Hepatocellular Toxicosis Associated with the Alternate Administration of Carprofen and Meloxicam in a Siberian Husky

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ABSTRACT. A 4-year-old female Siberian Husky was diagnosed with pyogranulomatous steatitis at the site of a recurrence of left anal sac rupture (day 1). Carprofen and orbifloxacin were given for 13 days without improvement. A single dose of meloxicam was administered prior to surgical resection of the anal sac, and based on elevated liver enzyme activity, liver supportive therapy was initiated. The dog received carprofen and orbifloxacin orally on the evening of day 14. The dog became anorectic the following morning, and began vomiting. Despite supportive therapy, the dog was unresponsive to treatment and died on day 16. Postmortem examination revealed severe vacuolar change and acute necrosis of hepatocytes consistent with carprofen and meloxicam induced-toxicosis.

KEY WORDS: canine, drug-intoxication, NSAIDs.

Appropriate pain management is essential to improving patient quality of life. Non-steroidal anti-inflammatory drugs (NSAIDs) relieve pain by reducing prostaglandin (PG) synthesis via inhibition of cyclooxygenase (COX) production. Carprofen and meloxicam preferentially inhibit COX-2, which promotes production of PG, a mediator of inflammation [2, 5, 7]. Prolonged oral administration of carprofen or meloxicam in dogs is rarely associated with the development of adverse reactions; however, when reactions do occur, vomiting, diarrhea, and anorexia have been emphasized [3, 6, 9, 11]. In addition, carprofen-induced hepatotoxicity has also been reported as an occasional adverse reaction, with some cases of canine fatality reported [10, 12]. However, there have been no reports of hepatotoxicity caused by alternate administration of carprofen and meloxicam. The present paper describes the case of a Siberian Husky that died of acute hepatocellular necrosis associated with alternate administration of carprofen and meloxicam.

A 4-year-old intact female Siberian Husky weighing 27.8 kg was presented with the chief complaint of anorexia and rupture of a mass located on the left ventral side of the anus. The patient had experienced the same problem twice in the past year. For the first event, the patient was given carprofen (4 mg/kg sid PO) and orbifloxacin (5 mg/kg sid PO) for 24 days. Complete blood count (CBC) and blood chemical analysis 17 days after initiation of medication revealed increases in alanine aminotransferase (ALT: 410 U/l; reference range: 10 to 118 U/l) and aspartate aminotransferase (AST: 316 U/l; reference range: 12 to 43 U/l) activities. Glutathione, ursodeoxycholic acid, and taurine were subsequently given orally for 1 week. Three months after cessation of carprofen and orbifloxacin administration, ALT activity had decreased to 38.3 U/l. For the second event, the patient was given the same medication for 1 week, and blood analysis was not performed. However, the dog did not show any clinical signs of adverse reaction to the medications. The dog had been inoculated with an eight-in-one combination vaccine containing antigens of Leptospira canicola, L. copenhageni, L. hebdomadis, and canine adenovirus 2, and a rabies vaccine, 6 months and 9 months prior to admission, respectively. The dog was kept inside the house, and fed only a regular commercial diet.

Based on cytological examination, the dog was diagnosed with pyogranulomatous steatitis associated with left anal sac rupture. The dog was treated with carprofen (4 mg/kg, PO, sid) and orbifloxacin (5 mg/kg, PO, sid) for 13 days. The steatitis did not resolve, however, so left anal sacculectomy was proposed. On the morning of day 13, the dog was given meloxicam (0.2 mg/kg, SC) due to no injectable form of carprofen being available for dogs at the time, and underwent preoperative screening, including physical examination and laboratory testing. More than 24 hr had elapsed since carprofen was given. Appetite and vigor were normal, and vomiting and diarrhea were not observed. On physical examination, mucous membranes were pink, capillary refill time was < 1 second, and femoral pulses were adequate. Rectal temperature, and pulse and respiratory rates were also normal. No cardiac murmurs or arrhythmias were auscultated, and breathing sounds were normal. CBC results were within reference ranges. Blood chemical abnormalities included increases in ALT (342 U/l) and AST (126 U/l) activities and total cholesterol concentration (343 mg/dl; reference range: 125 to 270 mg/dl). Blood gas analysis was normal. Because hepatic dysfunction was suspected, additional testing was performed, including pre- and post-prandial serum ammonia and total bile acid (TBA) concentrations, prothrombin time (PT), activated partial thromboplastin time (APTT), and abdominal radiography and ultrasonography. The ammonia level, PT, and APTT values were within reference ranges. Pre- and post-prandial TBA concentrations were 3.6 and 51.2 µmol/l, respectively.

