

## CANINE &amp; FELINE PAIN MANAGEMENT:

# Expert Insight into Practitioners' Top Questions

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The first annual *Today's Veterinary Practice* symposium—**Insights from Experts**—took place at the 2016 NAVC Conference in Orlando, Florida. This article reviews the information provided by Dr. Duncan Lascelles and Dr. Mark Epstein in the session **Pain Management: Top Questions from Practitioners**.

The second annual *Today's Veterinary Practice* symposium—**Diagnosis & Management of the Acute Abdomen**—takes place on Sunday, February 5, at the 2017 NAVC Conference. For more information, visit [navc.com/conference](http://navc.com/conference).

Pain management in dogs and cats can be challenging because clinicians often have to rely on the observations of owners to determine whether a prescribed analgesic is having a positive effect on the pet. In addition, patients with concurrent major organ disease present unique challenges for pain management. Following are some of the most common questions from practitioners about pain management.

## Q: IS TRAMADOL EFFECTIVE IN DOGS & CATS?

### Tramadol Use in Dogs

Clinical evidence of oral tramadol as an analgesic in dogs is scant—to the point of being almost nonexistent. There is a parenteral version of tramadol in Europe for which the clinical evidence demonstrating a pain-modifying effect is good, especially in the surgical environment.<sup>1-5</sup>

### Pharmacodynamics

Tramadol—predominantly through its negative enantiomer metabolite—modulates the serotonergic and noradrenergic pathways, which underpin the most powerful endogenous analgesic system in mammals. Using various inhibitory neurotransmitters, especially serotonin and

norepinephrine, these pathways descend from the higher centers down to the rostroventral medulla and, from there, feed to the spinal cord.

Basically, tramadol is a drug that may modulate, enhance, or “pep up” the endogenous inhibitory analgesic system. In some, but not all species (eg, human and cat but not dog), tramadol’s M1 metabolite is opioidergic.

### Pharmacokinetics

The pharmacokinetic profile of oral tramadol in dogs is poor. After oral administration, very low plasma levels of the parent compound and metabolites exist, and the plasma half-lives are very short compared with humans and cats. If tramadol is administered orally to dogs over a period of days to weeks, those low plasma levels decrease to negligible and, sometimes, undetectable levels.<sup>6,7</sup>

There is no reason—from a pharmacokinetic profile perspective—to expect that oral tramadol has a really robust pain-modifying effect in dogs. If it does—perhaps if it has been administered parenterally—the pain-modifying effect is presumptively from inhibition of reuptake of serotonin and norepinephrine, which enhances the effect of these neurotransmitters, rather than due to any opioid activity.

### ***In the Literature***

Literature describes tramadol as a synthetic mu-receptor opioid-like agonist compound. One metabolite is O-desmethyltramadol, an M1 metabolite, which humans make in abundance. In contrast, dogs make very little—in some cases, undetectable amounts—of the M1 metabolite, and what they do make has an extremely short half-life.

Any hearsay that tramadol has any significant opioid or opioid-like activity in the dog, for all intents and purposes, is not true. Insofar as current research has shown, tramadol has negligible to no opioid activity in the dog. In humans, tramadol's opioid activity provides much, if not most, of its analgesic effect. It is also worth noting that the caregiver placebo effect (aka *client feedback*) can be very strong.

Studies in the literature that are performed in a blinded manner are trying to answer the question: Is this therapeutic better than giving nothing or something that is ineffective? In clinical practice, there is not enough time to try to understand whether feedback is the caregiver placebo effect or a real effect.

The published studies of oral tramadol administration in dogs include a total of less than 30 dogs, and the results are mixed. A number of entities have tried to develop a veterinary formulation of oral tramadol as an analgesic for dogs, but they have failed because a beneficial effect could not be measured. While that doesn't negate the fact that tramadol may have a beneficial effect, it is very difficult to measure it.

### ***Use in Practice***

I (D.L.) occasionally prescribe tramadol for dogs (5–10 mg/kg Q 8–12 H), but do not use it as a first-line analgesic—it is a second- or third-tier therapy that can be added to therapies that have been proven to work. The higher doses, while required in some patients, may also result in more adverse effects related to serotonin and norepinephrine.

While clients have reported a perceived benefit of tramadol administration in their dogs, the feedback does not reflect significant relief. Furthermore, the caregiver placebo effect in dogs is about 40% to 50%; therefore, it could very well be that anything perceived in terms of a pain-modifying effect is a placebo effect.

From a pharmacokinetic perspective, and due to the lack of clinical evidence, we are skeptical that

tramadol has any significant pain-modifying effect in the dog.

### ***Tramadol Use in Cats***

Tramadol has much more potential when administered to cats.

