<Case Report>

Acute kidney injury caused by administration of zaltoprofen in a cat

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Abstract: A 5-year-old, 2.7 kg, spayed female Scottish Fold cat presented with hematemesis after administration of oral zaltoprofen, a non-steroidal anti-inflammatory drug, by the owner. Diagnostic imaging and blood analyses indicated development of acute kidney injury (AKI) resulting from zaltoprofen ingestion. To correct dehydration and anemic conditions, the cat received intravenous fluid therapy with whole blood transfusion and peroral N-acetylcysteine. Clinical signs resolved, but persistent azotemia was unresolved indicating that AKI could progress to chronic kidney disease. This case suggests that although zaltoprofen may have low adverse effects on humans, administration of zaltoprofen in cats can have serious adverse effects.

Keywords: cats, non-steroidal anti-inflammatory agents, pyranoprofen, renal insufficiency

In veterinary and human medicines, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used for their anti-inflammatory, analgesic, and antipyretic effects on acute and chronic pain [5, 8, 9]. The US Food and Drug Administration has recently approved the use of six NSAIDs (carprofen, meloxicam, tepoxalin, firocoxib, deracoxib, and etodolac) for degenerative joint disease and chronic pain in dogs [1, 5]. However, in cats, NSAIDs have severe adverse effects such as renal and hepatic toxicities [2-4, 8] due to low capacity of hepatic glucuronidation in cats compared to other species including dogs and humans. Hepatic glucuronidation is the major mechanism for the metabolism and excretion of these drugs [8]. Therefore, caution is needed when using NSIADs, and the increased monitoring and careful adjustment of therapy to find the lowest effective dose of NSAID are generally required in cats [13].

Zaltoprofen is a NSAID with strong inhibitory effect on acute and chronic inflammation. NSAIDs are classified according to their chemical structures or selective inhibition on cyclooxygenase (COX)-1 and COX-2. Zaltoprofen, a preferential COX-2 inhibitor, is used to treat arthritis and relieve inflammation and pain after surgeries in human medicine [6]. Due to its low adverse effect on gastric and intestinal mucosa [14], zaltoprofen has been increasingly used in humans. However, zaltoprofen has never been used in dogs and cats. There is no report on its efficacy, safety, or clinical toxicity of zaltoprofen in cats. Here, we describe a case of zaltoprofen toxicity in a cat.

A 5-year-old spayed female Scottish Fold cat weighing 2.7 kg presented with hematemesis and anorexia. The cat had a history of oral administration with zaltoprofen (Soletone 80 mg, CJ HealthCare, Korea) for treatment of stomatitis by the owner. Zaltoprofen (20 mg) was administered twice a day for 2 days before the presentation of hematemesis and anorexia. On physical examination, the cat appeared lethargic with prolonged capillary refill time and dehydrated over 7%. Initial diagnostic evaluation included complete blood count (CBC), serum biochemistry profile, urinalysis (Table 1), survey radiography, and abdominal ultrasonography. No abnormality in CBC, blood gas analysis, or coagulation panel was found. However, serum biochemistry revealed severe azotemia with hyperphosphatemia and increased amylase (2808 U/L; reference interval [RI], 433-1248 U/L) and lipase activities with high serum feline pancreas-specific lipase activity (Spec fPL: 6.4 µg/L; RI, ≤ 5.4 µg/L). On blood smears, Heinz body was not detected. Abdominal radiographs revealed enlarged kidneys (Fig. 1). Abdominal ultrasonography revealed increased cortico-medullary definition and echogenicity in both kidneys (Fig. 2) but a decreased echogenicity of the pancreas. These findings were suggestive of an onset of acute kidney injury (AKI) caused by zaltoprofen ingestion with acute pancreatitis (AP).

In the intensive care unit, intravenous fluid therapy was promptly provided to correct azotemia. N-acetylcysteine (140 mg/kg then 70 mg/kg quarter [q] 4 h per orally [PO] for 5 doses; Muteran; HanWha Pharma, Korea) was given to the cat using a nasoesophageal tube [11]. Dehydration was corrected by administration of Hartmann’s solution (JW Phar-
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Pharmaceutical, Korea) at a rate of 18 mL/kg/h for the first 6 h followed by the administration of 2.2 mL/kg/h of famotidine (0.5 mg/kg, intravenously [IV]; Gaster; Dong-A Pharmaceutical, Korea), taurine (2 mL/cat, IV, q12h; Samyang Anipharm, Korea), and vitamin B (0.2mL/cat, IV, q12h; Beecom-hexa; Yuhan, Korea). Cefotaxime (20 mg/kg, IV, q8h; Wooridul ceftaxime sodium; Wooridul Pharmaceutical, Korea) and metronidazole (7.5 mg/kg, IV, q12h; Trizele; JW Pharmaceutical) were prescribed due to concern of bacterial translocation. Maropitant (1 mg/kg, subcutaneous [SC], q24h; Cerenia; Zoetis, USA) was given for vomiting.

On day 3, despite critical supportive care, clinical signs including anorexia, depression, and melena were not improved and hematocrit was decreased to 7.6% (Table 1). Subsequently, a whole blood transfusion was given. Sucralfate (250 mg/cat, PO, q8h; Ulcermin; JW Pharmaceutical) was added. Clinical signs including anorexia, anemia, and depression were resolved. However, azotemia persistently showed in blood analyses. AKI appeared to be progressed the aspects of chronic kidney disease (CKD). At 10 months after presentation, the cat continued to do well clinically with CKD management.

