Switching NSAIDs in Practice: Insights from the Previcox (Firocoxib) Experience Trial

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Veterinarians currently have a choice of six registered NSAIDs for use in the management of canine osteoarthritis. There is a need for data to clarify whether there is an increased risk of side effects occurring in the event of a switch between different members of the NSAID class. In this retrospective analysis of extensive data collected in the 1,000 dog Previcox (firocoxib, Merial) Experience Trial, the incidence of side effects in dogs reported as treated with an NSAID 7 days or less before enrollment was compared with that in dogs reported as not having received an NSAID in the equivalent period. Statistical analysis of the data indicates that observation of an interval of up to 1 week between beginning treatment with firocoxib and cessation of treatment with a different NSAID was not associated with any increased risk of adverse events.

**INTRODUCTION**

Canine osteoarthritis (OA) is indiscriminate in its occurrence, afflicting dogs of various breeds, gender, body weights, and ages, although older dogs appear to be more susceptible.1,2 Growing recognition of the pain caused by OA, its negative impact on a dog’s quality of life, and the potential effects on the human–companion animal bond has led to an increase in the use of NSAIDs to alleviate clinical signs. The benefits of this class of drug have been established from the time of the discovery of aspirin late in the 19th century, and six NSAIDs are now registered by the FDA for use in dogs.3,4

As the number of available NSAIDs has grown, there has also been an expanded aware-
The issues associated with the concurrent use of NSAIDs links to questions about how best to switch a patient from one NSAID to another.
This paper reports a retrospective analysis of study outcomes for dogs enrolled in the PET within 7 days of ceasing treatment with a different NSAID. Dogs so treated were compared with dogs in the study that had not received an NSAID within 7 days before enrollment.

**MATERIALS AND METHODS**

The detailed protocol for the PET has been described previously. Before enrollment, dogs considered for the study were subjected to a detailed physical examination and diagnosed with OA. Owners of dogs that were receiving an NSAID or corticosteroid at the time of the enrollment visit were asked to observe a washout period thought to be sufficient for clearance before initiating treatment with firocoxib (Table 1). For dogs being switched from another NSAID, the recommended trial washout period ranged from 1 day for injectable carprofen to 5 days for orally administered meloxicam. This recommendation was developed under the guidance of an expert panel of ACVIM-boarded surgeons. It was based on the half-life of each drug, according to the published prescribing information, with an allowance that the risk of drug–drug interactions would be minimal and clinically insignificant after an interval equivalent to three to four times the half-life of the initial drug. For aspirin, a previously suggested washout interval was at least 7 days, which was conservatively extended to 10 to 14 days for the PET.

Contingent on the attending veterinarian’s clinical assessment, owners were provided Previcox to be administered according to label rec-

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**TABLE 1. Number of Dogs Receiving an NSAID within 7 Days before Enrollment in the Previcox Experience Trial (PET)**

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Washout Period Requested in the PET (days)</th>
<th>No. of Days before Study Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products approved by the FDA for use in dogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carprofen</td>
<td>2–3 (oral); 1 (injectable)</td>
<td>0 1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>1–2</td>
<td>1 9 17 21 16 19 23</td>
</tr>
<tr>
<td>Etodolac</td>
<td>2–3</td>
<td>7 10 9 13 13 8</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>3–5</td>
<td>2–3</td>
</tr>
<tr>
<td>Total no. of dogs/day receiving other drugs</td>
<td>—</td>
<td>2 1 21 36 39 46 50 51</td>
</tr>
</tbody>
</table>

*No data were available for piroxicam to allow a withdrawal recommendation.
ommendations at a dosage of 5 mg/kg PO once daily. The protocol required that treatments be administered over a period of 40 days, with an interim visit to the veterinary clinic at 7 to 10 days after treatment began and a final veterinary assessment at the time of the final dose (i.e., 40 ± 2 days after treatment was initiated). The dogs’ owners were asked to complete a daily diary of observations of their dog throughout the treatment period.

