

## WHAT EVERY PRACTITIONER SHOULD KNOW ABOUT NSAIDS IN CATS

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“Cats are not small dogs.” Every cat practitioner knows this, but it is particularly true in regards to the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The pharmacokinetics, metabolism, toxicity, and the degree of inhibition of cyclo-oxygenase 1 (COX-1), cyclo-oxygenase-2 (COX-2) and lipoxygenase (LOX) of NSAIDs are very species specific. [1, 2] Accurate descriptions of the behavior of NSAIDS in cats are few in number, although recently more attention has been paid to this species.

The pharmacodynamics (the therapeutic effects of a drug) of NSAIDs are very different from the pharmacokinetics (a description of the drug's absorption, distribution, metabolism, and elimination). NSAID drug concentrations do not correlate well with drug activity. Thus, in order to really understand how a NSAID is acting, not only do the drug concentrations need to be measured, but accurate measures of drug activity also need to be assessed.

One of the easiest pharmacodynamic activities to measure is the production of fever after some challenge, such as endotoxin. [3] The length of time that a NSAID suppresses fever can be determined and this can be correlated with a given dose of the drug. More subjective measurements have been used to measure NSAID activity as well. The degree of swelling or heat associated with injection of an irritating substance can be measured. [4] The duration of analgesia after a standard challenge can be measured using various behavioral pain scoring systems or assessing the wound tenderness with a device that measures the pressure needed to get the animal to respond.[5]

Since the mechanism of action of NSAIDs is thought to be inhibition of COX and LOX enzymes, measuring the activity of these enzymes should be a good method of assessing drug activity. Assays have been developed to assess the COX-1, COX-2, and LOX activity in the blood of cats.[6] The degree and time course of this inhibition allows pharmacologists to accurately describe the drug's activity. The pharmacodynamic profile can then be matched to the pharmacokinetic profile to give an accurate picture of the drug's behavior.

Why is this important? Let's look at some examples.

Meloxicam is approved for use in the cat at a dose of 0.3 mg/kg SQ once, prior to surgery. Where did this dose come from? It came from a study of cats, in which single iv doses of 0.1, 0.3, or 0.5 mg/kg, were given 30 minutes before endotoxin challenge. [3] Body temperatures were measured for 300 minutes after the administration of endotoxin. Dose-related prevention of fever was demonstrated. The degree of fever prevention gained by increasing from 0.3 to 0.5 mg/kg was minimal, compared to that gained by increasing from 0.1 mg/kg to 0.3 mg/kg. How do we know that this dose prevents pain after surgery? A study was performed in which 64 female cats and 74 male cats undergoing onychectomy were assigned to get meloxicam (0.3mg/kg SQ) or butorphanol (0.4 mg/kg SQ) before surgery. [7] Cats in the meloxicam group were less lame and had lower pain scores. Fewer cats given meloxicam required rescue analgesia. Cortisol concentrations were significantly higher at extubation and lower at 3, 5, 12, 24 hours after extubation in the meloxicam group. General impression scores were excellent or good for 75% of the cats in the meloxicam group and 44% of the cats in the butorphanol group. There was no difference in buccal mucosal bleeding time between the groups, Packed cell volume and BUN, decreased in both groups, while glucose decreased in meloxicam group, after surgery.

There are also some older studies examining the efficacy of meloxicam in the prevention of acute pain in cats undergoing ovariohysterectomy. [5, 8] In one study there were 10 cats per group, with different groups being given carprofen, meloxicam, ketoprofen, or tolfenamic acid. The dose of meloxicam was 0.2 mg/kg SQ, given at extubation. Pain was assessed using a visual analogue scale (VAS) and there was no difference between groups. One cat in each of the meloxicam, tolfenamic acid and ketoprofen groups required rescue analgesia. Nine of ten cats per group had good overall score at 18 hours. There was no

difference between groups in mechanical threshold at incision site, as measured using a finger mounted device. In a study of 80 cats undergoing flank ovariohysterectomy were assigned to carprofen (4 mg/kg) or meloxicam (0.3 mg/kg) SQ before surgery. Pain was assessed using a VAS over 20 hours and there were no significant difference between groups. Two cats in the meloxicam group and one cat in the carprofen group required rescue analgesia. There were no differences between groups in the values for blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) after surgery. In both groups, BUN decreased and AST increased after surgery. These studies show that there is no difference between meloxicam and the other NSAIDs studied in the prevention of postsurgical pain.

Why use the 0.3mg/kg dose only once? In vitro studies, using standardized whole blood assays for measurement of COX-1 and COX-2 inhibition demonstrated inhibition of COX-1 was 43%, and COX-2 was 90% at a plasma concentration of 3.95  $\mu$ M, which would be the maximum concentration for the label dose. For this dose, the time during which COX-2 was inhibited more than 50% (IC<sub>50</sub>) was 23 hours, while the time during which it was inhibited more than 80% (IC<sub>80</sub>) was 8.8 hrs. The time during which COX-1 was inhibited more than 10% was 109.5 hours, while the time during which COX-1 was inhibited more than 20% was 64 hrs. If COX-1 inhibition above some minimal amount can result in gastrointestinal side effects, then the label dose would likely result in toxicity, if given more than once. These studies also found that there was no meloxicam concentration at which COX-2 inhibition could be demonstrated, for which COX-1 was not also inhibited at least 20%. At meloxicam concentrations showing > 80% inhibition of COX-2, a reasonable therapeutic target, COX-1 inhibition was greater than 40%. Meloxicam is thus not a COX-2 selective drug in the cat. [1, 2, 6]

