Evaluation of the adverse effects of oral firocoxib in healthy dogs

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This study evaluated the adverse effects of oral firocoxib in dogs. Six dogs (20.2 ± 6.3 kg) were studied. Values for complete blood count (CBC), serum urea, creatinine, alanine transaminase, alanine phosphatase, $\gamma$-glutamyl transferase, occult blood in feces, platelet aggregation, and buccal mucosal bleeding time were measured before and 7, 14, 21, and 29 days after SID treatment with firocoxib 5.3 ± 0.34 mg/kg (FG) or lactose 1 mg/kg (LG) for 28 days, in a randomized crossover study. Gastrointestinal (GI) tract endoscopy was performed before treatment began and at 29 days. Lesions were scored from grade 0 to 6. Data were analyzed using ANOVA and paired $t$-tests ($P < 0.05$). None of the dogs presented adverse clinical effects. There were no significant changes in CBC, biochemical profiles within groups, or differences between groups. Pretreatment mean ± SD bleeding time (LG, 70.7 ± 32.1 sec; FG, 75.8 ± 38.1 sec) and platelet aggregation (LG, 86.4 ± 10.2%; FG, 85.6 ± 9.2%) were not significantly different from readings at 29 days (LG, 95.2 ± 25 sec; FG, 91.7 ± 24 sec and LG, 73.2 ± 15.1%; FG, 84 ± 10.3%) nor the groups were different. None of the dogs had positive fecal occult blood tests, and endoscopic lesion scores were grade 0 both before treatment and at 29 days. Administration of firocoxib did not cause any adverse effects on GI, or hematological or serum biochemical variables and appears to have been well tolerated by dogs.

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INTRODUCTION

After the recent introduction of preferential and selective cyclooxygenase (COX)-2 inhibitors with improved safety profiles, they are the most widely used analgesics in veterinary medicine (Lascelles et al., 2005a). Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular for their anti-inflammatory, analgesic, and antipyretic effects on acute and chronic pain. They have rapid onset and are convenient for oral and once-daily administration (Mathews, 1996; Lascelles et al., 2005a).

The primary action mode of NSAIDs is inhibiting cellular expression of COX enzymes in cell membranes (Vane, 1971). There are at least two COX isoforms. COX-1 isoenzyme is a constitutive form of the enzyme found in many tissues and regulates normal homeostasis by producing prostaglandins in the gastrointestinal (GI) mucosa, and by platelet aggregation and renal blood flow. The COX-2 isoform is also constitutively expressed in a range of tissues and organs, including ovarian and renal tissue, but it is primarily induced by damage or tissue injury as a proinflammatory inducible enzyme and is responsible for the production of inducible enzymes which are converted into various eicosanoids, other specific prostaglandin end products which are inflammation mediators and amplify nociceptive input and transmission to the spinal cord (Fu et al., 1990; Kujubu et al., 1991; Lees et al., 2004).

All NSAIDs inhibit both COX-isoforms, suppressing the synthesis of homeostatic and proinflammatory prostaglandins and consequently have a narrow therapeutic index with primary side effects being gastric irritation, development of protein-losing enteropathy, hepatic and renal damage, articular degradation and prolonged bleeding time by prevention of platelet aggregation (Mathews, 1996; Pollmeier et al., 2006).

NSAIDs were classified by Lees et al. (2004), according to their capacity to inhibit the different COX isoforms. Based on this, they can be divided into nonselective inhibitors (aspirin, indomethacin, phenylbutazone, ketoprofen, meclofenamate), preferential...
COX-2 inhibitors (meloxicam, carprofen, nimesulide, etodolac and celecoxib), and selective COX-2 inhibitors (valdecoxib, rofecoxib, lumbaricob, etoricoxib). In dogs, carprofen can be considered as a strongly preferential COX-2 inhibitor or selective COX-2 inhibitor, on basis of in vitro ratios. Deracoxib and firocoxib are selective COX-2 inhibitors for veterinary use (Lees et al., 2004; Pollmeier et al., 2004). Another drug class is called dual inhibitors of NSAIDs: liclofelone and tepoxalin inhibit both COX and 5-lipooxygenase (Lees et al., 2004).