Zaltoprofen has never been used to treat cats or dogs. In the present case, the administered dose of zaltoprofen was 14.81 mg/kg. Relatively few NSAIDs are licensed for feline use and their usage is generally limited to administration over a short period of time [7, 8]. Meloxicam is licensed as a single dose of 0.3 mg/kg SC for cat. In European Union, a much lower dosage of meloxicam at 0.05 mg/kg can be administered orally for long-term therapy with unrestricted duration [7]. In human medicine, zaltoprofen is a COX-2 preferential NSAID. It is known to have minimal adverse effect on gastric and small intestinal mucosa [14]. Therefore, the adverse events of zaltoprofen in humans might be lower than other NSAIDs. However, it is currently unclear whether these severe adverse effects are caused by dose-dependent problem or toxicity of zaltoprofen in cats after administration of

Table 1. Results of blood analyses obtained from a cat administered with zaltoprofen

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Reference range</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 45</th>
<th>Day 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>24–45%</td>
<td>25.8</td>
<td>22.1</td>
<td>19.9</td>
<td>7.6</td>
<td>23.2</td>
<td>19.9</td>
<td>12.0</td>
<td>32.8</td>
<td>33.8</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8–15 g/dL</td>
<td>9.1</td>
<td>7.6</td>
<td>6.2</td>
<td>2.3</td>
<td>7.1</td>
<td>5.9</td>
<td>3.7</td>
<td>10.8</td>
<td>ND</td>
</tr>
<tr>
<td>Total Protein</td>
<td>5.5–7.1 mg/dL</td>
<td>6.0</td>
<td>5.1</td>
<td>5.5</td>
<td>4.3</td>
<td>6.9</td>
<td>6.2</td>
<td>4.6</td>
<td>7.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.7–3.9 mg/dL</td>
<td>1.6</td>
<td>1.4</td>
<td>1.4</td>
<td>1.2</td>
<td>1.8</td>
<td>1.7</td>
<td>1.3</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.8–3.2 mg/dL</td>
<td>4.4</td>
<td>3.7</td>
<td>4.1</td>
<td>3.1</td>
<td>5.1</td>
<td>4.5</td>
<td>3.3</td>
<td>5.6</td>
<td>4.5</td>
</tr>
<tr>
<td>AST</td>
<td>6–44 U/L</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>68</td>
<td>48</td>
<td>ND</td>
<td>230</td>
<td>ND</td>
<td>31</td>
</tr>
<tr>
<td>ALT</td>
<td>20–107 U/L</td>
<td>60</td>
<td>70</td>
<td>49</td>
<td>68</td>
<td>166</td>
<td>ND</td>
<td>465</td>
<td>ND</td>
<td>32</td>
</tr>
<tr>
<td>GGT</td>
<td>1–10 IU/L</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>1</td>
<td>0</td>
<td>ND</td>
<td>2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ALP</td>
<td>23–107 U/L</td>
<td>11</td>
<td>12</td>
<td>29</td>
<td>79</td>
<td>46</td>
<td>ND</td>
<td>125</td>
<td>ND</td>
<td>50</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.1–0.5 mg/dL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>ND</td>
<td>0.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>BUN</td>
<td>18–33 mg/dL</td>
<td>248.2</td>
<td>179.5</td>
<td>90.5</td>
<td>45.9</td>
<td>118.1</td>
<td>62.6</td>
<td>29.8</td>
<td>35.9</td>
<td>34.5</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7–1.8 mg/dL</td>
<td>17.9</td>
<td>13.7</td>
<td>4.4</td>
<td>1.8</td>
<td>8.3</td>
<td>4.3</td>
<td>1.4</td>
<td>3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

PCV, packed cell volume; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; ND, not determined.
zaltoprofen.

In this case, the cat had AKI after administration of zaltoprofen. It might be direct or indirect effects of zaltoprofen on the kidneys. Zaltoprofen might have caused direct damage to the kidneys and potentially contributed to the development of AKI, similar to adverse effects caused by other NSAIDs [8]. Prostaglandin inhibited by NSAIDs may reduce renal blood flow and glomerular filtration rate, resulting in potential complication of AKI in humans [15]. COX-2 preferential NSAIDs will not completely negate the possibility of adverse effects. They may not confer any renal protective effect compared to non-selective NSAIDs [13]. Therefore, zaltoprofen might have contributed to the development of AKI.

In this case, AP was diagnosed with possible association with the ingestion of zaltoprofen. There are some possibilities that AP was developed in this case. First, zaltoprofen can trigger directly inhibition of prostaglandins, phospholipase A2, and neutrophil-endothelial interaction in the pancreas which plays an important role in the pathogenesis of AP in human medicine [10]. However, pancreatitis caused by zaltoprofen has not been reported in human medicine. Second, AP in cats is frequently associated with gastrointestinal tract disease and vomiting signs [12]. Thus, it is possible that AP is a complication caused by the administration of zaltoprofen. Thirdly, there was a possibility that AP would be a complication of AKI although further study would be necessary to clarify an association between AKI and the development of AP in dogs. In the present case, hematemesis and anemia were observed. Hematemesis could be resulted from gastrointestinal ulceration. It might have contributed to the development of anemia. It is well known that COX-2 preferential NSAIDs are less likely to cause gastrointestinal ulceration [10]. However, these drugs still have some activities against COX-1. Gastrointestinal ulceration and perforation can occur if these drugs are used inappropriately. Using NSAIDs in animals with poor visceral perfusion may also increase the risk of gastrointestinal ulceration. Therefore, the high-dose of zaltoprofen might have caused gastrointestinal ulceration, eventually progressing to anemia.

In conclusion, this case report describes the development of AKI, AP, and anemia resulting from zaltoprofen ingestion in a cat. Although zaltoprofen has low incidence of adverse effects in humans, zaltoprofen and other NSAIDs might have similar toxicities in cats.

Acknowledgments

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References

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