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Ketoprofen Plaster Toxicity Induced Gastrointestinal Hemorrhage in a Dog

Hyung-Jin Park, Joon-Hyuk Choi, Woo-Nam Lee, Kun-Ho Song and Kyoung-Won Seo[1]

College of the Veterinary Medicine, Chungnam National University, Daejeon 305-764, Korea

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Abstract : A 14 year-old Shih-tzu was referred to the Veterinary Medical Teaching Hospital of Chungnam National University with a history of foreign body ingestion and vomiting. The vomitus contained ketoprofen plaster, which is used for orthopedic analgesia in humans. Supportive care and gastrointestinal (GI) protective agents were administered, including famotidine, misoprostol, sucralfate, omeprazole, and fluid therapy. However, the clinical signs worsened, and anemia, melena, leukocytosis, and azotemia developed. The patient was diagnosed with GI hemorrhage and underwent a whole blood transfusion followed by barium sulfate administration. After administering barium sulfate as a GI protectant, the clinical signs improved, and the patient was discharged.

Key words : ketoprofen plaster, NSAID toxicity, barium sulfate.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are one of the most commonly used pain relievers (10). They have both analgesic and anti-inflammatory effects and inhibit spinal nociceptive transmission (2). NSAIDs are classified into three types, non-selective NSAIDs (ketoprofen and flunixin meglumine), COX-2 preferred inhibitors (meloxicam), and highly selective COX-2 inhibitors (coxibs) (6,12). Ketoprofen (2-[3-bensoylphenyl]-propionic acid) is a non-selective COX inhibitor used to treat rheumatic disorders, as well as mild to moderate pain and fever (3). In dogs, a 1 mg/kg therapeutic dose is used to treat acute pain and inflammation, while 0.25 mg/kg is used to treat chronic pain (7). Although the broad range of indications for non-selective NSAID makes it an attractive treatment choice, it is also accompanied by gastrointestinal (GI) toxicity (14). Chronic non-selective NSAID administration in dogs is associated with serious GI side effects, including hemorrhage, ulceration, perforation, peritonitis, melena, anemia, anorexia, and abdominal pain (1,15). GI ulceration and hemorrhage can occur in the gastric phylum, ileum, and jejunum in dogs and is sometimes accompanied by anemia and hypoproteinemia resulting from hemorrhage and protein loss (9). NSAID toxicity is diagnosed based on history and clinical signs (15).

Ketoprofen plasters have been used to treat osteoarthritis and rheumatoid arthritis in humans (5). Ketoprofen plasters 70 cm^2 in size manufactured using DuroTak1® acrylic adhesive polymers contain either 30 mg (Ketotop-L) or 60 mg (Ketotop-P) of active drug (5). Due to the adverse effects associated with non-selective NSAIDs, a non-oral ketoprofen delivery system was required, and as a result, ketoprofen plasters have been developed (5). These ketoprofen plasters minimize adverse effects while maximizing local analgesic effects locally. In the present report, we describe a case of ketoprofen plaster ingestion that induced gastrointestinal hemorrhage in a dog.

[1]Corresponding author.
E-mail : kwseo@cnu.ac.kr

Case

A 14-year-old Shih-tzu was referred due to a history of foreign body ingestion and three days of vomiting. The patient was being treated for mitral valve insufficiency (MVI, ACVIM grade C) and renal calculi for one year. On physical examination, the vital signs were normal, but during the examination, the patient vomited ketoprofen plaster, a medication used to alleviate orthopedic pain in humans. On the complete blood count (CBC), the RBC ($4.67 \times 10^3/\mu l$; reference range: 5.5-$8.5 \times 10^3/\mu l$) and hematocrit (32.8%; reference range: 35-55%) were mildly decreased. On serum chemistry analysis, the ALP (247 U/L; reference range: 15-127 U/L), AST (59 U/L; reference range: 15-43 U/L), BUN (130 mg/dl; reference range: 8-31 mg/dl), and phosphate (8 mg/dl; reference range: 3-6.2 mg/dl) were elevated.

To correct the azotemia, vomiting, and anorexia, the patient was hospitalized, and fluid therapy along with gastrointestinal protectants was administered. Abdominal radiography revealed gastric gas distention (Fig 1). Renal calculi were also found and appeared identical to those on a previous examination. On abdominal ultrasonography, there were no specific findings associated with GI hemorrhage and ulceration. To further evaluate the stomach and duodenum, and detect any remaining ketoprofen plaster, endoscopy was recommended, but the owner declined further examination. Despite supportive care, the anorexia and depression worsened, and melena was detected after 3 days of hospitalization. The hematocrit

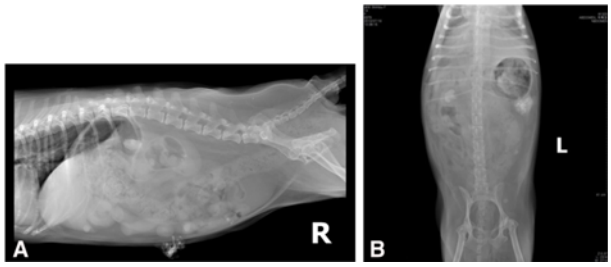

Fig 1. Abdominal radiograph showing the (A) ventrodorsal, and (B) lateral views. Gastric gas distention was observed.

