Use of an activity monitor to detect response to treatment in dogs with osteoarthritis

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Objective—To determine whether an activity monitor (AM) could be used to detect changes in activity in dogs with osteoarthritis treated with carprofen or a placebo.

Design—Randomized controlled trial.

Animals—70 dogs with no clinically important abnormalities other than osteoarthritis for which they were not currently being treated.

Procedures—Dogs wore an AM continuously for 21 days. On days 8 through 21, the dogs were treated with carprofen (n = 35) or a placebo (35). Total activity counts for days 1 through 7 (baseline) were compared with total activity counts for days 15 through 21 (endpoint). The change in total activity count from baseline to endpoint was assessed within each treatment group as well as between groups. Linear regression analysis was performed to test for an association between treatment and percentage change in activity counts while controlling for other variables.

Results—For placebo-treated dogs, median baseline total activity count was not significantly different from median endpoint total activity count (1,378,408 vs 1,310,112, respectively). For dogs receiving carprofen, there was a significant increase in median activity count from baseline to endpoint (1,276,427 vs 1,374,133). When age and baseline activity counts were controlled for, dogs in the carprofen-treated group had a 20% increase in activity counts, compared with placebo-treated dogs (95% confidence interval, 10% to 28%).

Conclusions and Clinical Relevance—Results suggested that the AM used in the present study may be a valid outcome assessment tool for documenting improved activity associated with treatment in dogs with osteoarthritis. (J Am Vet Med Assoc 2010;237:66–70)

The impact of chronic pain and inflammation on activity levels of dogs has been well documented.1–6 When treating a patient for painful conditions such as OA or bone cancer, veterinarians frequently rely on the owner’s description of a dog’s activities at home to help determine whether a treatment may be effective. A valid and reliable method to record the activity level of companion dogs in their routine home environment could be useful for documenting the efficacy of interventions designed to treat diseases such as OA to decrease pain.

To date, studies8–11 designed to test the efficacy of treatment interventions intended to decrease chronic pain and improve function in companion dogs with OA have relied largely on objective data obtained by use of gait analysis. This technique, although reliable, is time-consuming and requires specialized equipment and training. In addition, gait analysis restricts evaluation to a specific point in time, outside of the normal home environment. Furthermore, gait analysis predominantly captures changes in weight bearing on an affected limb, which is only one of many behaviors that can be altered in companion dogs with chronic pain due to OA.12–16

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>AM</th>
<th>Activity monitor</th>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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Recently, a watch-sized, omnidirectional, accelerometer-based AM7 that continuously measures the intensity, frequency, and duration of movement for extended periods has been used to document locomotor activity rhythms in laboratory-housed17–20 and companion21,22,25 dogs. It was reported22 that a sampling interval of 7 days provided a consistent estimate of routine activity for companion dogs in a home environment. The objective of the study reported here was to determine whether an AM could be used to detect activity changes in dogs with OA that were treated with carprofen (ie, an intervention with known efficacy) or a placebo. Our hypothesis was that there would be significant improvements in activity counts in dogs treated with carprofen, compared with counts in dogs treated with a placebo.

Materials and Methods

Study design—The study was a single-center, randomized, controlled clinical trial. All owners received a detailed written description of the protocol and gave written informed consent prior to enrollment of dogs in the study. Dogs could be withdrawn from the study at any time at the owner’s request. If a dog was believed to be in need of additional pain management while on the protocol, unblinding would occur, and the dog would be treated with standard-
of-care analgesics (NSAIDs, tramadol, or both). The study protocol was approved by the University of Pennsylvania Institutional Animal Care and Use Committee.