The introduction of preferential and selective COX-2 inhibitors veterinary approved NSAIDs, while also maintaining as much constitutive COX-1 effect as possible, have improved therapeutic index and resulted in less serious GI side effects than the nonselective NSAIDs (Luna et al., 2007), but even these drugs have been shown to cause GI tract perforation in dogs, mainly when approved dose levels and intervals are not respected or when given with other NSAIDs or corticoids (Reed, 2002; Duerr et al., 2004; Lascelles et al., 2005b; Moreau et al., 2005; Enberg et al., 2006). There is still concern about the adverse effects of NSAIDs, particularly because their most common use is for long-term administration (Luna et al., 2007).

Firocoxib is a new potent NSAID developed specifically for veterinary use with between 350 and 430-fold COX-2 selectivity by in vitro canine whole blood assay (McCann et al., 2004). Firocoxib plasma concentrations achieved by therapeutic regimens are able to inhibit COX-2 with little impact on COX-1 activity (McCann et al., 2004). In clinical reports, firocoxib was highly effective and acceptable for controlling pain and inflammation associated with osteoarthritis in dogs (Hanson et al., 2006; Pollmeier et al., 2006; Ryan et al., 2006); and dogs with experimentally induced synovitis, treated with firocoxib were significantly less lame than those treated with carprofen (McCann et al., 2004). Although no serious drug-related adverse effects were reported in these studies (Hanson et al., 2006; Pollmeier et al., 2006; Ryan et al., 2006), there are no studies evaluating the occurrence of adverse effects under controlled laboratory conditions.

More information is needed concerning the possible adverse effects of selective COX-2 inhibitors in dogs. The purpose of this study was to evaluate the safety of firocoxib orally administered to healthy dogs for 28 days. Endoscopy and blood and fecal analysis were used to examine and compare the gastroduodenal and hemostatic safety profile of firocoxib.

MATERIALS AND METHODS

This study was approved by the Animal Research Ethics Committee of the School of Veterinary Medicine and Animal Science, São Paulo State University, Botucatu, SP, Brazil, under protocol number of 73/2006.

Animals

All dogs were housed according to the Principles of the University Research Ethical Committee. Six crossbreed adult dogs were studied; two were male and four were female weighing 14–29 kg (20.2 ± 6.3 kg). Before the study, a preliminary laboratory investigation [complete blood count (CBC), urinalysis, and serum biochemical analyses] was performed to ensure that the dogs were healthy. Hemoparasites were also investigated. The dogs were de-wormed with 50 mg/kg of pirantel and praziquantel (Canex compound; Vetbrands, Jacareí, SP, Brazil) and vaccinated against distemper, leptospirosis, parvovirus, coronavirus, infectious hepatitis, adenovirus type II and parainfluenza (Recombinkte C6/VC; Merial Inc., Athens, GA, USA). Dogs were equally allocated into six collective 4 × 3.5 m isolated boxes with natural ventilation and fed commercial dry dog food and water was provided ad libitum. They had been well handled and familiarized to housing, feeding conditions, and group socialization for several months prior to the studies.

Experimental protocol

The study comprised two 4-week treatment periods with a washout period of 21 days between successive treatments using a randomized cross-over study design whereby each dog was each administered two treatments and served as its own control. All treatments were administered by the same investigator (FBM) who performed a general daily health examination for any evidence of vomiting, diarrhea, signs of depression, inappetence, or signs of abdominal pain during the study. Treatments were carried out for 28 days and given between 12:00 AM and 1:00 PM.

Values of CBC, serum urea, creatinine, alanine transaminase (ALT), alanine phosphatase (ALP), γ-glutamyl transferase (GGT), occult blood in feces, whole-blood platelet aggregation and buccal mucosal bleeding time (BMBT) were measured before and at 7, 14, 21, and 29 days after SID treatment with oral firocoxib (Previcox; Merial Saúde Animal LTDA., Paulinia, SP, Brazil) 5.3 ± 0.34 mg/kg or lactose 1 mg/kg as a drug-free negative control for 28 days. Urinalysis and endoscopy were performed before treatment and at 29 days. The FDA-approved firocoxib dose for dogs is 5 mg/kg. As this product comes in the form of 57.1 mg chewable tablets, it was administered by breaking the tablets into two halves, when necessary, to achieve doses as close as possible to 5 mg/kg for each dog.

Hematology procedures

Blood (10 mL) was withdrawn from the jugular vein by venipuncture: part was put into a glass tube containing EDTA (Vacutainer; Beckton Dickinson-BD, Franklin Lakes, NJ, USA) for CBC and part into a tube without anticoagulant (Vacutainer; Beckton Dickinson) for serum biochemical analyses. Considerable effort was made to minimize stress and maintain consistency during sample collection and handling. All samples were analyzed within 2 h of collection.

