NSAIDs are the most widely used analgesics in veterinary medicine, and all have some toxic potential. The most common adverse class effects are gastrointestinal, renal, hepatic, and coagulation disorders. When treating chronic pain associated with osteoarthritis, the effectiveness of NSAIDs can be enhanced by physical therapy, use of nutraceutical agents and/or certain adjunctive drugs, and diet and exercise to control weight. To treat acute perioperative pain, NSAIDs are more effective when used preemptively, in the context of balanced (multimodal) analgesia, and in well-hydrated patients with normal blood pressure and renal function. Screening and monitoring to identify high-risk candidates for NSAID treatment should include a physical examination and patient history, identifying preexisting diseases or conditions, obtaining baseline and periodic hematologic and clinical chemistry values, and ensuring that other NSAIDs or contraindicated drugs are not used concurrently. When switching a patient from one NSAID to another (when no side effects have been seen), a washout period of 5 to 7 days minimizes chances for adverse drug interactions. Informing clients of the potential adverse effects of NSAID therapy and signs of NSAID toxicity greatly increases the likelihood of safe use of this class of drugs.

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**INTRODUCTION**

The most widely used analgesic medications in veterinary as well as human medicine are the NSAIDs, which target peripheral and central nervous system (CNS) pain mediators. Acceptance of veterinary NSAIDs increased dramatically in the 1990s with the introduction of newer NSAIDs with improved safety profiles (Table 1).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Approved Indications</th>
<th>Dose</th>
<th>Precautions and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen (Rimadyl, Pfizer Animal Health)</td>
<td>Caplets (25, 75, and 100 mg), chewable tablets (25, 75, and 100 mg), and injectable (50 mg/ml)</td>
<td>Pain and inflammation associated with osteoarthritis and pain associated with soft tissue or orthopedic surgery</td>
<td>4.4 mg/kg PO sid, 2.2 mg/kg PO bid, or 4.4 mg/kg SC</td>
<td>Safety not evaluated in dogs ≤ 6 wk, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
<tr>
<td>Deracoxib (Deramaxx, Novartis Animal Health)</td>
<td>Chewable tablets (25 and 100 mg)</td>
<td>Pain and inflammation associated with osteoarthritis and postoperative pain and inflammation associated with orthopedic surgery</td>
<td>Osteoarthritis: 1–2 mg/kg PO sid Postoperative: 3–4 mg/kg PO sid (7-day limit)</td>
<td>Safety not evaluated in dogs &lt;4 mo, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
<tr>
<td>Etodolac (EtoGesic, Fort Dodge Animal Health)</td>
<td>Tablets (150 and 300 mg)</td>
<td>Pain and inflammation associated with osteoarthritis</td>
<td>10–15 mg/kg PO sid</td>
<td>Safety not evaluated in dogs ≤12 mo, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
<tr>
<td>Firocoxib (Previcox, Merial)</td>
<td>Chewable tablets (57 and 227 mg)</td>
<td>Pain and inflammation associated with osteoarthritis</td>
<td>5 mg/kg PO sid</td>
<td>Safety not evaluated in dogs &lt;10 wk, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
<tr>
<td>Meloxicam (Metacam, Boehringer Ingelheim Vetmedica)</td>
<td>Oral suspension (1.5 mg/ml) and injectable (5 mg/ml)</td>
<td>Pain and inflammation associated with osteoarthritis</td>
<td>0.2 mg/kg PO on day 1, then 0.1 mg/kg PO sid; or 0.2 mg/kg IV or SC of injectable preparation on day 1, followed by 0.1 mg/kg PO sid</td>
<td>Loading dose can be administered SC or IV; not evaluated in dogs ≤ 6 mo, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
<tr>
<td>Tepoxalin (Zubrin, Schering-Plough Animal Health)</td>
<td>Tablets (50, 100, and 200 mg)</td>
<td>Pain and inflammation associated with osteoarthritis</td>
<td>10 or 20 mg/kg on day 1, then 10 mg/kg/d PO</td>
<td>Not evaluated in dogs ≤ 6 mo, dogs used for breeding, or pregnant or lactating bitches</td>
</tr>
</tbody>
</table>

*General precautions for NSAIDs: Do not use in patients with GI or renal disease; discontinue use if vomiting or diarrhea occurs; not recommended in hypovolemic or dehydrated patients or those with bleeding disorders; not for concurrent use with other NSAIDs or corticosteroids.*
These medications were initially used for long-term treatment of osteoarthritis (OA) in dogs. Subsequent approval of two NSAIDs, carprofen and deracoxib, for canine acute perioperative use further broadened NSAID applications in veterinary medicine. Several characteristics have contributed to the well-founded popularity of NSAIDs:

