Long-term efficacy and safety of firocoxib in the treatment of dogs with osteoarthritis

A. Autefage, F. M. Palissier, E. Asimus, C. Pepin-Richard

Thirty-nine client-owned dogs with osteoarthritis were treated with 5 mg/kg firocoxib administered orally, once a day for 52 weeks. Veterinary examinations were performed on approximately days 0, 15, 90, 180, 270 and 360. Twenty-five dogs completed the study. The withdrawal rate associated with gastrointestinal side effects was low (5.1 per cent of dogs). Based on the owners’ assessment, 82 per cent of the dogs had improved at day 15, 84 per cent of the 32 remaining dogs had improved at day 90, and 96 per cent of the 25 dogs that completed the trial had improved at day 360. During this trial, 12 (48 per cent) of the 25 remaining dogs showed an improvement in their lameness from day 90 to day 360 (P<0.05).

OSTEOARTHRITIS is a progressive degenerative joint disease characterised by pain and disability associated with destruction of the articular cartilage along with bone remodelling. Osteoarthritis often develops in dogs with hip dysplasia, elbow dysplasia and partial or total rupture of the cranial cruciate ligament. It has been suggested that 20 per cent of dogs over one year of age are affected by this condition (Johnston 1997). NSAIDs are commonly used to control the pain and the inflammatory processes associated with osteoarthritis (Bergh and Budsberg 2005, Pollmeier and others 2006, Mansa and others 2007). The pain associated with osteoarthritis is often chronic, defined as lasting for more than three to six months (Mansa and others 2007). NSAIDs are increasingly used for their ability to reduce pain. The anti-inflammatory properties (as well as the adverse effects) of NSAIDs are related to the inhibition of prostaglandin synthesis, through the inhibition of cyclooxygenase 1 (COX-1) and COX-2. There are several NSAIDs licensed for use in dogs in Europe and the USA. The newer NSAIDs, the coxibs, are selective COX-2 inhibitors and thus have the potential to spare COX-1 activity at therapeutic levels. Firocoxib was developed specifically for veterinary use and has a 384-fold selectivity for COX-2 in canine blood (McCann and others 2004). There is strong evidence in the literature for the use of firocoxib in the management of canine osteoarthritis (Sanderson and others 2009).

In the late stages of osteoarthritis, dogs may experience pain even when the affected joint is not being used. This chronic pain must be suppressed, and long-term treatment with NSAIDs can be recommended (Mansa and others 2007, Innes and others 2010). In veterinary medicine, none of the previous studies of long-term treatment with NSAIDs exceeded three months (Pollmeier and others 2006, Raekallio and others 2006, Luna and others 2007, Mansa and others 2007). In studies in human medicine, coxibs have been used for 52 weeks (Cannon and others 2000, Curtis and others 2005). To the authors’ knowledge, data have not been published regarding the use of a coxib over 52 weeks for the treatment of osteoarthritis in dogs.

Clinical evaluation of firocoxib has largely been carried out in dogs, but over periods of treatment that did not exceed 90 days (Hanson and others 2006, Pollmeier and others 2006, Ryan and others 2006). The aim of this clinical trial was to evaluate the clinical efficacy and safety of firocoxib (Previcox; Merial) in a one-year continuous period for the treatment of osteoarthritis in dogs.

Materials and methods

The investigation was planned as a prospective case study at a single site. Thirty-nine dogs diagnosed with osteoarthritis were enrolled over a 12-month period. The mean (sd) weight was 33.8 (9.5) kg, and mean (sd) age was 7.4 (3.8) years. Fifteen of the dogs were female (10 of them neutered), and 24 were male (four of them neutered). Twenty-three breeds were represented. The trial was concluded 12 months after the last dog was enrolled.

Osteoarthritis was diagnosed based on history (lameness, difficulty in jumping, difficulty in getting up after a rest period), physical findings (pain on manipulation/palpation, or decreased range of motion of one or more joints) and radiography (narrowed joint space, periarticular osteophytes, subchondral bone sclerosis). Dogs with bilateral osteoarthritis or with involvement of multiple joints were eligible for inclusion in the study. In these cases, only one joint, the most severely clinically affected, was considered.

The owners were required to sign an informed consent form before the treatment began.

Dogs were excluded if they had received either NSAIDs or nutraceutical agents in the previous seven days. They were also excluded if they had received corticosteroids in the previous four weeks. Surgical procedure(s) performed within the previous 14 days or a planned elective surgery during the study period precluded enrolment in the study.