So what happens if you give meloxicam more than once? Using the data from the above studies, if an IC<sub>50</sub> of COX-2 was chosen as a therapeutic target, the extrapolated dose was 0.11 mg/kg/24 hr. If an IC<sub>80</sub> of COX-2 was chosen as a therapeutic target, the extrapolated dose was 0.17 mg/kg/24 hrs. There is one study assessing the effect of meloxicam on chronic pain. Sixty nine lame cats were assigned to meloxicam (0.3 mg/kg PO on day 1, followed by 0.1 mg/kg daily for 4 days) or ketoprofen (1 mg/kg PO daily for 5 days). Both groups improved in measures of demeanor, feed intake, and weight bearing. There were decreases in measures of lameness, pain on palpation, and inflammation. There were no significant differences between groups. [9]

What about toxicity? Safety studies performed to assess the safety of the one time 0.3 mg/kg SQ meloxicam dose demonstrated a narrow margin of safety. Cats given 0.3 mg/kg for eight days developed vomiting, diarrhea, lethargy, and decreased food consumption. Two of 4 cats were moribund or dead by day 9, and reddened GI mucosa was seen at necropsy in 3 of 4 cats. Repeated use of meloxicam in cats in clinical settings has been associated with renal failure and death. (package insert) Since there are no studies examining the pharmacokinetics and pharmacodynamics of repeat dosing of meloxicam, it is not known if there is an effective long term dose with minimal toxicity. Thus, recommended long term doses of 0.025 mg/kg daily or every other day are based solely on clinician experience.

Some NSAIDs have very complicated and variable pharmacokinetics and pharmacodynamics in the cat. Carprofen is an example of such an NSAID. First, it has a long and variable half-life, ranging from 9-49 hours, with a mean of 20 hours. [10] Second, carprofen is a chiral molecule, meaning that there are two mirror-image forms: R(-) and S(+). The commercial drug is a 50:50 mixture of these two forms. In the body, the two forms are essentially two different drugs, with different kinetics and different activities. The S(+) form is the more active form of the molecule, and may be up to 100 times more potent at inhibiting COX enzymes. It is thus important to relate activity to a specific form of carprofen, and to measure drug concentrations of both forms. [6, 10] Studies that have done this have shown that at the peak concentration of S-carprofen obtained with the label dose of commercial carprofen, COX-2 is inhibited 100% and COX-1 is inhibited 44%. Calculations show that COX-2 would remain > 50% inhibited for 72 hours, while COX-1 would remain > 20% inhibited for 20 hours. This data helps to explain why repeat dosing of carprofen is dangerous in the cat. First, it is difficult to predict what the half-life of the drug will be in a given cat. Second, at the label dose, there is severe and prolonged inhibition of both COX-1 and COX-2. If the cat is re-dosed during the time period during which COX-2 is inhibited to a far greater degree than COX-1, COX-2 selectivity will be lost. It has been suggested that smaller doses of carprofen may be more appropriate. If a target of 95% inhibition of COX-2 at the peak concentration of S-carprofen is set, the

calculated dose of the commercial product would be 1 mg/kg. In the average cat, this could be repeated every 24 hours, but the variable half-life of carprofen may preclude repeat dosing of even small doses.

Interestingly, there are some NSAIDs that cat eliminates rapidly. Piroxicam has a half-life of 12-13 hours in the cat, which is shorter than in the dog, in which elimination half-lives of 37 and 40 hours have been measured. In a study in which cats were given flunixin at a dose of 1 mg/kg PO q 24 hr for 7 days, there was no accumulation of drug. [4] In fact, the maximal concentration and the AUC<sub>0-24</sub> were less on day 7 than on day 1, suggesting that the drug was eliminated more rapidly. Serum thromboxane concentrations were < 75% of baseline up to 7 hours after giving flunixin on day 1, but only 2 hours on day 7. (Liver enzymes were increased at 7 days, suggesting that a 7 day course may not be prudent.)

The bottom line is that in order to understand how a given NSAID will behave in the cat, it is necessary to determine the pharmacokinetics and the pharmacokinetics in the CAT. One cannot extrapolate from studies performed in other species, nor can one assume that because one NSAID acts a certain way, that other NSAIDs will be similar. It will also be necessary to perform studies on the chronic administration of NSAIDS to determine how the drug acts when given for a period of time.

There is no doubt that NSAIDs are very useful drugs in the cat, particularly when single doses are used to treat acute pain or fever. Chronic dosing is much more problematic, since few studies have carefully evaluated the effects of repeat dosing. Recommended off-label repeat doses are based solely on clinical experience. When NSAIDs are used, it is important to monitor for toxic side effects. Occult GI bleeding can be monitored by measuring serial packed cell volumes. Renal and liver toxicity can be monitored by following serum biochemical markers. Perforating duodenal ulcers are difficult to detect, so any episode of anorexia or nausea should be treated as a potential emergency until it can be shown that perforation has not occurred.

Table: Recommended doses of NSAIDs in cats. Not all drugs are approved for use in the cat.

Drug	Suggested dose
Meloxicam	0.3 mg/kg IV, SQ, PO once. Do not repeat this dose.  0.2-0.1 mg/kg IV, SQ, PO, followed by reduction to 0.1-0.05 mg/kg q 24 hrs, followed by reduction to 0.025 q 24-48 hrs
Ketoprofen	2 mg/kg IV, SQ, PO, followed by reduction to 1 mg/kg q 24 hrs for up to 5 days. If used for surgical pain, give after surgery,
Carprofen	1 mg/kg IV, SQ, once. Do not repeat.
Flunixin	0.25-1 mg/kg SC, may repeat at 0.25 mg/kg once at 12-24 hrs.
Piroxicam	0.3 mg/kg every 24-48 hrs. Monitor for GI bleeding.
Tepoxalin	5 mg/kg q 12 hrs.

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