- A dual therapeutic effect (antiinflammatory and analgesic) plus antipyretic properties
- Proven analgesic effect for acute perioperative and chronic pain
- High protein-binding capabilities, enabling consistent delivery to target tissue
- Rapid onset of action (usually within 30 to 60 minutes) and extended duration of effect (up to 24 hours)
- Convenience of administration (oral forms for dispensing and parenteral forms for perioperative use)
- No immunosuppressive effect, as distinct from corticosteroids, contributing to suitability for long-term use
- Affordability for long-term use
- A nonscheduled drug class that requires no government-mandated recordkeeping

CYCLOOXYGENASE—THE NSAID TARGET ENZYME

The primary mode of action of NSAIDs is blocking cellular expression of the enzyme cyclooxygenase (COX) in cell membranes. The COX-1 isoform, which is constitutively present in virtually all cells, synthesizes prostaglandins (PGs) that regulate normal homeostasis, including cytoprotection of the gastric mucosa. The COX-2 isoform is induced by proinflammatory stimuli. It has been shown that COX-2 is also constitutively expressed in a narrow range of tissues and organs (neural, reproductive, and renal), where it has an apparent homeostatic function. Also, COX-1 has been shown to be involved in pain and inflammation. Thus, COX has a bifunctional role depending on the isoform and target tissue.

Nonselective NSAIDs inhibit both COX-1 and COX-2, suppressing synthesis of PGs that mediate homeostatic processes and pain and inflammation alike. In simplistic theoretic terms, NSAIDs that selectively target COX-2 and spare COX-1 have antiinflammatory and analgesic effects while having a minimal effect on the homeostatic functions regulated by COX-1.

The two most noteworthy toxic effects of COX-1 inhibition are gastrointestinal (GI) ulceration and prolonged bleeding time, whereas renal impairment is associated with inhibition of either COX isoform. PGs synthesized by COX-1 in the alimentary tract aid gastric mucosa–protective mechanisms against the ulcerative effects of acid, bacterial toxins, and other local insults. When COX-1 expression is inhibited, its cytoprotective function is impaired and GI ulceration may result.

COX-1 has other “housekeeping” functions. Prothrombotic hemostasis is maintained by COX-1 in situations of vascular injury and bleeding. When hypovolemia (either relative hypovolemia, such as with hypotension induced by anesthetic agents, or absolute hypovolemia, such as with bleeding) occurs, COX-1 and to some extent COX-2 are highly regulated in response to changes in intravascular volume to help maintain renal perfusion. Animals that are dehydrated, hypotensive while under anesthesia, or geriatric are at greater risk for renal side effects regardless of the COX selectivity of the NSAID administered.

SIGNIFICANCE OF COX SELECTIVITY

Conventional wisdom may suggest that the greater the degree of COX-2 selectivity and
sparing of COX-1, the less toxic the NSAID. Prevailing expert opinion and available data suggest that this is not always the case and that it is an oversimplification to consider COX-2 selectivity or COX-1 sparing to be the sole factor in NSAID safety. COX-2 has a secondary but important role in regulating certain normal functions, which, if compromised, would likely have adverse consequences. Because COX-2 is induced in ulcerated GI tissue, it has been suggested that it has a homeostatic role in ulcer repair. This may have clinical significance if selective COX-2 inhibitors follow an episode of ulceration or drug treatment that may induce ulceration. COX-2 is also part of the normal enzyme complement of the canine kidney, the brain and other neural tissue, and ovarian and uterine tissue, indicating homeostatic renal, CNS, and reproductive roles. COX-2 also regulates prostacyclin, an anticoagulant that opposes synthesis of thromboxane by COX-1. Thus, it appears that in addition to its proinflammatory effect, COX-2 coexists in balance with COX-1 to govern a restricted range of significant normal body functions.

It is apparent that NSAIDs with COX-2–selective/COX-1–sparing properties are associated with fewer GI side effects in humans. For example, the incidence of serious GI events in humans taking COX-2–selective NSAIDs has been shown to be significantly lower (a 50% relative risk reduction) than with traditional NSAIDs. The same may be true in dogs, but no appropriate studies have been completed to date. However, there is no evidence that COX-2 selectivity reduces the incidence of renal toxicity or idiosyncratic side effects (i.e., those that are unpredictable, not dose-related, and not consistently inducible) in human patients. Current thinking is that all NSAIDs have some toxic potential in humans regardless of their degree of COX-2 selectivity and that the same is probably true in dogs. It must also be remembered that for some NSAIDs, their COX-1–sparing or COX-2–selective characteristics may become lost at higher-than-approved doses, thus leading to side effects that might be unexpected considering their COX selectivity.