Inclusion and exclusion criteria—Client-owned dogs weighing ≥ 8 kg (≥ 17.6 lb) with a medical history, clinical signs, physical examination findings, and radiographic findings consistent with OA were recruited for inclusion in the study by use of e-mail messages, advertising circulars, and newspaper advertisements. Only dogs with a diagnosis of OA made while screening for the study that had not commenced treatment of any type (including nutraceuticals, special diets, and over-the-counter supplement-type products) and dogs with a prior diagnosis of OA that the owners had elected not to treat were eligible for inclusion in the study. Dogs that had received NSAIDs during the 2 weeks prior to evaluation for study enrollment, glucocorticoids during the 4 weeks prior to evaluation, or opioids during the 4 weeks prior to evaluation were excluded. Dogs with any clinically important neurologic disease or orthopedic disease other than OA, as determined on the basis of history and results of a physical examination, and dogs with any chronic disease that required daily medication were also excluded from the study, as were dogs with a history of coagulopathy, unexplained bleeding episodes, or hypersensitivity to NSAIDs. In addition, dogs with clinically important abnormalities detected on a CBC and serum biochemical testing at the time of the initial evaluation were referred to an internist for follow-up evaluation and excluded from the study.

Sample size—A total of 70 dogs were enrolled in the study. Because no data on activity counts of dogs with OA were available for sample size calculation, the size was established by determining the sample size that is necessary for a positive outcome to be documented in placebo-controlled carprofen efficacy studies. Ideally, for activity monitoring to be a useful outcome assessment instrument, it should be able to detect a positive outcome with the same or fewer animals as for other outcome assessment instruments currently in use. Gait analysis and owner assessment can detect a positive response to carprofen treatment with 35 dogs in each arm of a placebo-controlled trial.

Randomization procedure—Dogs were randomly assigned to 2 groups (carprofen and placebo; n = 35/group) by use of a simple randomization sequence generated by an off-site pharmacy. The sequence was concealed so that members of the study team (ie, investigators, data collectors, and nurses) were not aware of which group a dog would be allocated to during the initial evaluation process. Sequential study numbers were assigned to dogs that passed the initial evaluation process and were eligible for assignment to a study group. The study number and body weight for each dog were then forwarded to the pharmacy, and pharmacy personnel matched study numbers to the randomization sequence, formulated the appropriate treatment (carprofen or placebo), and packaged the pills in blister packs for collection by study personnel.

Blinding procedures—Dogs in the carprofen and placebo groups were treated with commercially available carprofen (4.4 mg/kg [2 mg/lb], PO) or a placebo once daily for 14 days. Three additional doses were included in the blister pack provided to each owner in the event that the owner had a delay in returning the dog for its follow-up appointment. The placebo pills were compounded to appear identical to the carprofen pills, and the packaging for both pills was the same.

Thus, study personnel and participating owners were unaware of group assignments for dogs enrolled in the study.

AMs—A watch-sized, omnidirectional, accelerometer-based AM that continuously measured the intensity, frequency, and duration of movement was used to measure activity levels of dogs in the study. The AM included an accelerometer that was sensitive to movement in all directions. A piezoelectric sensor generated a voltage when the device was subjected to a change in velocity per unit of time. The voltage was converted to a digital value that was used to adjust a baseline value, permitting filtering of constant accelerations such as those caused by gravity. For each 1-minute measurement period, the digital value during that period was compared with the baseline value, and the difference from baseline was used to create a raw activity value for the measurement period. The raw activity value was then converted by use of standard software to an activity count. Thus, an activity count was generated for every 1 minute of monitoring.

Outcome measure—An AM was attached to the collar of each study dog and positioned ventrally on the neck on day 0. Dogs wore the AM continuously for 21 days. On days 8 through 21, dogs received either carprofen or the placebo, as determined according to the randomization scheme. Total activity counts during days 1 through 7 (baseline period), when the dogs were not receiving treatment, were compared with total activity counts of days 15 through 21 (endpoint period), when dogs were being treated with either carprofen or placebo. The time interval between 1 AM and 5 AM was excluded from calculation of total activity counts because this was considered the time when dogs would most likely be sleeping, and increases in activity during this time would generally not be considered a positive outcome. To assess the ability of the AM to detect an overall effect of treatment with carprofen, the change in activity counts from the baseline to the endpoint period for dogs in the placebo group was compared with the change in activity counts from the baseline to the endpoint period for dogs in the carprofen group.

Follow-up—Following collection of data on day 21, a 2-week supply of carprofen was dispensed so that all owners could evaluate their dogs for a potential benefit of carprofen treatment. Owners were counseled to continue treatment and to follow up with their regular veterinarian.

