

## Comparison of the Upper Gastrointestinal Effects of Etodolac and Aspirin in Healthy Dogs

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**ABSTRACT.** Fifteen healthy castrated male dogs were separated into three treatment groups that were administered etodolac, aspirin and a placebo orally, respectively. All treatments were continued for 28 days. The animals were examined endoscopically on days 0, 3, 7, 10, 14, 17, 21, 24 and 28. There were no gastrointestinal mucosal lesions in either the etodolac or the placebo group, whereas some gastric lesions developed in the aspirin group after day 17. We considered that etodolac could be used for long-term treatments in dogs with fewer side-effects on the gastric mucosa than aspirin.

**KEY WORDS:** canine, etodolac, gastric lesion.

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In veterinary medicine, nonsteroidal anti-inflammatory drugs (NSAIDs) generally are used for the treatment of musculoskeletal and joint diseases and the management of postoperative pain as analgesics [7, 9, 10]. But NSAIDs therapy, including aspirin in dogs, frequently causes gastrointestinal (GI) bleeding, erosion, and ulceration [8, 9]. In human medicine, etodolac is a recently developed NSAID that has a lower potential for causing these side effects [5]. In veterinary medicine, etodolac is also used to manage pain and inflammation in dogs with osteoarthritis [3, 4]. The purpose of this study was to compare the effects of aspirin and etodolac on the GI mucosa of healthy dogs endoscopically, and to determine if etodolac was suitable for long term administration.

Fifteen castrated male mature dogs were assigned to the study. Their body weights were 9.5 kg to 18 kg. They were randomly assigned to three treatment groups, which received placebo, aspirin, and etodolac, respectively, as follows: four dogs were orally given the lactose placebo every 12 hr, five dogs were given aspirin 25 mg/kg twice daily, and six dogs were given etodolac (Osteluc®; Nippon Wyeth Lederle Ltd., Tokyo Japan) 15 mg/kg once daily. The daily dose was based on the reports of Davidson [4] and Tennant [11] at the maximum dose of managing pain as an anti-inflammatory drug. The dogs which were given etodolac were also administered a placebo at the second treatment time to make the number of administration times of each group the same. Drug administration was started after an endoscopic examination on day 0, and continued for 28 days. Drug tablets were given in a small amount of canned food at the time of feeding. The endoscopic examination for the upper GI tract, hematological analyses, and biochemical analyses were performed on days 0, 3, 7, 10, 14, 17, 21, 24

and 28 of treatment. Hematological analyses included a complete blood count (CBC) and an analyzed blood smear, and biochemical analyses included total protein and plasma albumin concentrations. After 12 hr of fasting, all of the dogs were premedicated by medetomidine (Domitor®; Meiji Seika Ltd., Tokyo Japan), 0.05 mg/kg SC, for sedation and anesthetized with pentobarbital sodium (Nembutal®; Dai-nippon Pharmaceutical Ltd., Osaka Japan), 5 mg/kg IV, for endoscopic examination of the upper GI tract. The number of erosions and bleedings and the locations of these lesions in the upper GI mucosa were recorded on endoscopic examination. The Kruskal-Wallis test was used for statistical analysis of endoscopic examination, and analysis of variance (ANOVA) of repeated measures was used for those of hematological analyses and biochemical analyses. For all statistical analyses, a probability of less than 0.05 was considered significant.

During the experiment, none of the animals had any abnormal constitutional symptoms with regards to activity, appetite, vomiting and melena, except for defecating occasional soft stools.

In the endoscopic examinations, there were no lesions in the upper GI mucosa of the dogs that were administered placebos and etodolac during the study. One dog that was given aspirin developed mucosal erosions and bleedings in the pyloric antrum on day 14. All of the dogs in the aspirin group had mucosal erosions and hemorrhages in the pyloric antrum, cardia, and lesser curvature of the stomach on days 17, 21, 24 and 28 (Figs. 1, 2). Many mucosal lesions were especially observed in the pyloric antrum. Significant differences were found on days 17, 21, 24 and 28 ( $P < 0.0013$ ). No significant differences (between groups or within groups) were found in hematological or biochemical analyses.

In our endoscopic examination, the duodenum was not examined, because there was the potential of influencing the

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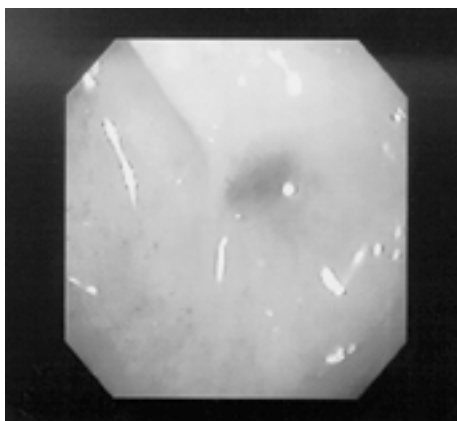


Fig. 1. An example of a submucosal hemorrhage in the pyloric antrum observed in an aspirin-treated dog.

experimental results through injury to the pylorus by mistakes in the endoscopic technique when passing the endoscope through the pylorus. Therefore we only examined the number of gastric lesions. For the same reason, a biopsy of the upper GI mucosa was not conducted.

