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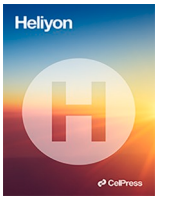

Development of acute pancreatitis after oral administering a praziquantel, pyrantel pamoate, and febantel combination in a dog: A case report

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ABSTRACT

Oral praziquantel, pyrantel pamoate, and febantel combination (PPFC) is a highly safe anthelmintic treatment commonly administered for the purpose of canine gastrointestinal parasites with mild adverse effects such as anorexia, vomiting, lethargy, or diarrhea. A 12-year-old castrated Chihuahua was brought to our hospital for a periodic health examination. Although his general physical examination showed no abnormalities, blood test results showed increase in the liver enzyme, lipase activity, total bile acid, total cholesterol, and triglyceride concentration. Moreover, the dog had underlying tricuspid regurgitation that was not treated. PPFC was prescribed on the suspicion of gastrointestinal tract parasites. Following the oral administration of PPFC at home, anorexia and lethargy were found, and vomiting and diarrhea were noted after 30 h. The dog was diagnosed with acute pancreatitis based on clinical course of the disease and subsequent pathology results. Although intravenous drip was initiated upon hospitalization, the treatment was discontinued owing to financial reasons. The onset of acute pancreatitis can be considered an adverse effect of PPFC. Although the association between PPFC administration and the onset of acute pancreatitis could not be clarified in this case, the onset of acute pancreatitis may have been associated with a decrease in liver function and/or increase in the false activity of lipase. PPFC has been considered highly safe in dogs, although care should be taken when administering medications to dogs suspected of having an underlying disorder.

1. Introduction

Praziquantel, pyrantel pamoate, and febantel combination (PPFC) is a broad spectrum anthelmintic treatment commonly administered in domestic dogs [1]. Praziquantel, a safe anthelmintic drug in human medicine, has been hypothesized to increase the permeability of the parasite cell membrane for calcium ions resulting in muscle contraction and paralysis [2,3].

While oral administration of praziquantel can cause anorexia, vomiting, lethargy, or diarrhea in dogs, incidence rates of <5% have been reported [4]. Furthermore, no adverse effects have been reported in dogs treated with pyrantel pamoate or febantel [4], with no severe adverse effects reported with their combination in the field of veterinary medicine.

Although the etiology of pancreatitis is yet to be clarified, it may involve diet, hyperlipidemia, hypertriglyceridemia, drugs, toxins, obesity, hypercalcemia, diabetes, hypothyroidism, hyperadrenocorticism, pancreatic duct obstruction, pancreatic surgery or trauma,

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local anemia or reperfusion, infection (Babesia), and autoimmune and idiopathic conditions. Moreover, pancreatitis is reportedly caused by drugs such as L-asparaginase, azathioprine, estrogen, furosemide, potassium bromide, salicylic acid, sulfonamide, tetracycline, thiazide diuretics, zinc, organic phosphate, vinca alkaloid, and cisplatin [5,6].

Acute pancreatitis developed after orally administering PPFC, suggesting that PPFC may have been involved in these developments. This report details our experience regarding the aforementioned case.