Statistical analysis—An intention-to-treat analysis was used. That is, all dogs randomly assigned to the treatment or placebo group were included in the analysis. Continuous data (age, weight, and activity counts) were summarized as median and range; categorical data (sex and breed) were summarized as frequencies. Be-
cause total activity count data were not normally distributed, nonparametric methods of data analysis were used. For each group, the Wilcoxon signed rank test was used to compare total activity counts for the baseline and endpoint periods. The Mann-Whitney U test was used to compare change in total activity counts between groups. Two-tailed assessments were used for all analyses; values of $P < 0.05$ were considered significant.

Multiple linear regression analysis was performed to test for an association between treatment (placebo vs carprofen) and percentage change in activity counts while controlling for other variables (age, weight, sex, breed, and baseline activity counts). Two-way interactions among the main effects were investigated. Variables with a $P$ value < 0.20 in univariate analyses were tested for inclusion in the model. Variables were retained in the model if the $P$ value for that variable was $\leq 0.05$ or if addition of the variable to the model changed the coefficient for the treatment effect by $> 15\%$. Model assumptions were evaluated. Normality of residuals was assessed with a kernel density plot. The constant variance of residuals was checked with the Cook-Weisberg test for heteroscedasticity. The variance inflation factor was calculated to test for multicollinearity. Residual scatterplots were used to check for nonlinearity.

In addition to evaluations of group data, data for individual dogs were evaluated. A responders graph was constructed to demonstrate the proportion of dogs in each treatment group that had increased activity (i.e., percentage change in total activity count greater than the cut point) over a full range of possible activity increase cut points. All analyses were performed with a commercially available statistical software program.

**Results**

One hundred twenty-nine dogs were screened to obtain the 70 dogs eligible for inclusion in the study and random assignment to treatment groups (Table 1). No dogs were lost to follow-up. According to owner report and review of the blister packs, all 70 dogs received the prescribed treatment for 14 to 16 days. One dog in the carprofen group had unilateral rupture of a cranial cruciate ligament on day 14 of the study and was referred to the university’s orthopedic service for care, which included surgery. In accordance with the intention-to-treat analysis, data from this dog were included. The owner removed the AM on day 15; therefore, for this dog, endpoint data were the 7-day activity counts from days 8 to 14, rather than days 15 to 21. All other dogs were in compliance with the protocol. None of the other dogs received any additional medications, and all of the other dogs wore the AM continuously for 3 consecutive weeks.

For dogs in the placebo group, there was no significant difference in total activity counts between the baseline (median, 1,378,408; range, 596,196 to 2,443,275) and endpoint (median, 1,310,112; range, 575,859 to 2,561,322) periods. For dogs in the carprofen group, total activity counts in the endpoint period (median, 1,374,133; range, 387,497 to 2,896,685) were significantly ($P < 0.002$) greater than total activity counts in the baseline period (median, 1,276,427; range, 482,662 to 3,245,226). The change in total activity counts from the baseline to the endpoint period was significantly ($P < 0.005$) greater for dogs in the carprofen group than for dogs in the placebo group.

In univariate analyses of factors potentially associated with the percentage change in total activity counts from the baseline to the endpoint period, 5 factors had $P$ values $< 0.20$ (treatment group [$P = 0.006$], age [$P = 0.06$], body weight [$P = 0.12$], sex [$P = 0.12$], and baseline activity counts [$P = 0.050$]). These factors were subsequently included in the multiple linear regression analysis, but only treatment group, age, and baseline activity counts were significantly ($P \leq 0.05$) associated with the percentage change in total activity counts (Table 2). When age and baseline activity counts were

### Table 1—Demographic characteristics for 70 dogs enrolled in a study to determine whether an AM could be used to detect activity changes in dogs with OA that were treated with carprofen ($n = 35$) or a placebo (35).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group</th>
<th>Carprofen group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breed</td>
<td>Mixed</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rottweiler</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Doberman Pinscher</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Other purebred</td>
<td>10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>39 (16–77)</td>
<td>39 (8–76)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9 (3–14)</td>
<td>8 (3–14)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>24</td>
</tr>
<tr>
<td>Baseline activity count</td>
<td>1,405,980 (626,554–2,491,392)</td>
<td>1,326,694 (502,914–3,355,430)</td>
</tr>
</tbody>
</table>

Data are given as number of dogs or median (range). Baseline activity counts represent activity counts for days 1 through 7, prior to initiation of treatment.