### ***Pharmacokinetics***

With regard to pharmacokinetics, studies have demonstrated that, when cats metabolize tramadol, they make enough of the M1 metabolite to produce an opioid pain-modifying effect, with a plasma half-life similar to that in humans.<sup>8–11</sup> Analgesic effects have been observed in cats in experimental situations at relatively low doses of approximately 2 to 3 mg/kg.

### ***Use in Practice***

The biggest challenge is administering tramadol to cats—tramadol is bitter. Cats tend to drool terribly when they taste it, and obtaining a palatable formulation is very difficult. Even when tramadol is compounded into gelatin capsules, a little tramadol dust on the outside of the capsule can put cats off of the medication and their food, upsetting owners and the animal-owner bond.

A very appealing route for cats is transdermal medication. However, while compounding pharmacies will compound tramadol into a transdermal formulation, there should not be an expectation that it will achieve significant plasma levels. For example, fentanyl moves through the skin easily in a transdermal fentanyl patch, but, in cats, fentanyl compounded in pluronic lecithin organogel (PLO) transdermal cream does not move through the skin.

Much more needs to be understood about the bases in which these various drugs are combined, as well as the assumptions made about transdermal delivery.

### ***Tramadol Safety & Toxicity***

Currently there is no information on dose titration, safety, or toxicity of tramadol in either dogs or cats. However, there are case reports of dogs and cats experiencing toxic effects, particularly at higher doses.<sup>12</sup> Clinical signs commonly associated with these effects include anorexia, vomiting, behavioral or mentation changes (eg, agitation), and tremors.

Tramadol enhances serotonin, and if it is administered concurrently with fluoxetine or any other serotonergic drug, the likelihood of adverse effects increases. Clinical signs associated

with serotonin toxicity are similar to those for tramadol toxicity.

In rodent models, there is conflicting evidence that tramadol may worsen the gastrointestinal (GI) toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) due to increased serotonin levels affecting platelet aggregation and regulation of vasoconstriction.

### **Q: CAN NSAIDS BE USED FOR LONG-TERM PAIN CONTROL IN CATS WITH CHRONIC KIDNEY DISEASE?**

#### **NSAIDs in Cats with CKD**

Historically, NSAIDs have been contraindicated in cats with chronic kidney disease (CKD). However, to treat chronic pain effectively in a cat population, it is likely that NSAIDs will need to be used in conjunction with CKD—approximately 70% of cats with painful degenerative joint disease (DJD) have concurrent CKD.<sup>13</sup>

It has been recognized that many cats—even young cats—have DJD. In one study, just over 90% of all cats (between 6 months and 20 years of age) had radiographic changes consistent with DJD.<sup>14</sup> In order to properly manage the inflammatory component of the disease, which, at its core, causes pain, the prospect of using NSAIDs chronically needs to be cautiously considered.

#### ***In the Literature***

In cats with stable International Renal Interest Society (IRIS) Stage 1 and 2 CKD, clinical data have shown that CKD is not necessarily worsened by NSAIDs.<sup>15-17</sup> This includes patients that have been treated with the NSAIDs meloxicam (Metacam, metacam.com) or robenacoxib (Onsior, us.onsior.com).

In the studies that demonstrated meloxicam did not hasten the severity of CKD in cats, meloxicam was administered for 6 months at a dose of 0.02 mg/kg PO Q 24 H, which is almost half of the lowest dose that has been shown to be effective.<sup>16</sup> That low dose did not hasten CKD, but it has not been confirmed whether meloxicam is effective at that dose. The lowest dose of meloxicam that has demonstrated efficacy is 0.035 mg/kg Q 24 H.<sup>18</sup>

In a retrospective study of cats with DJD-related pain and CKD, one group of cats was administered meloxicam and one group was not.<sup>16</sup> However:

- The groups were not blinded or randomized.
- CKD cats that appeared relatively healthy with reasonable body condition scores were administered meloxicam, while CKD cats that appeared slightly unthrifty or had poor body

condition scores did not receive meloxicam.

Therefore, the cats that may have done poorly on the drug did not receive meloxicam.

- Cats were withdrawn from meloxicam as soon as their appetites started to decrease or if they demonstrated any other negative clinical signs.
- The survival time of the IRIS Stage 1 and 2 CKD cats that received low-dose meloxicam was not shortened in comparison to the cats that did not receive meloxicam.

In another clinical study, robenacoxib was administered at the label dose of 1 to 2 mg/kg PO Q 24 H for 30 days in cats with IRIS Stage 1 and 2 CKD.<sup>17</sup> Results demonstrated that robenacoxib did not worsen CKD in that time period; some cats improved and some worsened in both the placebo and treatment groups. Similar to the meloxicam study, in the robenacoxib clinical study the drug was administered to CKD cats that were, in general, fairly healthy.