The NSAIDs function as anti-inflammatory drugs through inhibition, with varying differences, of cyclooxygenase (COX), which ultimately reduces the production of prostaglandins (PG) [1, 5–7]. Acid NSAIDs generally used in veterinary clinical treatments, induce ulceration, erosion, and bleeding of the upper GI mucosa, breaking epithelial cells of the GI mucosa directly and inhibiting production of PG, mostly PGE<sub>2</sub>, which regulates blood flow and micro-circulation of the upper GI mucosa [8]. Two forms of COX

are recognized, COX-1 and COX-2 [1, 6]. COX-1, which is considered a constitutive form of COX, is normally associated with tissues in which PG serves a physiologic function; for instance, in the gastric mucosa PG have a cytoprotective function and are synthesized via a COX-1 pathway. COX-2 appears and increases in concentration in response to some form of stimulus, which is commonly seen at sites of inflammation. Therefore the side effects of NSAIDs are thought to result from the inhibition of COX-1, whereas the COX-2 enzyme seems to be inducible. For one study using assays based on canine tissues, etodolac was selective for canine COX-1 (COX-1 versus COX-2 ratio was below 0.5), the same as aspirin which has a ratio of less than 0.3 [7]. For the human study, however, etodolac was determined to have inhibited COX-2 selectively in an *in vitro* test (COX-1 versus COX-2 ratio was 5.0, which indicated etodolac was the COX-2 selective inhibitor) [7]. In addition, it is interesting to note that the *in vivo* tests did not provide such a clear definition between the selective COX-2 inhibitor and the non-selective drug [7]. In this study, no lesions of gastric mucosa were found in dogs of the etodolac group or the placebo group, while one dog which received aspirin had gastric erosions on day 14, and all of the dogs in the aspirin group had erosions after day 17 (Fig. 2). These results suggest etodolac does not have an intensive effect on the inhibition of COX-1, and may support the differences of selectiveness of etodolac between *in vitro* tests and *in vivo*. Recently, carprofen, which is a selective NSAID for COX-2 *in vitro*, has been approved and is commercially available. Like, etodolac, carprofen may also have a clinical advantage from point of view of side effects.

Generally, lesions formed by NSAIDs are on the upper GI mucosa, especially on the pyloric antrum and the pylorus

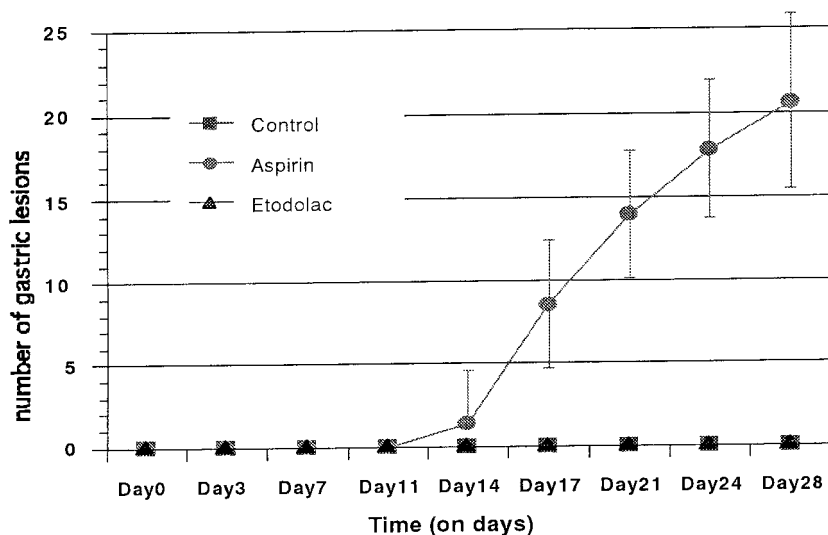


Fig. 2. The changes in the median and standard deviation (SD) of number of gastric lesions in each treatment group of control (■), aspirin (●) and etodolac (▲). On day 17, 21, 24 and 28 the differences were significant ( $P < 0.05$ ).

[8]. Most of the gastric lesions we found were also formed on the pyloric antrum.

Simultaneous administration with PG E1 analogue (misoprostol) effectively prevents NSAIDs-induced ulcers [2, 10]. However misoprostol is thought to be less useful in veterinary clinical medicine, because it needs to be administered more than three times a day and that is troublesome. Etodolac is more practical because it only needs to be administered once a day, and is also effective in managing pain and inflammation in dogs with osteoarthritis [3, 4].

In conclusion, the results of this study suggest that etodolac could be used for long-term treatments in dogs with osteoarthritis, with fewer side effects on the upper GI mucosa.

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