### Table 2—Results of multiple linear regression analysis of factors associated with percentage change in activity counts from baseline (7 days of no treatment) to endpoint (7 days of treatment) for 70 dogs with OA treated with carprofen or a placebo.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>$t$</th>
<th>$P$ value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline activity count</td>
<td>$-1.03 \times 10^4$</td>
<td>-2.40</td>
<td>&lt; 0.001</td>
<td>$-1.88 \times 10^4$ to $-0.13 \times 10^4$</td>
</tr>
<tr>
<td>Treatment with carprofen*</td>
<td>0.199</td>
<td>3.77</td>
<td>&lt; 0.001</td>
<td>0.099 to 0.258</td>
</tr>
<tr>
<td>Age</td>
<td>0.027</td>
<td>2.98</td>
<td>0.004</td>
<td>0.009 to 0.046</td>
</tr>
</tbody>
</table>

*Reference comparison is placebo treatment.

$CI =$ Confidence interval.

Controlling for treatment group and age, for every 200,000 increase in baseline activity count, there was a 2.0% (95% CI, 0.3% to 3.7%) decrease in the percentage change in total activity count. Controlling for baseline age and count and age, dogs treated with carprofen had a 20% (95% CI, 10% to 26%) greater change in total activity count, compared with dogs treated with the placebo. For baseline activity count and treatment group, for each 1-year increase in dog age, there was a 2.7% (95% CI, 0.9% to 4.6%) increase in total activity count.
controlled for, dogs in the carprofen group had a 20% greater change in total activity counts, compared with dogs in the placebo group (P < 0.001; 95% confidence interval, 10% to 26%).

For all activity-increase cut points, the proportion of dogs in the carprofen group that had a percentage change in total activity count greater than the cut point was higher than the proportion of dogs in the placebo group that had a percentage change in total activity count greater than the cut point (Figure 1). For example, 77% (27/35) of dogs in the carprofen group had at least a 10% increase in total activity count from the baseline to the endpoint period, compared with only 20% (7/35) of dogs in the placebo group. Similarly, 37% (13/35) of dogs in the carprofen group had at least a 30% increase in total activity count from the baseline to the endpoint period, whereas no dogs in the placebo group had an increase in total activity count ≥ 30%.

Discussion

Results of the present study suggested that the AM used may be a valid outcome assessment tool for documenting improved activity associated with treatment in dogs with OA. Specifically, dogs treated with carprofen had a significant increase in total activity counts, as determined with the AM, from the baseline to the endpoint period, whereas dogs treated with the placebo did not. Controlling for age and baseline activity counts, dogs in the carprofen group had a 20% greater increase in activity counts, compared with dogs in the placebo group (95% confidence interval, 10% to 26%). Because carprofen has been approved by the US FDA for the relief of pain and inflammation associated with OA in dogs, if the AM had been unable to detect increased activity in dogs with OA treated with carprofen in the present study, we would have questioned whether the monitor was sensitive enough to detect such changes and could not recommend it as an outcome assessment tool in studies designed to evaluate interventions for the treatment of OA and associated clinical signs. In contrast, not only was the AM able to detect significant increases in activity in carprofen-treated dogs, it was also able to detect expected smaller improvements in activity in some of the placebo-treated dogs.