(23.7%), albumin (2.4 g/dl; reference range: 2.9-4.2 g/dl), and total protein (3.8 g/dl; reference range: 5.7-7.4 g/dl) were decreased. Based on examination, GI hemorrhage induced by NSAID toxicity was diagnosed, and the patient underwent a whole blood transfusion. Barium sulfate (RAYDIX SOLN®, Dongindang Ltd., Korea) diluted to 60% was administrated as a GI protectant at 6 mg/kg orally using an esophagotomy tube. The patient recovered clinically within 3 days, and normal activity, appetite, and feces were observed one week after discharge.

Discussion

Most NSAIDs have no antidotes; therefore, treatment is devised based on the clinical severity. Within the first 2 hours of toxicity, gastrointestinal decontamination is a critical component of case management. Administration of activated charcoal and emetics, such as syrup of ipecac and 3% hydrogen peroxide, is preferred (4). However, if the patient is examined beyond this period, then treatment is focused on symptomatic and supportive care including fluid therapy and GI protectants (15).

Ketoprofen plaster contains approximately 30 mg / 70 cm^2 of ketoprofen (5). The patient weighed 5 kg, and assuming that the entire ketoprofen dose in the plaster was absorbed, the patient ingested a 6 mg/kg ketoprofen dose, which is six times higher than the therapeutic ketoprofen dose (13). The lethal dose (LD) 50 in dogs after oral ketoprofen ingestion is reportedly 2000 mg/kg, but exposure as low as 0.44 mg/kg may induce GI ulceration in some dogs (13). Topical ketoprofen application onto the joints or muscles in humans can increase the drug concentration at the target site and lower the systemic drug concentration, thereby reducing stomach irritation and liver toxicity (5). Although the bioavailability of ketoprofen plaster is one tenth that of the oral form, tissue concentration is three times higher than that in plasma (16). This indicated that ketoprofen administered in the plaster formulation penetrates the tissue more effectively than in the oral form. Potentially, ketoprofen plaster that has attached to the GI mucosa may induce more severe damage than oral administration at the same dose. The patient vomited ketoprofen plaster 3 days after ingestion, and in this case, prolonged gastric irritation from the ketoprofen plaster may have caused GI hemorrhage. Furthermore, ketoprofen plaster contains isopropyl myristate to improve drug absorption; this compound has its own adverse effects such as esophageal and GI irritation and ulceration (11). Direct effects on the gastric mucosa from both the ketoprofen plaster and isopropyl myristate irritation may aggravate GI ulceration.

In the current case, the gastrointestinal protectants famotidine, misoprostrol, and omeprazole were administrated. As a prostaglandin analogue, misoprostrol can be used for NSAID toxicity, while famotidine inhibits histamine release from the gastric parietal cells (7). As a proton pump inhibitor, omeprazole decreases gastric acid release more effectively than famotidine and is used in severe cases of gastric ulceration (7). All three medications were prescribed initially, and sucralfate was prescribed as a GI mucosal protectant. However, the clinical sings did not improve, and GI hemorrhage worsened, with a decreased PCV by day three. Barium sulfate is commonly used as a contrast medium because of its safety; it does not injure the gastrointestinal mucosa (8). Barium sulfate may cause constipation should it remain in the gut for a prolonged time, and barium impaction within colonic diverticula often persists for weeks after barium administration without causing mucosal injury. These facts suggest that barium sulfate could be used therapeutically in diverticular hemorrhage (8), likely by filling the hemorrhaging area, and protecting the injured mucosa from dietary or GI contents. Barium persists for a long time, and may be superior to sucralfate in its ability to coat mucosal defects (8). In the current case, oral barium sulfate was administered to protect the GI hemorrhagic lesions after the whole blood transfusion. After treatment, the prognosis was good, and the GI hemorrhage did not recur.

There are previous reports describing NSAID toxicity, but none describe ketoprofen plaster ingestion. This is the first case report of ketoprofen-plaster-induced GI hemorrhage in a dog.

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케토프로펜 플라스터 독성에 의한 개에서의 위장관 출혈

박형진 · 최준혁 · 이우남 · 송근호 · 서경원[1]

충남대학교 수의과대학

요 약 : 14년령의 Shih-Tzu 개가 이물섭취 및 구토를 주 증으로 본원에 내원하였다. 구토물은 인의에서 사용되는 부착형 제제인 ketoprofen plaster 였다. 대증치료로 위장관 보호제 투여와 수액요법을 실시하였다. 하지만 임상증상은 점점 악화되어 빈혈 및 흑색변, 백혈구 증가증, 고지혈증이 관찰되었다. 환자는 위장관 출혈이 있는 것으로 평가되었고, 수혈 및 위장관 보호제로 바륨제제를 도포하였다. 바륨제제를 위장관 보호제로 사용한 후 임상증상의 개선이 확인 되었다.

주요어 : Ketoprofen plaster, 비스테로이드성항염증제제 중독, 황산바륨