Dogs were withdrawn from the study before their treatment had been completed for the following reasons: treatment failure, severe side effects, post-treatment observations unavailable, or the appearance of illness unrelated to the treatment but requiring the cessation of NSAID medication.

Dogs received firocoxib at a dose of 5 mg/kg orally once daily for 360 days. The dosage for each animal was calculated on the basis of its bodyweight at the initial physical examination and the commercial presentation of firocoxib (57 mg and 227 mg of oral tablets). Dogs were given a full clinical examination at recruitment and after approximately 15, 90, 180, 270 and 360 days of treatment. The
clinical examinations were performed for the duration of the study by the same investigator. At the same time, for each dog, urinalysis was performed and blood samples were collected for routine haematology and serum biochemical analysis. Radiographs were taken at the initial visit and on days 180 and 360.

Scoring was based on a scale of 0 Normal to 3 Severe for each evaluated variable (l lameness, pain on manipulation/palpation and range of motion) (Table 1). As previously proposed by Pollmeier and others (2006), an overall clinical score was calculated by the investigator for each dog at each examination. This was defined as 2 x lameness + pain on manipulation/palpation + range of motion; the factor of 2 was applied to place more weight on lameness as part of the clinical picture.

Radiographic scoring was based on a scale devised by the authors, ranging from 0 to 3, which could be used regardless of the joints involved: 0 No osteophytes, 1 Osteophytes on one location of the joint, 2 Osteophytes on two locations of the joint, 3 Osteophytes in all compartments of the joint. The scores were assigned to the most severely clinically affected joint, as determined at the initial evaluation.

Each owner scored any change, in comparison with the initial visit, on approximately days 15, 90, 180, 270 and 360 for the ability of the dog to go for a walk, to go up/down stairs, to jump, to play and to get up after a long rest period. The scoring of these variables was based on a scale of 0 Extremely severe to 10 Normal behaviour. The owner also had to provide an overall assessment of the relative improvement in the dog’s condition in comparison to the initial visit (Table 2). The owners completed daily observation forms, where any changes in the dogs’ behaviour, appetite, thirst, health, vomiting, diarrhoea, polyuria/polydipsia, and any other medication they received were recorded.

Statistical analysis
All the data were analysed using two factors (days and dogs), using the analysis of variance test followed by the Tukey test to investigate differences over time for each variable. Dogs were withdrawn from the study before their treatment had been completed because of unavailable post-treatment observations or the development of illness unrelated to the treatment had their last scores carried forward. Using the last observed value as an estimate for the missing observations avoided a decrease in the statistical power due to the missing data. In such a trial, where an improvement of the condition over time is expected, this statistical technique would underestimate the average improvement.

Dogs withdrawn from the study either because their condition deteriorated or because of an adverse reaction to the drug were included in the analyses as treatment failures and the unavailable observations were considered as missing values.

The descriptive statistics (mean, sd, percentages) were obtained from the data available for each assessment time.

Statistical significance was accepted at the 5 per cent level.

Results
Thirty-nine dogs with clinical and radiographic signs of osteoarthritis were included. The affected joints included the hip joint (23 [59 per cent], elbow joint (nine [23 per cent]), stifles joint (six [15 per cent]) and tarsal joint (one [3 per cent]). Twenty-five dogs completed the study. Four of the 14 dogs that were withdrawn from the study did so because of side effects related to the treatment: high creatinine concentrations (two dogs; 230.5 μmol/l and 431.8 μmol/l), diarrhoea (one dog) and a fatal duodenal perforating ulcer after accidental administration of a double dose (one dog). These dogs were withdrawn at days 15, 111, 7 and 101, respectively. One dog was withdrawn due to anaemia of unknown origin on day 102. Three dogs were withdrawn because their condition was not sufficiently improved, and were considered as treatment failures. Five dogs were withdrawn because it was necessary to change their medication while they were being treated for another disease, unrelated to the firocoxib treatment. One dog was unable to come to assessment visits because the owner had moved. The numbers of dogs remaining in the study were 39 at day 15, 37 at day 90, 32 at day 180, 27 at day 270 and 25 at day 360.

The majority of the dogs improved with firocoxib treatment in comparison with their baseline values. The change over time of the overall score calculated by the investigator is shown in Fig 1. The differences in the values between day 1 and the other times of evaluation were significant (P<0.05). The score differences between day 90 and day 360 were significant.