It is likely that improvements demonstrated in the responders graph for some of the dogs in the placebo group in the present study were attributable to regression to the mean, which is a ubiquitous phenomenon that can occur whenever there are repeated measurements on the same subject. Relatively high or low observations are likely to be followed by less extreme ones nearer the subject's mean because of natural variations in severity of pain and functionality in dogs with OA. Severity of clinical signs may vary, depending on such things as weather and activity level. These oscillations may influence when owners seek treatment for their pets. For example, they may be more likely to seek treatment when their animals are experiencing a period of more severe clinical signs. Thus, these dogs would have lower activity counts at the baseline assessment than they would have during a period of moderate clinical signs. As these dogs progress through the natural variability of clinical signs, they can be expected to regress back to their typical level of discomfort and functionality, and their activity counts would increase despite the fact that no intervention was initiated. This improvement in the placebo group has been documented with gait analysis in a similar study comparing the effects of carprofen and placebo in a randomized controlled trial in dogs with OA.

In the present study, 20% of the dogs in the placebo group had a 10% to 30% increase in activity counts. If an efficacy study were performed with no control group and a 30% increase in activity was reported in 20% of the dogs, this might suggest a beneficial effect from the intervention that does not actually exist. Thus, without a control group, there would have been no way to know how much of the change seen in the carprofen group in the present study was simply attributable to the natural variability of the disease. The finding that the AM was able to detect both the improvements in activity counts in the carprofen group and the difference in improvement between groups indicates that the AM was able to detect the true effect of the drug and not simply a placebo effect.

A blinded assessment was chosen in the present study because we believed that output from the AM (ie, activity counts) could be biased by knowledge of treatment group. For example, owners who knew that their dogs were receiving the placebo may have been less likely to encourage play or to take their dogs for a walk than owners who knew that their dogs were receiving a potentially effective intervention. This may have biased the results in favor of the intervention that was being studied.

In the present study, we chose to recruit dogs with OA that were not currently being treated because including dogs that were receiving anti-inflammatory or analgesic medications would have required a washout period prior to randomization. In addition to the ethical issues surrounding that type of study design, there would likely have been a number of dogs that were not compliant with the protocol because following assignment to a treatment group, they would have required a return to their original treatment regimen to maintain a reasonable level of comfort and functionality. We chose to minimize losses to follow-up and protocol deviations by including only untreated dogs in the present study.
We believe that results of the present study can be broadly generalized because dogs in the present study consisted of a wide range of ages (3 to 14 years), body weights (8 to 77 kg [18 to 169 lb]), and baseline activity counts (502,914 to 3,355,430). Although there were 17 different breeds of dogs represented in the study, 19 (27%) dogs were Rottweilers, which reflected the orthopedic patient population of our hospital. This may not represent the breed distribution at other practices. Although there were relatively even numbers of male and female dogs in the present study, they were not evenly distributed between the 2 groups. There were more males in the placebo group and more females in the carprofen group. The baseline activity counts for the carprofen group were also lower than the baseline activity counts for the placebo group. Although the goal of randomization is to evenly distribute animals between groups, it is not always successful, particularly when sample sizes are small. Because we used a concealed randomization scheme, the unequal distribution by sex and baseline activity counts occurred purely by chance,26 and we controlled for any significant effect of sex and baseline activity counts in the linear regression analysis. Although there was no effect of sex, dogs with lower baseline activity counts had higher percentage increases in activity counts in response to treatment. For example, a 9-year-old dog with a baseline activity count of 1,300,000 treated with carprofen would be expected to have a 16% increase in activity count, whereas a 9-year-old dog with a baseline activity count of 500,000 would be expected to have a 24% increase in activity count. It is possible that lower baseline activity counts represented more severely affected dogs, which would be expected to have the greatest response to effective treatment.

Linear regression analysis was used in the present study to identify those variables that may have affected activity counts.27 Body weight was relatively evenly distributed between the carprofen and placebo groups and was not associated with the percentage change in activity counts from the baseline to the endpoint period. Age, however, was found to have an impact. Because younger dogs generally have higher activity counts than do older dogs, one might expect that younger dogs would also have a greater percentage increase in activity counts in response to treatment. In the present study, however, older dogs had a greater response to treatment than did younger dogs. It is possible that older dogs were more severely affected and thus had a greater response to effective treatment.

References

a. Actical activity monitor, Mini Mitter Co Inc, Bend, Ore.


c. STATA, version 10, StataCorp LP, College Station, Tex.