#### ***Use in Practice***

If cats have GI upset, they are more likely to have decreased appetites rather than vomiting and/or diarrhea and then, by extension, they may not drink well, which may push them, especially those with IRIS Stage 1 and 2 CKD, into a renal crisis. Appetite is probably the most sensitive indicator as to whether or not a cat is doing well while receiving an NSAID.

Clinically, NSAIDs can be used to control pain in cats that have CKD, but we are most comfortable using NSAIDs in CKD cats that look relatively healthy with relatively good body condition scores. Once patients begin to lose their appetites, lose weight, and/or look unthrifty, we recommend exercising more caution.

#### ***Meloxicam versus Robenacoxib***

We have gravitated from meloxicam to robenacoxib; however, robenacoxib tablets are more expensive than the oral meloxicam suspension, which may make robenacoxib cost prohibitive for some owners.

Robenacoxib is generally palatable; about three-quarters of cats will eat it. In practice, we prescribe oral robenacoxib for chronic use either Q 24 H, Q 48 H, or sometimes owners will titrate it down to an “as needed” basis. Owners do report a positive analgesic effect but, in cats, the caregiver placebo effect is about 80% (unpublished data).

Robenacoxib remains at the site of inflammation for 24 hours, which is similar to many NSAIDs,



### **Learn More**

For further information on diagnosis of CKD, read **Early Diagnosis of Chronic Kidney Disease in Dogs & Cats: Use of Serum Creatinine & Symmetric Dimethylarginine** (March/April 2016), available at [tvjournal.com](http://tvjournal.com).

including meloxicam, as most NSAIDs are very highly protein bound, following the protein to the site of inflammation. The main difference between robenacoxib and meloxicam is plasma half-life: Robenacoxib's plasma half-life when administered orally is about 1.7 hours, while meloxicam's plasma half-life is significantly longer at approximately 15 to 20 hours. Therefore, if meloxicam is administered every day, it remains in the plasma on a sustained basis, bathing renal tubules, GI tissue, and other nontarget tissues, which may increase the chances of adverse effects.

### Other Long-Term Pain Control Options for Cats

When deciding whether or not to use an NSAID in a CKD cat, we consider the patient's:

- Blood analysis
- Severity/IRIS stage of CKD
- Physical condition.

For example, if the cat has IRIS Stage 2 CKD and is in poor physical condition, we consider administering steroids—in some cases, methylprednisolone acetate injectable (Depo-medrol, zoetis.com)—instead of NSAIDs.

### Use of Steroids

Cats with DJD often have a positive response to steroids. Of course, there are adverse effects associated with chronic use of steroids, including ligament deterioration, muscle mass deterioration, and development of diabetes mellitus. If there is concern regarding these adverse side effects, we recommend administering steroids intermittently.

### Neuropathic Pain

Many cats with longstanding pain are hyperaesthetic: They do not want to be touched and, if someone tries to touch them, they may walk away, yowl, or try to bite. It is likely that these cats—"grumpy" cats—have neuropathic pain. One of our first-line

drugs for these patients is gabapentin; however, there is no evidence in the current literature regarding the efficacy of gabapentin in cats.

### Other Adjunctive Therapies

In a blinded, placebo-controlled study, a prescription joint diet was shown to have measurable benefit in cats with DJD.<sup>19</sup> Many other adjunctive therapies may be tried (eg, amantadine, polysulfated glycosaminoglycans, amitriptyline) but none has been tested for efficacy in cats with DJD. One injectable polysulfated glycosaminoglycan product has demonstrated high bioavailability and distribution to joints when administered subcutaneously.<sup>20</sup>

### New Therapies

Recently, an anti-nerve growth factor antibody was shown to produce significantly improved activity in cats with DJD for up to 6 weeks after a single injection.<sup>21</sup>

### Q: WHAT MEDICATIONS SHOULD BE USED IN DOGS WITH ELEVATED LIVER ENZYMES AND CHRONIC KIDNEY DISEASE?

#### Elevated Liver Enzymes

It has been shown that, in the absence of liver dysfunction, elevated liver enzymes—serum alkaline phosphatase (ALP) and/or alanine aminotransferase (ALT)—are not necessarily a contraindication to the administration of NSAIDs in dogs.<sup>22</sup>

NSAIDs do not cause hepatotoxicity—in the classic sense—because toxicosis is dose-dependent. Acute hepatocellular necrosis that sometimes occurs due to NSAIDs is an exceedingly rare intrinsic reaction of a dog to the NSAID molecule; this reaction cannot be prevented or predicted as liver enzymes may be elevated or normal.