For bleeding time, each dog was restrained manually in lateral recumbency. Briefly, the upper lip was tied with a gauze tourniquet so that the buccal mucosal surface was exposed. A tri-faced lancet was used to make a puncture in an area of the
mucosa free of obvious vessels. A stop-watch was used to measure the time from puncturing until bleeding ceased and the value recorded as BMBT. Results were expressed in seconds.

A second 10 mL sample of blood was collected and transferred to tubes containing sodium citrate dihydrate and citric acid for whole-blood platelet aggregation determination. Platelet aggregation was expressed in percentage and analyzed by the addition of adenosine diphosphate (ADP) (ADP Reagent; Helena Laboratories, Beaumont, TX, USA) in the plasma-rich platelets.

Serum biochemical analysis

Serum urea, creatinine, ALT, ALP and GGT activities were determined using reagent kits and a centrifugal autoanalyzer (CELM Combate, Barueri, SP, Brazil). Data with normal distribution were compared by ANOVA for one-way repeated measurements followed by the Dunnett’s test to investigate differences over time in each treatment compared with baseline values, and a paired t-test to investigate differences between treatments at each time. Nonparametric data were compared by ANOVA followed by the Friedman test to investigate differences over time in each treatment and Wilcoxon signed-rank test to investigate differences between treatments at each time and to compare endoscopic lesion scores against baseline. Significance was set at $P < 0.05$.

RESULTS

All dogs completed the study without adverse clinical effects necessitating treatment. Physical examinations revealed no clinical signs of vomiting, anorexia, diarrhea, lethargy and weakness, or abdominal pain during the experiment. Mean weight of the dog did not change between testing sessions.

There were no changes in CBC, hemoglobin, hematocrit, total plasma protein, platelet count, whole-blood platelet aggregation, BMBT, urea, creatinine, GGT, ALT, and ALP between basal values and other measurement times for each group or between groups at each time, and all mean values (Table 1) were within reference ranges.

Serum urea was higher (63.3 mg/dL) in one firocoxib-treated dog at 7 days. The same dog showed increased serum urea (76.3 mg/dL) during lactose treatment at 21 days.
DISCUSSION

Although the safety and efficacy of preferential and selective COX-2 inhibitors have already been reported in dogs (Vasseur et al., 1995; Mathews et al., 2001; McCann et al., 2004), some studies have described adverse effects when these drugs are used in these species with several cases ending in death (MacPhail et al., 1998; Reed, 2002; Duerr et al., 2004; Lascelles et al., 2005b; Moreau et al., 2005; Enberg et al., 2006). Administration of NSAIDs is the most common predisposing factor for gastroduodenal ulceration in dogs (Stanton & Bright, 1989). In these cases, higher than approved doses were given (Lascelles et al., 2005b; Enberg et al., 2006) or dogs received another NSAID <24 h before or after treatment with the first one (Stanton & Bright, 1989; Dow et al., 1990; Lascelles et al., 2005b). Although oral firocoxib did not cause any adverse effects in the present study, it should only be prescribed at approved labeled dosages. Corticosteroids and other NSAIDs should not be administered in close temporal association because this may be a risk factor for inducing side effects (Mathews, 1996; Boston et al., 2003; Lascelles et al., 2005b).

Specific COX-2 inhibitors, like valdecoxib, rofecoxib and deracoxib claim to relieve pain without the serious GI side effects associated with older and less sensitive NSAIDs (Enberg et al., 2006). The development of COX-2 selective NSAIDs aims to improve the overall balance between efficacy and safety (Lascelles et al., 2005a). Firocoxib was the first veterinary NSAID that is a selective COX-2 inhibitor (McCann et al., 2004). This study supports the evidence for the benefits of COX-2 selectivity in causing less GI side effects. However, even COX-2 selective drugs are not side-effect free. In a recent report, rofecoxib, another selective COX-2 inhibitor was given to dogs for 56 days and caused severe gastric, duodenal, and gastroduodenal mucosal damage compared with placebo treatment (Moreau et al., 2005). Although rofecoxib is not approved and licensed for dogs, further studies evaluating the long-term use of firocoxib in dogs are necessary to know if the drug could cause similar GI damage to rofecoxib.