The database records were reviewed, and dogs withdrawn from the study for any reason as well as dogs in which any adverse events were reported were identified. If a dog’s withdrawal appeared to be for a reason other than an adverse event (e.g., owner noncompliance, absence of treatment response, owner moved, Hurricane Katrina–related issues), the owner diaries of the dogs in question were reviewed in detail to determine whether adverse events could have influenced the withdrawal (e.g., reports of vomiting between stopping treatment with the previous NSAID and being enrolled in the PET:

- 6 or 7 days before study enrollment
- 4 or 5 days before study enrollment
- 3 days or less before study enrollment

Reported adverse event reasons for noncompletion of the study were compared between the RNT and NRN groups using Fisher exact test, a $\chi^2$ procedure. Similar comparisons were made within the RNT group between the three subgroups described above. A significance level of $P < .05$ was used in assessing these data.

**RESULTS**

A total of 1,002 dogs were enrolled in the PET, and all but 135 completed the study. At the initial enrollment, 246 dogs (24.5%) were reported by the attending veterinarians as having received an NSAID within 1 week of being switched to Previcox. NSAIDs administered in this period included five that had been registered by the FDA for use in dogs (carprofen, deracoxib, etodolac, meloxicam, and tepoxalin) and two (aspirin and piroxicam) that were not registered (Table 1). Of the 135 noncompleters, 31 (23.0%) had received an NSAID within 7 days before entering the study. The noncompletion rates were similar for all dogs receiving the registered NSAIDs carprofen, deracoxib, etodolac, and meloxicam, ranging from 11% to 13%. Insufficient numbers were available for independent assessment of tepoxalin, as only three of the dogs that did not complete the entire study had received this

There was no significant difference in the total dropout rate between the two groups of dogs.

[or synonyms for vomiting] or other relevant clinical signs before the estimated withdrawal of the dog from the study). Dogs were then separated into two post hoc groups:

- **Recent NSAID Treatment (RNT):** Dogs reported to have received an NSAID within 7 days before being enrolled in the study
- **No Recent NSAID (NRN):** Dogs not reported to have received an NSAID within 7 days before being enrolled in the study (which therefore included dogs with no history of any NSAID use)

Dogs in the RNT group were further divided into three subgroups based on the interval between stopping treatment with the previous NSAID and being enrolled in the PET:

- 6 or 7 days before study enrollment
- 4 or 5 days before study enrollment
- 3 days or less before study enrollment

There was no significant difference in the total dropout rate between the two groups of dogs.
drug in the week before enrollment.

The average ages of the dogs in the NRN and RNT groups were 9.3 and 9.8 years, respectively, with no major differences evident in body weight, breed, or joint involvement. There was no significant difference ($P > .10$) between the two groups of dogs in the total dropout rate or in the noncompletion rate as a result of vomiting, diarrhea, vomiting plus diarrhea, death/euthanasia, owner noncompliance, or miscellaneous causes (Table 2). The overall proportion of deaths was similar in each group; details of dogs that died or were euthanized are available in the earlier report of this study. None of these deaths were attributable to the types of GI, renal, or hepatic events that are typically associated with NSAID side effects. An elevation in blood chemistry concentrations, mainly blood urea nitrogen (BUN), was the reason for withdrawal of 12 dogs that were classified as noncompleters. There was no significant ($P > .10$) difference between the NRN and RNT groups for noncompletion for this reason. Detailed review of case records identified an incidental report of reduced appetite in two dogs in the RNT group that had elevated chemistries. One of these dogs had been treated with carprofen until 3 days before enrollment and, 10 days after entering the study, showed elevations in BUN to 1.5 times ULN, with creatinine increased to ULN. Both of these dogs were removed from the study on the basis of chemistry findings, and no additional concerns or continuing effects were reported.