The scores for lameness and for pain on manipulation were significantly higher at day 1 compared with the scores on days 15, 90, 180, 270 and 360 (Table 3). For the overall score, after 90 days, the improvements for lameness and pain on manipulation were not significantly different except between day 90 (lameness 0.8 [0.7], pain 1.2 [0.8]) and day 360 (lameness 0.3 [0.5], pain 0.7 [0.7]). The range of motion scores improved significantly between day 1 (2.0 [0.7]) and day 360 (1.5 [0.8]).

From day 90 to day 360, 12 (48 per cent) of the 25 dogs that completed the trial improved for lameness, 10 (40 per cent) for pain, five (20 per cent) for range of motion and 16 (64 per cent) for overall score.

The radiographic scores did not change significantly between day 1 and day 360 (2.3 [0.8]).
The owners estimated that the condition of 82.1 per cent of their dogs had improved at day 15 (n=39), and 83.8 per cent, 87.5 per cent, 88.9 per cent and 96 per cent had improved after 90 (n=37), 180 (n=52), 270 (n=27) and 360 days (n=25), respectively. The scores for walking, going up/down stairs and getting up after a rest period were significantly lower at day 1 compared with scores assigned at the other evaluations (Table 4). For jumping and playing, the differences between day 1 and day 15 were not significant; apart from these scores, there were significant differences between scores at day 1 and day 15 compared with those obtained at days 90, 120, 270 and 360. For all the scores, the improvements after 90 days were not significantly different.

There were no changes over time in the values of serum proteins, activities of alanine aminotransferase and alkaline phosphatase, glucose, urinary pH and urinary protein:creatinine ratio. There was a significant difference in the urinary specific gravity between day 1 and day 90, but the difference was not clinically relevant. For urea and creatinine, there were significant differences between values at baseline and at the other measurements. After day 15, the differences between the measurements on the following measurement days were not significant. The basal values of serum urea (5.5 [1.9] mmol/l) and creatinine (101.8 [25.8] μmol/l for creatinine). However, none of these measurements on the following measurement days were not significant. The difference in the urinary specific gravity between day 1 and day 90, but the difference was not clinically relevant. For urea and creatinine, there were significant differences between values at baseline and at the other measurements. After day 15, the differences between the measurements on the following measurement days were not significant. The basal values of serum urea (5.5 [1.9] mmol/l) and creatinine (101.8 [25.8] μmol/l for creatinine). However, none of these measurements on the following measurement days were not significant. The difference in the urinary specific gravity between day 1 and day 90, but the difference was not clinically relevant. For urea and creatinine, there were significant differences between values at baseline and at the other measurements. After day 15, the differences between the measurements on the following measurement days were not significant. The basal values of serum urea (5.5 [1.9] mmol/l) and creatinine (101.8 [25.8] μmol/l for creatinine). However, none of these measurements on the following measurement days were not significant.

The low rate of adverse gastrointestinal events with firocoxib that has already been described (Hanson and others 2006, Ryan and others 2007) was very low (1 per cent for vomiting and 2.5 per cent for diarrhoea), and only one dog was withdrawn from the study due to diarrhoea. It was very rare that diarrhoea was reported as a reason for treatment being stopped, the concentration of creatinine increased, and only one dog was withdrawn from the study because of an excessive rise in serum creatinine concentration, at day 15 for the first dog and day 111 for the second. After the firocoxib treatment was stopped, the concentration of creatinine probably related to possible differences between the studies in case selection. Indeed, as the chronic pain of most of the dogs enrolled in the present trial related to the long duration of their osteoarthritis, the difference may be because it has been shown that long-term pain is more difficult to relieve and responds more slowly than acute pain (Mansa and others 2007).

Each criterion improved at each evaluation time. However, for most criteria, the differences were not significant after 90 days of treatment, showing that the greatest benefit occurred within the first three months.

The scores for lameness, pain on manipulation/palpation and the overall score obtained or calculated by the investigator showed that improvement was significant from the first visit at day 15. From the third month, this improvement was less obvious but real, since between three months and one year of treatment there was a significant improvement in these criteria. On the other hand, it was necessary to treat for six months to one year until the range of motion improved significantly.