The most common findings from NSAID-induced PG inhibition in the GI tract are vomiting, nausea, lethargy, weakness, diarrhea, abdominal pain, and blood in feces (Stanton & Bright, 1989; Lascelles et al., 2005a,b). More than 1000 dogs with osteoarthritis were enrolled in the Previcox Experience Trial across the USA. Firocoxib was associated with a few side effects, like diarrhea and elevated blood chemistry results; sometimes these were not considered by owners or investigators to be a

Table 1. Mean ± SD platelet aggregation, BMBT and serum biochemistry variables in dogs treated with firocoxib or lactose at baseline and 7, 14, 21, and 29 days of administration.

| Variable               | Baseline | 7 days | 14 days | 21 days | 29 days |
|------------------------|----------|--------|---------|---------|---------|
| Platelet aggregation (%) |          |        |         |         |         |
| Firocoxib              | 85.6 ± 9.2 | 88.6 ± 11.6 | 89.8 ± 10.2 | 85 ± 9.4 | 84 ± 10.3 |
| Lactose                | 86.4 ± 10.2 | 85.4 ± 8.4 | 76 ± 12.2 | 78.2 ± 12.5 | 73.2 ± 15.1 |
| BMBT (sec)             |          |        |         |         |         |
| Firocoxib              | 75.8 ± 38.1 | 84.3 ± 46.9 | 71.6 ± 23.8 | 92.5 ± 35.9 | 91.6 ± 24.2 |
| Lactose                | 70.6 ± 32.1 | 75.6 ± 18.6 | 79.4 ± 26.3 | 96 ± 15 | 95.2 ± 25.2 |
| Urea (mg/dL)           |          |        |         |         |         |
| Firocoxib              | 42.9 ± 13.9 | 43.3 ± 12.4 | 46.5 ± 10.1 | 43.1 ± 11 | 29.9 ± 11.1 |
| Lactose                | 42.8 ± 8.8 | 37.4 ± 5 | 38.8 ± 10.6 | 46.1 ± 17 | 34.9 ± 12.9 |
| Creatinine (mg/dL)     |          |        |         |         |         |
| Firocoxib              | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.1 ± 0.1 |
| Lactose                | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.1 ± 0.1 |
| ALT activity (UI/L)    |          |        |         |         |         |
| Firocoxib              | 32.3 ± 10.3 | 39.6 ± 14.8 | 33.6 ± 15 | 31.8 ± 10.4 | 61.9 ± 55.3 |
| Lactose                | 80.9 ± 123.3 | 50.5 ± 40 | 36.7 ± 22.9 | 55.1 ± 57 | 53.1 ± 55.6 |
| ALP activity (UI/L)    |          |        |         |         |         |
| Firocoxib              | 102.3 ± 77.5 | 123.9 ± 74.4 | 110.5 ± 64.9 | 87.9 ± 43 | 101.2 ± 71.7 |
| Lactose                | 99.9 ± 47.7 | 106.1 ± 49.6 | 98.6 ± 32 | 95 ± 42.5 | 69 ± 41.2 |
| GGT activity (UI/L)    |          |        |         |         |         |
| Firocoxib              | 3.6 ± 1.8 | 4.6 ± 2 | 6.4 ± 5.2 | 4.8 ± 1.7 | 3.2 ± 1.9 |
| Lactose                | 4.2 ± 2.6 | 5.1 ± 3.1 | 4.8 ± 2.3 | 3.9 ± 2.1 | 2.5 ± 0.9 |

BMBT, buccal mucosal bleeding time; ALT, alanine transaminase; ALP, alanine phosphatase; GGT, γ-glutamyl transferase.
reason to discontinue the treatment. Vomiting was the most common finding in <2% of that study population and also in another one involving 218 dogs (Pollmeier et al., 2006; Ryan et al., 2006). The absence of side effects in our study might be due to the small number of animals used. However, another study using the same number of dogs ($n = 6$), lesion scores, and the same veterinarian performing the gastroscopies after 90 days of treatment, the prevalence of GI lesions showed that long-term use of NSAIDs (carprofen, flunixin, meloxicam, ketoprofen and etodolac) caused gastric lesions and clinical signs of GI damage (Luna et al., 2007). Our findings, even with a small number of dogs, suggest the safety of firocoxib and are in accordance with previous clinical studies where its long-term use was well tolerated in dogs with osteoarthritis (Hanson et al., 2006; Pollmeier et al., 2006; Ryan et al., 2006). This study cannot be extrapolated to a clinical setting in which patients typically undergo painful surgical procedures and receive NSAIDs for several weeks afterwards. In such circumstances, GI lesions may be exacerbated and result in clinical consequences.

