At some point in a cat’s life, it will most likely suffer from pain related to an injury, disease, or surgery, and veterinarians have a duty to try to alleviate this pain. In the January/February 2014 issue of *Today’s Veterinary Practice*, Dr. Sheilah Robertson addressed the challenges of acute pain assessment in cats. However, deciding how to effectively treat this pain presents its own difficulties.

Pain in cats—both acute and chronic—is difficult to treat because cats:

- Metabolize some drugs more slowly than dogs, potentially increasing the risk of adverse drug reactions
- Are prone to a gradual decline in renal function; one recent study found that up to 50% of cats may have chronic kidney disease
- Can be difficult to medicate and often resist administration of oral medication
- Often do not show obvious outward signs of pain or illness, making evaluation of medication efficacy a challenge, especially in stoic cats
- Have a limited number of options when it comes to veterinary approved pain medications.

### TABLE 1. Characteristics of an Ideal NSAID for Use in Cats

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Spares COX-1 and targets COX-2</td>
<td>Prolonged action in targeted tissues</td>
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<tr>
<td>2. Provides targeted action</td>
<td>Appropriate duration of action in the central nervous system</td>
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<tr>
<td></td>
<td>Spares ‘non target’ tissues</td>
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<tr>
<td>3. Can be administered with ease and accuracy</td>
<td>Injectable and oral forms available, which are interchangeable</td>
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<td></td>
<td>Simple dose determination and titration</td>
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<td></td>
<td>Palatable and easy-to-administer oral form</td>
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<tr>
<td>4. Displays wide safety margins and evidence-based clinical safety in target population</td>
<td>Toxicity studies demonstrate a wide safety margin in cats</td>
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<td></td>
<td>Appropriately safe in the target population (eg, cats undergoing elective surgeries)</td>
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<tr>
<td>5. Demonstrates robust evidence of clinical efficacy</td>
<td>Effective for acute and postoperative pain control</td>
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<td></td>
<td>Effective for alleviation of prolonged, maladaptive pain associated with chronic diseases</td>
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</table>
NSAIDs are one of the most common drug classes used to treat pain, and there is a robust body of information indicating that NSAIDs are effective in treating acute pain in cats. They have antipyretic, analgesic, and anti-inflammatory properties, which make them appealing therapeutic options; however, remember that there is not, and never will be, a completely safe NSAID for use in cats.

**IS THERE AN IDEAL NSAID FOR USE IN CATS?**

Based on our current understanding and the information available, if we were to design an ideal NSAID for use in cats, it would have certain important characteristics (Table 1).

1. **Sparcs COX-1 & Targets COX-2**
   NSAIDs work by inhibiting the production of prostaglandins (see **The Role of Prostaglandins** from arachidonic acid by the enzyme cyclooxygenase (COX). There are 2 forms of the COX enzyme:

   - **COX-1**: Generally constitutive and involved in production of prostaglandins that protect gastric mucosa and maintain normal platelet function and renal perfusion.
   - **COX-2**: Generally induced during inflammation and plays a role in healing and pain signaling. However, its activity also produces prostanoids involved in the normal function of certain tissues, such as the kidneys, brain, and reproductive system.

   The ideal NSAID strikes a balance between COX-1 and COX-2 inhibition:

   - **Nonselective COX inhibitors** equally inhibit COX-1 and COX-2. These NSAIDs tend to be associated with classic NSAID side effects, such as gastrointestinal (GI) ulceration, anorexia, vomiting, diarrhea, and renal and liver toxicity.
   - **COX inhibitors that selectively inhibited COX-2** demonstrated a greater safety margin than nonselective COX inhibitors in initial studies in healthy humans. However, this greater safety margin does not hold true for humans at risk for GI side effects. Nothing is known about the relative risk of selective COX-2 inhibitors in veterinary medicine.

   **THE ROLE OF PROSTAGLANDINS**

   Prostaglandins are required for both everyday and compensatory functions of all organs and tissues. For example, prostaglandins are involved in GI protection and healing of GI ulcers as well as normal renal function and compensatory protective mechanisms of the kidney during hypovolemia. Prostaglandins are a predominant player in the production of pain in the periphery through sensitization of nerves. They are also involved in the processes of facilitation and amplification of noxious stimuli during central sensitization at the level of the dorsal horn of the spinal cord (Figure 1). Central sensitization has been shown, in veterinary species, to become established within 24 hours of a surgical procedure, and it contributes to postoperative pain and likely chronic pain.
These 2 formulations should be usable and approved for use, interchangeably. For example, an injectable formulation facilitates both perioperative and immediate postoperative pain management, when it may be difficult or impossible to medicate animals orally. However, an oral formulation is beneficial for postoperative pain management upon discharge and long-term chronic pain management because it allows the drug to be administered in the home environment.

For cats specifically, palatable oral formulations facilitate administration and compliance—important components of pain management. Cats are selective about what they eat, and it is difficult to hide an unpalatable pill or medication in food or a treat, as is often done with dogs. If the cat won’t willingly take the medication, it must be restrained and dosed.