NSAIDs are considered as a first-line treatment for osteoarthritic pain despite numerous adverse effects. The most common side effects of NSAIDs in dogs include damage to the gastrointestinal mucosa and kidneys. In this study, four dogs (10.5 per cent) were withdrawn before the fourth month because of side effects. The percentage of days of vomiting or diarrhoea relative to the total number of days of treatment was very low (1 per cent for vomiting and 2.5 per cent for diarrhoea), and only one dog was withdrawn from the study due to diarrhoea. The low rate of adverse gastrointestinal events with firocoxib that caused the owner or the investigator to discontinue the treatment has already been described (Hanson and others 2006, Ryan and others 2006). In a recent study using firocoxib for 90 days, endoscopic examination demonstrated the absence of significant gastrointestinal tract lesions developing during treatment, even in dogs with a history of previous digestive disorders (Lecoindre and Pepin-Richard 2010). In the present clinical trial, one dog died from a perforating duodenal ulcer a few days after administration of a double dose of firocoxib. Gastrointestinal tract perforation has been observed after excessive COX-2 inhibitors were given at a dose higher than the approved dosage (Lascelles and others 2005). Although it is impossible to conclusively associate this perforating duodenal ulcer to the double dose of firocoxib, this fatal event suggests that the approved dosage regimes should be followed carefully.

In this trial, two dogs were withdrawn from the study because of an excessive rise in serum creatinine concentration, at day 15 for the first dog and day 111 for the second. After the firocoxib treatment was stopped, the concentration of creatinine was slightly lower than that previously reported for firocoxib (93.4 per cent) or carprofen (92.4 per cent) (Pollmeier and others 2006). The small difference in the shortest assessment time can be explained by the fact that the range of possible values for the enzyme creatinine (101.8 [25.8] μmol/l for creatinine). However, none of these measurements on the following measurement days were not significant.
In this clinical trial, over a long period, the percentage of no-treatment days relative to the total number of prescribed days of treatment was 1 per cent. This treatment adherence was excellent compared with a trial in human beings with a 225-day period of treatment with NSAIDs for ankylosing spondylitis, in which the patients took only 81 per cent of the prescribed doses (de Kleer and van der Linden 1996).

The present study has several limitations, including the relatively low number of dogs included in the trial, the high drop-out rate and the fact that the clinical trial was not controlled. The numbers of dogs enrolled and the drop-out rate were related to the inclusion criteria, that is, dogs with a long duration of osteoarthritis that had not received NSAIDs in the previous seven years, or corticosteroids in the previous four weeks; the daily administration of the drug during the 360-day period; and the schedule of reassessment visits.

These limitations, and more particularly the absence of a control group and the lack of investigator and owner blinding, preclude definitive conclusions on the overall efficacy of firocoxib. However, the efficacy of firocoxib in the treatment of canine osteoarthritis has already been demonstrated (Hanson and others 2006, Pollmeier and others 2006, Ryan and others 2006, Drag and others 2007), but most often over a short period of treatment. The well-known side effects of NSAID treatment are often a limiting factor for veterinarians when considering prescribing a NSAID for a long period of time. The aim of this study was to determine the efficacy of the drug and to evaluate the effect of its long-term administration in dogs suffering from chronic osteoarthritis. Although the control of chronic osteoarthritis pain with coxibs over a 52-week period had already been studied in human medicine (Cannon and others 2000, Curtis and others 2005), this is the first time it has been studied over such a long period in veterinary medicine.

This trial showed that from day 90 to 360, 45 per cent of the dogs that completed the trial improved for lameness, 40 per cent improved for pain, 20 per cent improved for range of motion and 64 per cent improved for overall score. These high proportions of dogs showing improvement between three months and one year of treatment in clinical parameters such as lameness or pain on manipulation of the joint support the long-term administration of firocoxib in the management of osteoarthritic pain in dogs.

This clinical trial provides information on the efficacy and safety of firocoxib during long-term treatment (one year) and, thus, should be beneficial for veterinarians.

In this study, the investigator and the majority of the dogs’ owners were satisfied with the firocoxib therapy. The overall improvement of the dogs treated with firocoxib appeared to increase with time over the 360-day study period. Thus, it seems reasonable to prescribe firocoxib over one year for the treatment of chronic pain related to osteoarthritis in dogs. However, the treatment should be accompanied by a regular follow-up of clinical and biochemical evaluations.