Endoscopy is considered a sensitive method for detecting early NSAID-induced gastric injury in dogs. Gross endoscopic evaluation of gastric lesions correlates with gross lesions at necropsy and is therefore a reliable method of evaluating ulceration and gastric adverse effects (Dow et al., 1990; Boston et al., 2003). Animals may show gastric lesions in endoscopy, even if they do not present any clinical signs of side effects from the use of NSAIDs (Moreau et al., 2005; Dowers et al., 2006; Luna et al., 2007). In this study, firocoxib did not cause any abnormal signs of GI toxicity or lesions, or any laboratory abnormalities when compared with healthy dogs where lactose was administered. In another study, dogs receiving carprofen and deracoxib for only 5 days showed gastric lesions during endoscopy (Dowers et al., 2006). However, the presence of ulcers might have been due to the short evaluation periods in that study (Dowers et al., 2006). In our study, endoscopy was performed before and after 28 days treatment, enough time for the gastric adaptation phenomenon (Graham et al., 1988; Papich, 1997; Dowers et al., 2006). Evaluation of the mechanisms involved in NSAID-induced GI injury was beyond the scope of this study.

Although false positives for fecal occult blood may be found in dogs fed meat-based diets (Vasseur et al., 1995) and the test does not have 100% sensitivity and specificity (Narita et al., 2006), it was apparently reliable in our study, because dogs from the control group yielded negative results even when fed commercial dog food. Clinicians should therefore be aware that in routine investigation using fecal occult blood tests, the gastroduodenal damage caused by NSAIDs often goes undetected, as some studies reported that fecal examinations did not detect abnormalities, even when there were erosive and ulcerative lesions (Forsyth et al., 1998; Moreau et al., 2005). This was not the case in our study, because endoscopy did not reveal GI damage.

Renal function was assessed by measuring serum urea and creatinine concentrations. They can be used on their own to evaluate renal function, but are not highly sensitive markers of decreased renal function as they only increase with severe renal damage and are not reliable for early diagnosis of renal failure (Vasseur et al., 1995; Raekallio et al., 2006). For a better renal function assessment, glomerular filtration rate or renal scintigraphic imaging should be used because it is a good progress marker for renal insufficiency and nephropathies, even in the early stages (Raekallio et al., 2006). Acute renal damage is more likely to result from NSAID use in animals which already have compromised renal function or are under anesthesia (Mathews et al., 1990; Ko et al., 2000).

In general, firocoxib did not affect serum liver enzyme activities. Hepatotoxicosis has been associated with the use of carprofen and other NSAIDs in dogs (MacPhail et al., 1998) and is generally considered an idiosyncratic reaction. The number of dogs used in this study was too low to draw a proper conclusion, but other studies have not detected hepatotoxic effects from the use of firocoxib in dogs (Hanson et al., 2006; Pollmeier et al., 2006; Ryan et al., 2006). Some of our dogs had increased ALT and GGT values but these were not firocoxib related as some of them were also found in the lactose group. The reasons for increased serum ALT activity in one lactose-treated dog before and at 7, 21, and 28 days are unknown. After the end of the study, this dog was submitted to abdominal ultrasound which did not reveal any abnormality. Another dog treated with firocoxib had increased serum GGT activity at 7 and 14 days but its subsequent GGT values were within reference values. This increased GGT activity was not apparently related to firocoxib.

Primary hemostasis is mediated by the interaction between vascular endothelium and platelets. Inhibition of COX-1 activity by nonselective NSAIDs decreases thromboxane A2 formation and therefore can reduce blood platelet aggregation disturbing or even inhibiting primary hemostasis (Fresno et al., 2005). Bleeding time determination is the best in vivo test because it is inexpensive and a quick means of assessing primary hemostasis (Fresno et al., 2005). In this study, BMBT, platelet count and blood platelet aggregation values were not altered during firocoxib administration. Results suggest that firocoxib, given at the recommended therapeutic dose, did not impair primary hemostasis in healthy dogs.

Analysis of our results suggests that oral administration of firocoxib may not result in clinically important adverse effects and was well tolerated in healthy and young adult dogs. These results may not be necessarily applied to the whole target population. Periodical CBC serum biochemical analysis and endoscopy must be performed to monitor adverse effects when NSAIDs are used long term.

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