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According to the owner, the dog did not have any opportunities to take unsanitary food or water, or to be exposed to any chemicals that could induce hepatotoxicity. The increase in liver enzyme activity was therefore thought to be related to drug administration. Intravenous fluid therapy was initiated using an acetate Ringer’s solution and a 5% xylitol solution supplemented with glycyrrhizic acid. Glutathione (100 mg/head IV) was also administered, and orbifloxacin was administered continuously. On day 14, appetite and vigor were normal, and vomiting and diarrhea did not develop. Fluid therapy was continued and ursodeoxycholic acid (50 mg/head, bid, PO) and aminoethylsulfonic acid (1 g/head, bid, PO) were also administered. Carprofen (4 mg/kg, PO) was administered in the evening. More than 24 hr had elapsed since meloxicam was given. The dog became anorectic early in the morning of the following day, and vomited a small amount of digested ingesta. Administration of all NSAIDs was discontinued. The dog was treated with the same therapy as on day 13. The dog was recumbent, and icterus was noted by the afternoon of day 15. CBC and serum chemistry revealed neutrophilia (17,098/µl; reference range, 3,000 to 11,500/µl), significant increases in ALT (3480 U/l; reference range, 10 to 90 U/l), AST (2630 U/l; reference range, 10 to 90 U/l), and ALP (211 U/l; reference range, 0 to 100 U/l). Monosodium L-glutamate was also given intravenously to treat hyperammonemia. The following morning, the ALT (1,675 U/l), AST (530 U/l), ALP (174 U/l), and bilirubin (6.6 mg/dl) values had decreased, however, the serum ammonia concentration was >400 µmol/l. On the afternoon of day 16, the dog died.

Postmortem examination revealed hepatomegaly and a scattering of smooth-surface white foci with a diameter of about 5 mm on all lobes of the liver. Hemorrhagic lesions were present in the diaphragm and both kidneys. Hepatocytes had a giant nucleus that included an enormous nucleolus, and multinucleated hepatocytes also present. The most characteristic features of the hepatocytes were periacinar to paracentral necrosis of the hepatocytes with ballooning degeneration (vacuolar change). Accumulation of intrahepatocellular and canalicular bile pigment was observed. There were no intranuclear or cytoplasmic inclusion bodies. In the kidneys, diffuse acute tubular necrosis was confirmed. These findings were consistent with a toxic reaction. Other findings included a hemorrhagic cystitis and hemorrhage of the heart and diaphragm.

The present dog had been given courses of carprofen and orbifloxacin on 3 occasions in the preceding 12 months. At the first administration, the dog showed increased liver enzyme activity, was removed from the medication, and was given glutathione, ursodeoxycholic acid, and taurine for 1 week. Liver enzyme activity had returned to reference ranges 3 months later. Blood analysis was not performed with the second administration. The dog also showed increased liver enzyme activity at the third dosing. After start of the prescriptions of carprofen and orbifloxacin, the liver enzyme activities consistently increased within 3 weeks. However, the dog did not develop any other clinical signs. Therefore, the increased liver enzyme activities were related to the carprofen and/or orbifloxacin. Meloxicam was prescribed only during the third occurrence of anal sac rupture. In general, marked acute elevations in liver enzyme values indicate acute hepatic necrosis [4]. Based on these findings, it may appear that this dog died due to acute hepatic necrosis induced by meloxicam and subsequent carprofen administration. There are at least 6 mechanisms proposed in the development of acute hepatic necrosis [8]. Because hepatocytes were predominantly affected in the present case, high-energy reactions involving cytochrome P-450 enzymes might have led to covalent binding of the drug to intracellular proteins. Apparently, intracellular dysfunction is produced that induces the loss of ionic gradients, a decline in ATP levels, actin disruption, cell swelling, and cell rupture [8].

Hepatocellular toxicity associated with the administration of meloxicam and alternate administration of meloxicam and carprofen has not been reported to our knowledge. In dogs, the peak plasma concentration is achieved at between 1 and 3 hr for a single oral dose of carprofen, and approximately 2.5 hr for a subcutaneous injection of meloxicam, after the administration. The mean half-life in blood is approximately 8 hr for carprofen and 24 hr for meloxicam [1, 3]. In the present dog, at the point in time when carprofen achieved its peak plasma concentration, half of the meloxicam dose would still have remained in the body. This may have exacerbated the adverse effect of carprofen,
resulting in fulminant hepatic failure.

REFERENCES