The miscellaneous category included a range of reasons for withdrawal of dogs, all of which were unrelated to NSAID treatment used during the study (see Table 2 footnote). A review of individual records of dogs and the owner diaries in this category, as well as in the “no improvement” and “noncompliance” categories, identified incidental reports of vomiting in four dogs within the first week after study enrollment. This category also included three

<table>
<thead>
<tr>
<th>Withdrawal Explanations</th>
<th>RNT (No. of Dogs [%])</th>
<th>NRN (No. of Dogs [%])</th>
<th>P Value (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>3 (1.2)</td>
<td>16 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0)</td>
<td>6 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting plus diarrhea</td>
<td>0 (0.0)</td>
<td>4 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated laboratory values</td>
<td>4 (1.6)</td>
<td>8 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Death or euthanasia</td>
<td>4 (1.6)</td>
<td>7 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>9 (3.7)</td>
<td>42 (5.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Insufficient/no improvement</td>
<td>6 (2.4)</td>
<td>2 (0.3)</td>
<td>.0037</td>
</tr>
<tr>
<td>Owner noncompliance</td>
<td>5 (2.0)</td>
<td>19 (2.5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31 (12.6)</strong></td>
<td><strong>104 (13.8)</strong></td>
<td>NS</td>
</tr>
</tbody>
</table>

*Includes concurrent use of corticosteroids or other NSAIDs (see text for detail), alternative diagnosis made, new disease developed, owner moved, no reason given, Hurricane Katrina–related issues, surgery required, mitral valve disease developed, dog was lost, palatability, dog weighed <7 lb (minimum weight limit for Previcox per product label), and incontinence.

NRN = no recent NSAID; NS = not statistically significant ($P > .10$); RNT = recent NSAID treatment.
Six dogs (2.6% of the RNT group) were withdrawn from the study for failure to show improvement, and this was statistically significantly \((P = .0037)\) greater than the two dogs in the NRN group (0.3%) that were withdrawn for the same reason. It was not possible to determine whether this nonperformance assessment was based on improvement versus the previous treatment or improvement versus baseline lameness. Two of these six dogs in the RNT group had no veterinarian or owner rating available at the scheduled day 10 visit; based on veterinarian and/or owner ranking of the other four dogs, one was rated worse at the day 10 visit, one as showing mild improvement, and two as showing moderate improvement. In withdrawing these dogs from the study, neither owners nor veterinarians indicated that there was any additional health-related reason for the withdrawal decision.

There were no significant differences \((P > .10)\) in the overall rate of noncompletion between dogs in the RNT group that entered the study with washout periods of 3 days or less, 4 or 5 days, or 6 or 7 days and no significant differences \((P > .10)\) between dogs in the RNT group and dogs in the NRN group (Table 3 and Figure 1). The only significant difference \((P < .05)\) measured in any variable between the RNT and NRN groups and within the RNT group was related to the number of dogs in the RNT group with owners wishing to discontinue participation in the study because their dog’s response to treatment did not meet expectations. In this “insufficient/no improvement” category, significantly more dogs with a washout period of 3 days or less were withdrawn compared with dogs with a washout period of 6 or 7 days. The four dogs with a washout of 3 days or less before study enrollment had received deracoxib \((n = 2)\), carprofen \((n = 1)\), and meloxicam \((n = 1)\). Overall, as described in the initial report of this study, improvements in dogs that had received carprofen, deracoxib, or meloxicam in the week before enrollment did not differ from those that had no such history.1

### TABLE 3. Reasons for Noncompletion of Dogs in the RNT Group Based on the Period between the Last Dose of the Previous NSAID and Enrollment in the Previcox Experience Trial (PET)

<table>
<thead>
<tr>
<th>Withdrawal Explanations</th>
<th>Days before Enrollment of Last Dose of NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;3) ((n = 60) dogs)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting plus diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Elevated laboratory values</td>
<td>2</td>
</tr>
<tr>
<td>Death or euthanasia</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>3</td>
</tr>
<tr>
<td>Insufficient/no improvement</td>
<td>4(^a)</td>
</tr>
<tr>
<td>Owner noncompliance</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10 (16.7%)</strong></td>
</tr>
</tbody>
</table>

\(^a\)Includes concurrent use of corticosteroids or other NSAIDs (see text for detail), alternative diagnosis made, new disease developed, owner moved, no reason given, Hurricane Katrina-related issues, surgery required, mitral valve disease developed, dog was lost, palatability, dog weighed <7 lb (minimum weight limit for Previcox per product label), and incontinence.  

\(^b\)Significant difference between these groups \((P < .05)\).  