References


### Papers

**TABLE 6: Mean (sd) haematology variables in dogs with osteoarthritis in the course of a 360-day trial of 5 mg/kg/day firocoxib**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Day 15</th>
<th>Day 90</th>
<th>Day 180</th>
<th>Day 270</th>
<th>Day 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes (x 10^9/l)</td>
<td>8.96 (2.40)</td>
<td>9.46 (3.25)</td>
<td>9.64 (2.88)</td>
<td>10.49 (4.01)</td>
<td>9.57 (2.79)</td>
<td>9.03 (2.52)</td>
</tr>
<tr>
<td>Lymphocytes (x 10^9/l)</td>
<td>1.86 (0.59)</td>
<td>2.20 (1.21)</td>
<td>2.30 (1.09)</td>
<td>2.45 (1.05)</td>
<td>2.28 (0.95)</td>
<td>1.93 (1.06)</td>
</tr>
<tr>
<td>Monocytes (x 10^9/l)</td>
<td>0.43 (0.30)</td>
<td>0.43 (0.32)</td>
<td>0.48 (0.25)</td>
<td>0.50 (0.43)</td>
<td>0.49 (0.31)</td>
<td>0.45 (0.31)</td>
</tr>
<tr>
<td>Neutrophils (x 10^9/l)</td>
<td>6.13 (2.08)</td>
<td>6.18 (2.44)</td>
<td>6.13 (2.30)</td>
<td>6.51 (3.53)</td>
<td>6.17 (2.27)</td>
<td>5.99 (1.95)</td>
</tr>
<tr>
<td>Eosinophils (x 10^9/l)</td>
<td>0.54 (0.39)</td>
<td>0.61 (0.48)</td>
<td>0.72 (0.56)</td>
<td>0.75 (0.48)</td>
<td>0.62 (0.55)</td>
<td>0.56 (0.33)</td>
</tr>
<tr>
<td>Basophils (x 10^9/l)</td>
<td>6.27 (0.75)</td>
<td>6.72 (0.69)</td>
<td>6.83 (0.83)</td>
<td>6.93 (0.80)</td>
<td>7.05 (0.74)</td>
<td>7.33 (0.44)</td>
</tr>
<tr>
<td>Platelets (x 10^9/l)</td>
<td>363 (99)</td>
<td>358 (124)</td>
<td>344 (124)</td>
<td>293 (77)</td>
<td>301 (94)</td>
<td>267 (53)</td>
</tr>
<tr>
<td>MCHC (g/l)</td>
<td>368 (15)</td>
<td>367 (1.5)</td>
<td>367 (1.5)</td>
<td>358 (16)</td>
<td>353 (11)</td>
<td>353 (10)</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>66.1 (2.8)</td>
<td>66.2 (2.80)</td>
<td>67.1 (2.6)</td>
<td>66.5 (3.1)</td>
<td>66.1 (3.4)</td>
<td>65.8 (3.5)</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>168 (19)</td>
<td>164 (19)</td>
<td>164 (21)</td>
<td>162 (19)</td>
<td>163 (19)</td>
<td>170 (19)</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.46 (0.05)</td>
<td>0.45 (0.05)</td>
<td>0.45 (0.05)</td>
<td>0.46 (0.05)</td>
<td>0.45 (0.05)</td>
<td>0.47 (0.05)</td>
</tr>
<tr>
<td>Mean platelet volume (fl)</td>
<td>8.6 (1.6)</td>
<td>8.4 (1.3)</td>
<td>9.3 (1.5)</td>
<td>10.0 (1.3)</td>
<td>10.1 (1.1)</td>
<td>10.3 (1.1)</td>
</tr>
<tr>
<td>Red cell distribution width (%)</td>
<td>15.6 (1.9)</td>
<td>15.5 (1.5)</td>
<td>16.0 (1.6)</td>
<td>16.1 (1.8)</td>
<td>16.1 (1.8)</td>
<td>16.7 (1.9)</td>
</tr>
</tbody>
</table>

† Prescribed doses = number of days x number of animals

**TABLE 7: Adherence to treatment in the course of a 360-day trial of 5 mg/kg/day firocoxib**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Day 15</th>
<th>Day 90</th>
<th>Day 180</th>
<th>Day 270</th>
<th>Day 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treated dogs</td>
<td>39</td>
<td>36</td>
<td>31</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Number (%) of non-adherent dogs¹</td>
<td>4 (10.3)</td>
<td>5 (13.8)</td>
<td>4 (12.9)</td>
<td>4 (15.4)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Prescribed doses²</td>
<td>585</td>
<td>2700</td>
<td>2790</td>
<td>2340</td>
<td>2250</td>
<td>10,665</td>
</tr>
<tr>
<td>Number (%) of no-treatment days³</td>
<td>4 (0.7)</td>
<td>32 (12.2)</td>
<td>28 (1.0)</td>
<td>42 (1.8)</td>
<td>1 (0.04)</td>
<td>107 (1.0)</td>
</tr>
</tbody>
</table>

¹ Non-adherent dogs are animals that had not received the drug at least once during the respective period of time

² Prescribed doses = number of days x number of animals

³ No-treatment days are the total number of days without drug administration in all dogs
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