2. Case history

2.1. Results of the periodic health examination, and medication

A 12-year-old castrated Chihuahua was brought to our hospital for a periodic health examination. It had been diagnosed with tricuspid regurgitation a year prior to presentation, which was left untreated for financial reasons. A general physical examination of the dog showed that its body weight was 4.1 kg, rectal temperature was 38.3 °C, heart rate was 120 beats/min, and respiratory rate was 30 breaths/min, and a heart murmur was heard in the right heart region. A blood test, including a heartworm antigen test, was performed as part of the periodic health examination. A complete blood count (CBC) (Celltac alpha; NIHON KOHDEN CORPORATION, Tokyo, Japan) showed an increase in platelet count [723,000/μL; reference interval (RI), 200,000–500,000/μL]. Biochemical analyses (BioMajesty JCA-BM6070; JEOL Ltd., Tokyo, Japan) in a commercial laboratory (Animal Medical Technology, Nagoya, Japan) revealed some abnormalities, including increased activities of alanine aminotransferase (ALT) (221 U/L; RI, 16–98 U/L), alkaline phosphatase (ALP) (159 U/L; RI, 18–98 U/L), and γ-glutamyl transpeptidase (γ-GTP) (66 U/L; RI, 0–12 U/L) and increased concentrations of blood urea nitrogen (BUN) (34.2 mg/dL; RI, 5.4–30.9 mg/dL), total cholesterol (493 mg/dL; RI, 109–349 mg/dL), triglycerides (494 mg/dL; RI, 20–121 mg/dL), phosphorus (5.7 mg/dL; RI, 2.1–5.1 mg/dL), and cystatin C (0.48 mg/dL; RI, <0.39 mg/dL) (Table 1). The in-house heartworm antigen test (Canine Heratworm Antigen Test Kit; ARKRAY Factory, Inc., Shiga, Japan) using immunochromatography was negative.

Because the owner noted that the dog's stool contained parasites, which were likely nematodes or tapeworms, half of a PPFC tablet (Drontal® Plus; Bayer, Tokyo, Japan) (each tablet containing 50 mg of praziquantel, 144 mg of pyrantel pamoate, and 150 mg of febantel and 6.1 mg/kg of praziquantel, 17.6 mg/kg of pyrantel pamoate, and 18.3 mg/kg of febantel after conversion to body weight) [1] was prescribed for oral administration at the owner's home for suspected gastrointestinal tract parasites.

2.2. Disease course after administration of PPFC

Approximately 4 h after the oral administration of PPFC, the dog were found anorexia and lethargy, and vomiting and diarrhea began after 30 h. Therefore, the dog was brought to the hospital 36 h later (Fig. 1). Upon presentation, its rectal temperature was 37.5 °C, heart rate was 140 beats/min, and respiratory rate was 30 breaths/min. Considering the generally good condition of the dog, symptomatic treatment with 80 mL of subcutaneous (SC) drip of Ringer's solution (SOLULACT; Terumo Corporation, Tokyo, Japan), famotidine (1 mg/kg, SC) (Gaster; LTL Parmra Co., Ltd., Tokyo, Japan), metoclopramide (0.5 mg/kg, SC) (Prinperan; Nichi-Iko

Table 1
Chemistry profiles before and after medication.

	Before medication		72 h post-medication	
		Reference range*		Reference range**
Total protein (g/dL)	6.7	5.1–7.3	7.2	5.0–7.2
Albumin (g/dL)	3.5	2.7–4.2	3.3	2.6–4.0
Total biliubin (mg/dL)	0.1	0–0.3		
AST (U/L)	36	16–42	668	17–44
ALT (U/L)	221	16–98	3094	17–78
ALP (U/L)	159	18–98	311	0–89
γ-GTP (U/L)	66	0–12	52	
BUN (mg/dL)	34.2	5.4–30.9	84.6	9.2–29.2
Cre (mg/dL)	0.97	0.40–1.39	1.87	0.4–1.4
Total Cholesterol (mg/dL)	493	109–349		
Triglyceride (mg/dL)	494	20–121		
Calcium (mg/dL)	8.9	8.9–11.3		
Phosphate (mg/dL)	5.7	2.1–5.1		
Glucose (mg/dL)	108	63–118	165	75–128
Sodium (mEq/L)	147	4.0–5.5	139	141–152
Potassium (mEq/L)	5.6	4.0–5.5	4.2	3.8–5.0
Chloride (mEq/L)	107	105–118	91	102–117
C-reactve protein (mg/dL)	0.53	<1.40	14.1	<0.9
Cystatin C (mg/L)	0.48	<0.39		
	*BioMajesty JCA-BM6070 **FUJI DRI-CHEM 7000v			
Total bile acid (μmol/L)	38.4***	<7.9		
Spec cPL (μg/dL)	460***		1202	≤200