\(^c\)RNT = recent NSAID treatment.
**DISCUSSION**

Accumulation of the database of more than 1,000 treated dogs in the PET provided an opportunity for data assessment not available in smaller studies. This study allowed comparison of a large population of dogs that had been reported by attending veterinarians to have received NSAIDs within 7 days of switching to firocoxib with a population of dogs that either had no reported history of NSAID use or had not been reported as receiving NSAIDs within 1 week of starting firocoxib. This comparison lends support to a conclusion that, following observation of an appropriate washout period, there is no increased risk associated with switching from another NSAID to firocoxib. However, several factors should be considered when switching NSAIDs.

The first and perhaps most important of these factors is that regardless of which NSAID is used, GI concerns remain. For example, a dog already in the process of developing GI ulceration will likely continue on that course, whether it is switched to firocoxib or another NSAID or remains on the current NSAID. Nonetheless, switching NSAIDs is necessary in some dogs to achieve effective pain management. Due diligence should be practiced with all dogs placed on any NSAID.

Second, the PET study was not specifically designed to compare the populations described in this analysis, as is true for all retrospective studies. However, statistical analyses were completed and supported the conclusion of no increased risk of adverse events following the switch to firocoxib, and this is the first report of post-switch outcomes in a large canine population. These data indicate that prior use of an NSAID, up to 1 week before switching to Previcox, was not clinically different than initiating treatment with Previcox with no prior NSAID use.

Third, the number of dogs receiving aspirin ($n = 8$), piroxicam ($n = 1$), tepoxalin ($n = 3$), and etodolac ($n = 8$) before being switched to firocoxib was too low to allow any conclusions on the relative safety of such a switch. It is noteworthy that a complicating factor in the use of other NSAIDs following aspirin administration is a reported potential to suppress aspirin-triggered lipoxin, which appears to act in a protective manner on the GI tract. However, there are no randomized controlled trials on the use of aspirin in dogs, no data on its sequential use with any NSAID registered for canine use, and no data to determine its level of safety in dogs in the general population.

Some dogs in the PET were switched from another NSAID to Previcox without observance of the recommended washout period. Within this small number of dogs, the rate of withdrawal attributable to a lack of improvement was significantly greater ($P < .05$) than for
dogs in which an appropriate washout period was observed. We strongly recommend that a washout period be observed in all cases of NSAID switching and designed the PET and its assessment parameters with this expectation. We also understand that the failure to observe recommended washout periods in some dogs in the PET might be attributed to the severity of the OA pain and to the veterinarian’s and/or owner’s concern about this pain. In turn, such disease severity would then have to be considered a limiting factor in response to treatment, leading to the higher rate of nonresponse in these few dogs. It is important to view this finding against the overall population response described in the initial PET report in which the recommended minimum washout period was observed for the great majority of dogs.\(^1\) When considering the entire pool of dogs included in the PET, it was demonstrated that the overall improvement in OA in dogs treated with firocoxib was similar whether firocoxib was the initial OA treatment attempted on the dog, the second or third option in a long history, or an immediate follow-up treatment from another NSAID.

Finally, management of canine OA cases should involve a multimodal approach, in which an NSAID may play an important role. In initial therapy for the condition, or when observing a less-than-expected response, practitioners should consider other modalities such as weight management, physical therapy, activity control, and assessment of potential benefits of surgical intervention.\(^2\)

## CONCLUSION

This analysis compared two populations of dogs in which firocoxib treatment was initiated. One population had received NSAIDs within 7 days of treatment; the other had not. The comparison found no difference between the populations in the rate of adverse events that occurred. This suggests that switching a dog from any NSAID to firocoxib while observing a washout period of up to 7 days before starting firocoxib treatment does not carry increased risk of adverse events when compared with dogs that do not receive an NSAID within that 7-day period. Regardless of whether such a switch is made under clinical conditions, the need remains for vigilance in monitoring the health of any dog receiving NSAID therapy. Although switching to firocoxib cannot be expected to reduce every risk present before the switch, these data provide assurance to veterinarians that switching to firocoxib following observation of an appropriate washout period will not increase the risk of NSAID adverse events.

## REFERENCES

9. Hampshire VA, Doddy FM, Post LO, et al: Adverse drug event reports at the United States Food And...