It is always a good approach to perform baseline blood analysis before initiating NSAID therapy; then perform blood analysis 2 to 4 weeks later.

**The animal-owner relationship**

must be considered when deciding which therapies are possible to administer to a particular cat. Generally, **our goal is to get one drug in the cat, maybe twice a day**, and then use adjunctive therapies.

In North America, with the label warnings on meloxicam and robenacoxib, there are concerns about using NSAIDs in cats beyond any label claim, which is a single dose of meloxicam or 3 doses of robenacoxib. The main concern is that, if something "goes wrong" with a patient prescribed off-label use of an NSAID, the owner has legal recourse due to the "black box" label warning on meloxicam or the standard label on robenacoxib.

We do not have owners sign a consent form when prescribing NSAIDs for cats, but we do make sure to clearly inform owners that long-term administration of NSAIDs in cats is off-label. We also inform owners that in Europe there is an infinite label for chronic use of meloxicam at 0.05 mg/kg PO Q 24 H in cats, which is over twice the dose being used here for musculoskeletal pain.

### Off-Label Use of NSAIDs in Cats

If there is a rise in liver enzymes, it is very often related to NSAID administration. Under those circumstances, discontinue the NSAID, perform blood analysis a few weeks later, and then consider administering a different NSAID. It is always prudent to assess liver function (serum bile acids) any time liver enzymes are raised.

We do not use NSAIDs in the face of liver dysfunction (eg, elevated serum bile acids). Many older dogs have elevated ALP; however, if ALT is elevated and at least twice the high end of the normal range, we recommend checking serum bile acids to evaluate liver function. If there is decreased liver function, there is an increased risk of GI irritation. Additionally, metabolism of the NSAID will be decreased, which translates to essentially higher than normal levels of the NSAID in circulation and a greater risk of GI irritation and ulceration.

We feel comfortable using NSAIDs in dogs with normal liver function, even if ALP and/or ALT are elevated, as long as liver function is normal and careful monitoring (including client communication) is pursued.

### Chronic Kidney Disease

NSAIDs can be nephrotoxic and, in general, the renal damage is dose-dependent.

When managing chronic pain in dogs with CKD, we have transitioned from use of classic NSAIDs to administration of non-acidic NSAIDs, such as acetaminophen. While we do not believe the efficacy of acetaminophen is as good as that of other NSAIDs, our clinical experience has shown us that acetaminophen appears to have a much lower risk of worsening CKD. However, there is a point at which quality of life becomes a concern, and classic NSAIDs may be more appropriate because acetaminophen does not have significant anti-inflammatory activity.

Serum creatinine can be used as a rough benchmark of glomerular filtration rate (GFR). For example, if serum creatinine is 3 mg/dL in a dog with CKD (reference range, about 1 mg/dL), NSAID administration can be decreased from once a day to once every 3 days. This administration interval provides more time for the kidneys to clear the drug. We may also lower the dose of the NSAID.

### Gastrointestinal Surgery

We do not administer preoperative NSAIDs to patients undergoing GI surgery; instead, we assess the GI tract during surgery and determine whether compromised GI mucosa is present at the end of surgery.

If compromised GI mucosa remains postoperatively, we do not administer NSAIDs because they can potentially inhibit, decrease, or retard the healing process of that mucosa. We would, instead, consider a local anesthetic or wound catheters for analgesia.

If only healthy GI mucosa remains, we administer an NSAID, but only in the first 24 hours. Our choice is one of the more “balanced” NSAIDs, which are less cyclooxygenase (COX)-2 selective (eg, meloxicam or carprofen) rather than more COX-2 selective (eg, deracoxib or firocoxib). This rationale is based on the concern that the natural healing process will be slowed if COX-2 is inhibited, as COX-2 induces vasodilation, which in turn promotes healing.

### IN SUMMARY

Options for pain control in patients with concurrent disease are not as limited as previously assumed. When used cautiously, often with decreased doses and careful monitoring, NSAIDs can be administered to dogs and cats with CKD or elevated liver enzymes. Tramadol is not likely to be very effective in dogs; however, its use as an analgesic is more promising



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in cats. When addressing perioperative analgesia, we recommend using an opioid, NSAID, and local anesthetic in combination for the best perioperative pain management of animals.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; CKD = chronic kidney disease; COX = cyclooxygenase; DJD = degenerative joint disease; GFR = glomerular filtration rate; GI = gastrointestinal; IRIS = International Renal Interest Society; NSAID = nonsteroidal anti-inflammatory drug; PLO = pluronic lecithin organogel

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