***These were measured with sera refrigerated at 4 °C for 3 days.

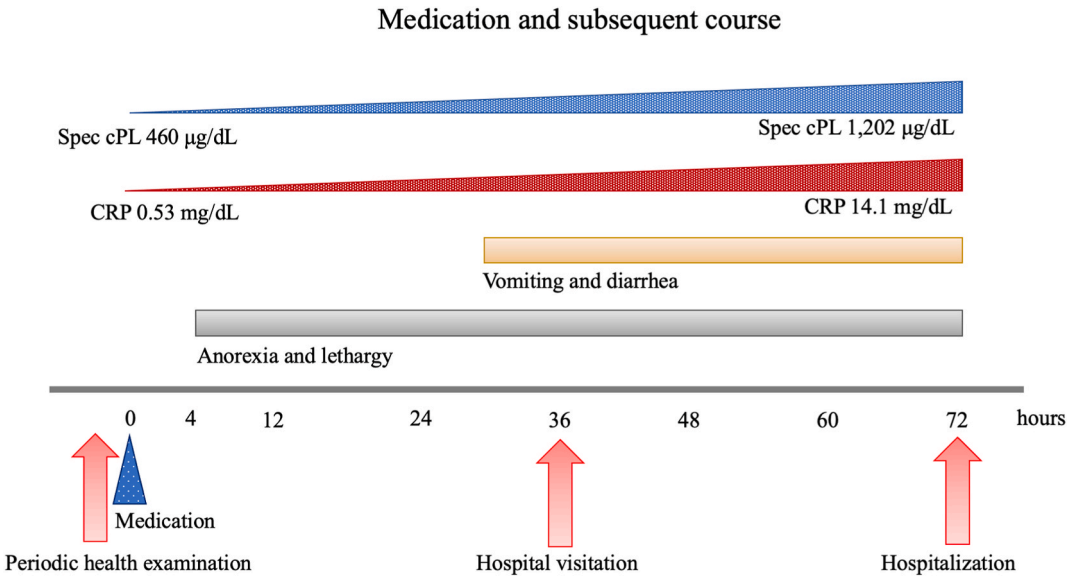

Fig. 1. Medication and subsequent course.

Pharmaceutical Co., Ltd., Toyama, Japan), and berberine tannate (0.3 mg/kg, SC) (Riken Vets Pharma Inc., Kawaguchi, Japan) was provided, after which the owner took the dog home.

However, because of continuous anorexia, lethargy, and frequent vomiting, the dog was brought back to the hospital the next day. Its heart rate was found to be 120 beats/min and rectal temperature was found to be low (36.6 °C). Tenderness was noted in the upper abdomen. CBC (ProCyte; Idexx Laboratories Inc., Tokyo, Japan) showed a slight increase in platelet count (536,000/μL). In-hospital biochemical analyses (FUJI DRI-CHEM 7000; FUJIFILM Corporation, Tokyo, Japan) revealed some abnormalities, including increased activities of ALT (3094 U/L; RI, 17–78 U/L), AST (668 U/L; RI, 17–44 U/L), ALP (311 U/L; RI, 0–89 U/L), and γ-GTP (52 U/L; RI, 5–14 U/L) and decreased concentrations of glucose (165 mg/dL; RI, 75–128 mg/dL), BUN (84.6 mg/dL; RI, 9.2–29.2 mg/dL), creatinine (1.87 mg/dL; RI, 0.4–1.4 mg/dL), *C*-reactive protein (CRP) (14.1 mg/dL; RI, <0.9 mg/dL), Na (139 mEq/L; RI, 141–152 mEq/L), and Cl (91 mEq/L; RI, 102–117 mEq/L). High concentration of canine pancreas-specific lipase (Spec cPL) (1202 μg/dL, RI, ≤400 μg/dL) were observed after commercial laboratory testing (Idexx Laboratories Inc., Tokyo, Japan) (Table 1). Thoracic radiography showed enlargement of the cardiac silhouette (vertebral heart size: 8.9), abdominal radiography showed hepatomegaly and increased radiopacity in the upper right abdomen, and abdominal ultrasonography showed liver enlargement and gallbladder mucocele-like findings. Several cysts were found in both the kidneys. Moreover, both the left (6.5 mm) and right (6.6 mm) adrenal glands were slightly enlarged. Peristalsis in the duodenum was reduced, and the fat surrounding the pancreas was hyperechoic. Urinalysis revealed no abnormalities other than low specific gravity (1.012).