An NSAID formulation should be easily titrated, if necessary, and/or have an easy-to-determine dose. In tablet form, it should have a wide dose range that allows for administration of whole tablets, rather than fractioning tablets in order to stay within the therapeutic range.

**CONCEPT OF TISSUE SELECTIVITY**

Tissue selectivity is a concept that involves the highly protein-bound nature of NSAIDs and the acidic environment of inflammation.

During the process of inflammation, there is extravasation, or leakage, of protein from blood vessels into the extracellular environment. Since NSAIDs are known to be “highly protein bound” at normal physiological pH, if an NSAID has been administered, it will be bound to this protein.

The acidic extracellular environment of the inflamed tissue causes dissociation of the drug from the protein due to the low pH, which is known as the dissociation constant of the drug. After the drug dissociates from the protein, the increased free fraction of the active drug facilitates its movement into the cells where it then remains due to a phenomenon called ion trapping (passive movement of the drug into cells due to differences in pH between the intracellular and extracellular environment).

This theory explains why NSAIDs may have a prolonged presence in inflamed tissue, while having a more rapid clearance from the central compartment—blood stream and other noninflamed organs.
4. Displays Wide Safety Margins & Evidence-Based Clinical Safety
First, toxicity studies of NSAIDs should demonstrate a robust and wide safety margin in healthy cats. No one has yet defined what a wide safety margin is, but veterinarians are encouraged to read the package inserts and Freedom of Information Summaries for the various NSAIDs.
Additionally, NSAIDs should have been evaluated and deemed to be appropriately safe in normal cats undergoing elective surgeries—the most common scenario for use of NSAIDs in general practice. Ideally, this information should be in the form of peer-reviewed literature, which gives the clinician a degree of comfort about the validity of the data.
Further, it would be ideal to have safety data in other target populations that would benefit from NSAID-induced pain relief, including cats with concurrent diseases, such as chronic kidney disease or cardiomyopathy.

5. Demonstrates Robust Clinical Efficacy
For feline acute pain, there should be robust evidence of clinical efficacy for the target problems, such as perioperative pain control. For feline chronic pain conditions, efficacy should be demonstrated for alleviation of prolonged, maladaptive pain associated with chronic disease in cats, such as degenerative joint disease, spinal pain, stomatitis, cystitis, and cancer. Until very recently, efficacy of NSAIDs was very difficult to measure, and there was little evidence they provided pain relief. A recent breakthrough in clinical study design, along with a Clinical Metrology Instrument, may now allow NSAIDs to be tested for efficacy in a wide variety of chronic diseases.

**AVAILABLE NSAIDS FOR USE IN CATS**
In the U.S., there are 2 FDA-approved NSAIDs for short-term use in cats: robenacoxib and meloxicam.

<table>
<thead>
<tr>
<th>NSAID RECOMMENDATION SOURCE</th>
<th>RECOMMENDED DOSE</th>
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<tbody>
<tr>
<td><strong>Robenacoxib</strong></td>
<td><strong>Recommended dose from manufacturer (FDA-approved)</strong></td>
</tr>
<tr>
<td><strong>Meloxicam (injection)</strong></td>
<td><strong>Recommended dose from manufacturer (FDA-approved)</strong></td>
</tr>
<tr>
<td><strong>Meloxicam (oral suspension)</strong></td>
<td><strong>Recommended dose from ISFM/AAPF for daily use</strong></td>
</tr>
<tr>
<td><strong>Meloxicam (oral suspension)</strong></td>
<td><strong>Other recommendations</strong></td>
</tr>
</tbody>
</table>

*Not FDA approved for use in cats*
SAFE NSAID USE FOR CHRONIC PAIN

With respect to chronic administration of NSAIDs, there is an urgent need for more safety data in older cats that:

1. Suffer from painful conditions requiring long-term pain management and

2. Have concurrent diseases, such as renal impairment, hyperthyroidism, and liver disease.

- The 2010 Consensus Guidelines: Long-Term Use of NSAIDs in Cats (available at www.catvets.com/guidelines/practice-guidelines/nsaids-in-cats) provides recommendations from the International Society of Feline Medicine (ISFM) and American Academy of Feline Practitioners (AAFP) for long-term daily dosing of meloxicam oral suspension in cats.10

- In addition to standard dosing protocols (Table 2), meloxicam has also been recommended at lower doses, such as 0.02 mg/kg/daily.18 At this dose, it is well tolerated, but there is currently no information on whether it is efficacious.19 However, a recent masked, placebo-controlled clinical study found a dose of 0.035 mg/kg to be efficacious over a 3-week period.17

In the U.S., the FDA issued a black box warning for meloxicam in 2010 (see Management of Chronic Pain in Cats, November/December 2012, at tvpjournal.com), indicating that repeated use of meloxicam in cats has been associated with acute renal failure and death. It is most likely that the combination of the higher perioperative dose and then follow-up dosing was responsible for these adverse events, but no details are available in the public domain.

AAFP = American Academy of Feline Practitioners; COX = cyclooxygenase; GI = gastrointestinal; ISFM = International Society of Feline Medicine; NSAID = nonsteroidal anti-inflammatory drug

References


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