the primary pathology but rather a consequence of the disease and its symptoms and may appear only later in the course of the disease. It is of interest to note that attempts to remove the affected glands surgically did not resolve the clinical signs (Dagan, 2011). This supports the assumption that it is not the physical effect of gland enlargement that is the primary pathology.

In the present report, no underlying disease was identified and the dog had complete resolution of clinical signs after treatment with PB. On the other hand, our report is concomitant with previous reports of PRS including, significant improvement within the first 72 hours, complete resolution of the clinical signs within 1 week and a decrease in the size of the salivary gland within 2 - 4 weeks of treatment with PB (Gilor *et*

al., 2010). The initial dosage of PB used in this report was 1.5 mg/kg twice daily and serum PB levels during treatment were around 6.4-7.3 µg/dl which was lower than therapeutic range for seizure control. Gilor *et al*. (2010) reported that PRS requires low doses and a shorter duration of PB treatment. Although, the actual mechanism of action of PB for the treatment of PRS is unknown, PRS has been associated with an unusual form of limbic epilepsy, therefore it can be treated with antiepileptic drugs such as PB. For antiepileptic properties, PB increases the seizure threshold and decreases the electrical activity of the seizure focus by potentiating the action of the neurotransmitter gamma - aminobutyric acid (GABA). Potentiating GABA increases the chloride conductant in neurons, stabilizes electrical activity and raises the potential necessary for depolarization (Riviere and Papich, 2009). PB also decreases the influx of calcium into the nerve cells and thereby decreases the release of neurotransmitters involved in the function of the central nervous system (CNS) and peripheral nervous system (PNS). Moreover, it is hypothesized that dysfunction of the autonomic nervous system (ANS) which is a part of PNS and innervation of the salivary glands may be a unifying factor in sialadenosis in both dogs and humans (Alcoverro *et al*., 2014). Previous studies have shown that chronic stimulation of the sympathetic innervation of the rat submandibular salivary gland can cause glandular enlargement (Wells and Munson, 1960) and adrenergic beta - receptors may play a part in the genesis of sialadenosis (Sozmen *et al*., 2000). In humans, frequency of vomiting is directly proportional to the degree of sialadenosis (Kinzl *et al*., 1993). If the same is true for dogs, then possibly sialadenosis is not necessarily the primary pathology but rather a consequence of the dysfunction of the ANS innervation of the salivary glands and its symptoms and may appear only later in the course of disease (Dagan, 2011). Since the sympathetic and parasympathetic divisions leave the CNS from the part of brain and spinal cord (Segal *et al*., 1996), inhibition of the CNS function using PB can decrease the function of both divisions. Therefore, PB may inhibit the chronic stimulation of sympathetic innervation which has been proposed as the cause of sialadenosis.

Table 1 Laboratory results before and after phenobarbital (PB) treatment

Parameter	Before PB treatment	2 weeks after PB treatment	4 months after PB treatment	6 months after PB treatment	Reference value*
RBC (x10⁶/µl)	5.6	6.9	7.77	-	4.9-7.8
Hb (g/dl)	12	14.7	18.1	-	11.9-18.9
Hct (%)	35.9	48.2	53.2	-	35-57
MCV (fl)	66.5	72.6	68.5	-	66-77
MCH (pg)	22.2	24.1	23.3	-	19.9-24.5
MCHC (g/dl)	33.4	33.3	34	-	31-34
Platelet (x10⁵/µl)	3.4	5.81	4.26	-	2.1-6.2
WBC (x10³/µl)	35.14	6.31	6.32	-	5.0-14.0
Neutrophil (x10³ /µl)	29.87	5.24	5.12	-	3.0-11.5
Lymphocyte (x10³/µl)	5.27	1.01	1.14	-	1.0-4.8
Eosinophil (x10³/µl)	0	0.63	0.63	-	0.1-1.2
Albumin (g/dl)	3.1	3.0	3.6	-	2.6-4.0
ALP (U/L)	232	193	-	173	47-254
ALT (U/L)	119	55	128	60	17-78
BUN (mg/dl)	24	15.1	19.0	21.0	9.2-29.3
Calcium-ionized (mmol/L)	1.13	1.24	-	-	1.12-1.4
Creatinine (mg/dl)	1.1	0.6	0.5	0.2	0.4-1.4
Glucose (mg/dl)	83	124	-	-	75-128
Sodium (mEq/L)	149	148	-	148	141-152
Potassium (mEq/L)	2.5	4.8	-	5.1	3.8-5.0
Chloride (mEq/L)	109	110	-	109	102-117
Cortisol (µg/dl)	10	-	-	-	2.0-10.0
Total T_4 (µg/dl)	1.9	-	-	-	1.0-3.1
Phenobarbital (µg/dl)	-	6.4	7.3	Less than 0.5	

Prognosis in this case is good because the dog responded to PB very well even though the duration of clinical signs was much longer than previous studies. However, some dogs can be weaned off PB after 3 months (Nam *et al*., 2014) and 6 months (Stonehewer *et al*., 2000).

This is the first published case report on PRS in a dog in Thailand. Until now, there has been no specific test to diagnose PRS; a definitive diagnosis may be indicated by exclusion criteria, and the rapid and complete remission of clinical signs after treatment with PB.

Acknowledgements

We would like to thank the owner of the dog, all veterinarians and staff at Suvarnachad Animal Hospital and Kasetsart animal hospital

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