Based on the aforementioned clinical signs and clinical pathological test results, a diagnosis of acute pancreatitis with renal failure was established, and symptomatic therapy was initiated during hospitalization, which mainly included fluid replacement (Fig. 1). However, the treatment was discontinued due to financial reasons, and the subsequent course remains unknown.

2.3. Measurement of spec cPL and bile acid concentrations in the stored blood sample before administration of PPFC

Spec cPL and serum bile acids were measured in the sera stored refrigerated at 4 °C for 3 days after the periodic health examination was conducted (immediately before the administration of PPFC). Accordingly, Spec cPL concentration showed a slightly high value of 460 μg/dL, whereas total bile acid concentration showed a high value of 38.4 μmol/L (RI, <7.9 μmol/L) (IMMUNO AU10V; FUJIFILM Corporation, Tokyo, Japan) (Table 1).

3. Discussion

Approximately 4 h after the administration of PPFC, anorexia and lethargy were noted in the patient, with frequent vomiting observed 30 h later. Accordingly, a diagnosis of acute pancreatitis with azotemia was made 72 h later. Given the time constraints of the owner, a considerable amount of time from the appearance of clinical signs after the administration of PPFC to hospital visitation had already elapsed. However, based on the current time series, we considered the onset of acute pancreatitis with azotemia to have likely been an adverse effect of PPFC. In particular, given the absence of reports regarding the adverse effects of pyrantel pamoate or febantel [4], this case was considered to have been an adverse effect of praziquantel alone or a combination of praziquantel with pyrantel pamoate or febantel. After conducting a search on PubMed, no studies reporting any serious adverse effects of praziquantel were found. Although adverse effects after the administration of praziquantel in humans have been rare, evidence has shown that they are caused

by both drug toxicity and stimulation by dead worms in neurocysticercosis [7]. Administration of praziquantel has been associated with inflammation caused by *Taenia solium* death and a subsequent increase in intracranial pressure, with only one case of mortality being reported [7]. Anaphylactic reactions have also been reported in five cases [8–10]. However, considering the location of the parasites in the gastrointestinal tract, clinical findings, and the time series of the adverse effects, the present case was not considered to have been caused by the death of worms or an anaphylactic shock.

Praziquantel is metabolized in the liver via cytochrome P450 3A enzymes, resulting in the formation of metabolites of unknown activity. It is excreted primarily in the urine, with an elimination half-life of 3 h in dogs [11]. Hepatic impairment may result in prolonged maintenance of higher praziquantel concentrations, with the elimination half-life being 1.5–3 times longer in humans with moderate to severe hepatic impairment [12]. Therefore, praziquantel should be administered cautiously to patients with hepatic impairment. The serum bile acid concentration was high in the preserved serum obtained during the periodic health examination of our case. Considering that these values were measured using preserved serum obtained with incomplete fasting, the effects of diet on serum bile acids may not accurately reflect the liver function. However, reports have shown that serum bile acid concentrations do not exceed 30 μmol/L even under the influence of diet [13]. Furthermore, in this case, considering that the liver enzyme activity was increased at the time of periodic health examination, it is possible that the liver function was reduced and the metabolism of praziquantel was prolonged. However, despite the fact that the metabolism of praziquantel was prolonged caused by decreased liver function, its association with the onset of acute pancreatitis remains unknown.

Spec cPL, which has been considered to have specific pancreatic lipase activity in dogs, also showed a slight increase in the preserved serum obtained during the periodic health examination. There are two possible explanations for this value. The first is that although no clinical symptoms observed, our case had already entered the early stages of acute pancreatitis, and the administration of PPFC was accidental. The second explanation is that some dogs exhibit a slight increase in pancreatic lipase activity owing to inter- and intraindividual variation [14]; therefore, only a slightly higher value was erroneously shown. In addition, Spec cPL activity has been known to be elevated in patients with heart disease, hyperadrenocorticism, renal failure, hepatitis, and cholecystitis [15–20], which we believe were present and quite profound in our case. The patient in this study had been diagnosed with tricuspid regurgitation for a year, which was left untreated. Furthermore, blood test results from the periodic health examination showed an increase in the hepatic enzyme activity and urea nitrogen, and suspected hepatitis, cholecystitis, hyperadrenocorticism, and chronic kidney disease. However, the presence or absence of these underlying diseases could not be confirmed. Moreover, given that the diagnostic criteria for acute pancreatitis depend on the presence of clinical signs and that most cases of acute pancreatitis are accompanied by increased CRP concentrations [21], the first explanation was determined to be unlikely. Regarding the second explanation, the increase in false activity of lipase was strongly suspected but was not clarified. Additionally, the relationship between the increase in pseudo-lipase activity and the onset of acute pancreatitis has not been elucidated, although it cannot be denied that it may have resulted in the onset of acute pancreatitis.

Reports have shown that common drug-induced acute pancreatitis exhibits symptoms every 2–36 weeks on average with continued use of the drug after its first dose. Most reactions are reversible and heal spontaneously within 3–7 days after discontinuing the causative agent [22]. Therefore, these general theories also did not appear to correspond to this case.

Although the association between PPFC administration and the onset of acute pancreatitis in this case could not be clarified, the following points were inferred from this study: (1) the dog had early stages of the acute pancreatitis or pseudo-lipase activity, and decreased liver function at the time of periodic health examination [14–20]. (2) PPFC was administered to the dog, but PPFC metabolism was delayed due to decreased liver function and dehydration due to anorexia, lethargy, vomiting, and diarrhea, which are common adverse reactions to PPFC [4,11,12]. (3) Due to dehydration, the early stages of acute pancreatitis or pseudo-lipase activity developed into acute pancreatitis [5]. It was hypothesized that this sequence of events may be the underlying mechanism of the onset of acute pancreatitis.

This report had some limitations worth noting. First, lipase activity and bile acids were measured using sera refrigerated at 4 °C for 3 days, which may not have produced accurate results. However, the stability of both samples was considered acceptable [23,24], and inter-assay coefficients of variability were reported as <4% and 13.1%, respectively [23,25], the lipase activity and bile acids are highly probable that it was above the RI. Second, the treatment was interrupted owing to financial reasons. As such, we could not confirm the presence or absence of the underlying disease or outcomes. Third, no blood tests were conducted at the visit 36 h after the administration of medication. Acute pancreatitis could have been detected earlier had a blood test been conducted at this point.

4. Conclusion

Despite the considerable safety of PPFC for anthelmintic treatment, caution may need to be exercised during administration when an underlying disease with decreased liver function or increased pseudo-lipase activity is suspected.

Author contribution statement

Masashi Yuki: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Hiroto Taira: Performed the experiments; Analyzed and interpreted data; Contributed reagents, materials, analysis tools or data.
Takanori Inden: Performed the experiments; Analyzed and interpreted data; Contributed reagents, materials, analysis tools or data.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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