COX selectivity does not appear to have any obvious bearing on NSAID efficacy. Individual patients may respond more favorably to one NSAID versus another. However, on a whole population basis, all veterinary NSAIDs have comparable antiinflammatory and analgesic efficacy for their approved indications. As investigators become better at measuring pain, it may become possible to indicate that a particular NSAID will be more efficacious than another for a particular condition.

If preferential inhibition of COX-2 (and sparing of COX-1) does not completely define NSAID safety, what does? Extensive clinical safety data, expressed as the number of incidents in relation to doses given in certain populations of animals, would be the most meaningful and reliable indicator of NSAID safety. Prelicensing safety data is the basis for product approval but usually involves limited numbers of animals. Once a product is introduced, adverse event tracking depends on voluntary reporting of such events to the manufacturer and the FDA by veterinarians and owners. By law, any adverse event reported to the manufacturer must be followed up by the manufacturer and subsequently reported to the FDA. Veterinarians thus have a pivotal role in determining whether postlicensing data are meaningful. The main drawback of such data is that the denominator (i.e., the total number of doses administered to dogs or the total number of animals treated) is not accurately known. Manufacturers estimate this figure in different ways. However, cumulative postlicensing adverse event data can provide an overall assessment of product safety under conditions of mass usage over time, even if the precise number of animals treated is unknown. Of course, valid-
ity of such data depends on the care with which it is collected and reported by the manufacturer and the FDA. Data are of limited value if they are not fully inclusive or are selectively screened in some way. Despite the limitations inherent in reporting adverse events, these data remain one of the best indicators of product safety, with validity increasing in proportion to the integrity of the reporting methods.

Clinicians are generally receptive to discussions and new data on the differing COX pharmacologies of NSAIDs. Of considerable interest is a recent study demonstrating that conventional in vitro assays of COX selectivity may not accurately predict the activity of NSAIDs in a living animal. The investigators used whole blood, synovial fluid, and gastric biopsies to directly measure in vivo production of PGs in dogs treated with carprofen, deracoxib, or etodolac at label dosages for 10 days. All three NSAIDs acted as COX-1–sparing drugs by preserving thromboxane and gastric PG synthesis and as COX-2–inhibiting drugs by suppressing PGs in synovial fluid from osteoarthritic joints. In these tissues, there was no statistical difference in PG values obtained following treatment with these NSAIDs, indicating that their in vivo effect appeared comparable irrespective of variances in their COX selectivity. More work of this kind is required to better define the actions of various NSAIDs in individual tissues in the various species of animals.

# ADVERSE CLASS EFFECTS OF NSAIDs

There are several adverse effects that can potentially occur with any NSAID in either human or animal models:

## Gastrointestinal Toxicity

As the classic NSAID toxicity, GI ulceration is the most common and important adverse class effect associated with NSAIDs. Although all NSAIDs approved for veterinary use have improved GI safety profiles over nonapproved NSAIDs, clinicians should nevertheless be vigilant for evidence of GI toxicity. Unfortunately, monitoring dogs for GI ulceration is easier said than done because there are no practical screening tests to detect early signs of gastric injury. Clinical signs for clinicians and clients to look for include depression, anorexia, reduced appetite, vomiting, diarrhea, and hema-

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**Clinical Significance of COX Selectivity—A Summary**

- GI side effects are less common with NSAIDs that selectively inhibit COX-2 and spare COX-1.
- COX-2 selectivity (expressed as a ratio of the quantity of drug needed to inhibit the COX-1 and COX-2 enzymes by 50%) is useful as a predictor of NSAID GI safety but not as the determinant of overall safety for such drugs.
- COX selectivity may have little effect on potential renal toxicity because both COX-1 and COX-2 are constitutively present in the kidneys; thus, suppression of either enzyme can have adverse effects, particularly in hypovolemic dogs.
- Liver toxicity is a rare, idiosyncratic class effect of all NSAIDs and does not appear to correlate with COX selectivity.
- COX-1 inhibition appears to be associated with prolonged bleeding times.
- While prelicensing safety data are a good indicator of product safety, long-term postlicensing data may reveal drug-associated adverse events that occur only rarely or as idiosyncratic events.
- All NSAIDs approved for veterinary use have comparable efficacy on a whole population basis regardless of their COX selectivity but may be more or less effective on an individual patient basis.
The NSAID should be stopped immediately. To limit the potential for serious complications and their sequelae, clinicians should take the following precautions before prescribing NSAIDs:

- Verify that corticosteroids, aspirin, or other NSAIDs are not being given concurrently with the prescribed NSAID (undeveloped interactions with other drugs or products, [e.g., herbal medicines] may come to light in the future).
- Proactively ask the client about posttreatment occurrence of clinical signs of GI toxicity.
- Adhere to the recommended dosage.
- Avoid use in at-risk cases (see box on left).
- Advise clients of potential safety risks and their clinical signs.

### Renal Toxicity

Renal toxicity is the second most important NSAID safety concern, after GI effects. Because COX-1 and COX-2 are both constitutively present in normal kidneys, there is likely to be little apparent difference in the incidence of renal toxicity associated with any of the various NSAIDs. Whether COX-1 or COX-2 selective, any NSAID can exacerbate renal insufficiency. The exact mechanism of NSAID-induced renal toxicity is unknown and may actually have little to do with COX selectivity. In dogs with underlying renal disease, further compromise could be significant. Use of NSAIDs in such animals should be avoided if possible. The concurrent use of other potentially nephrotoxic drugs, such as the aminoglycosides, with NSAIDs should be avoided (see also Hemostatic and Renal Safety section on page 245).

### Hepatotoxicity

Because all NSAIDs are metabolized by the liver, hepatotoxicity following administration
of a labeled dose can occur with any drug in this class, regardless of COX selectivity. Three- to fourfold increases in hepatic enzymes above the normal range or pretreatment baseline in a period of days to weeks concurrent with NSAID treatment, coupled with resolution of clinical signs and enzyme values when treatment is discontinued, are indicators of drug-associated hepatotoxicity. Biopsy and histopathologic evaluation help rule out other disease. In dogs with elevated liver enzymes before NSAID treatment, relatively more frequent liver enzyme monitoring may be warranted, although there is currently no evidence to suggest that raised liver enzymes are an intrinsic risk factor for developing a hepatopathy. While the reported rate of NSAID-associated hepatotoxicity is low, the possibility of its occurrence should not be ignored. There is growing consensus that baseline liver enzyme values should be obtained before initiating chronic NSAID therapy, followed by retesting 2 weeks later and periodically thereafter. Periodic testing allows veterinarians to assess trends as well as absolute values. Most NSAID-associated hepatopathies occur within the first 3 weeks of treatment; monitoring should continue, although the intervals for later retesting can be extended depending on the patient’s response. The relationship between NSAID use, use of other drugs that affect liver function and/or inhibit or induce metabolic enzymes, and liver disease is not clear. The two factors are the additive effect of hepatotoxicity and the decreased metabolism of NSAIDs if liver function is decreased. It is recommended that NSAIDs not be used with other drugs that have a significant risk of causing hepatic compromise.

Coagulation Disorders

Thromboxane, an end product of the COX-1 cascade, is a potent inducer of platelet aggregation and arterial constriction. Therefore, NSAIDs that inhibit COX-1 expression have a potential anticoagulative effect. Degree and duration of hemostatic effects of NSAIDs vary depending on the pharmacokinetic profile. Aspirin, even in low doses, is unique in that it inactivates COX-1–regulated thromboxane synthesis in platelets, an effect that persists for the lifespan of the platelet. This prolongs bleeding time for several days even after treatment is stopped. Other NSAIDs may also inhibit platelet synthesis of thromboxane during the dosing period. Veterinarians need to administer perioperative NSAIDs appropriately based on patient history and treatment status. Administration of carprofen to dogs for 5 days resulted in decreases in platelet aggregation, but the values remained within normal reference ranges and there was no change in buccal mucosal bleeding time. Available published studies suggest that the NSAIDs approved in the United States that have been evaluated do not have a significant clinical effect on bleeding time following perioperative administration. Some commonly administered drugs, such as certain cephalosporins, can affect platelet function; however, the clinical effect of combinations of these drugs and approved NSAIDs has not been defined.

Articular Degradation

It has been known for some time that aspirin given at high doses, indomethacin, ibuprofen, and naproxen contribute to cartilage degeneration in the arthritic joints of dogs, presumably because of decreased glycosaminoglycan synthesis. On the other hand, it has been suggested that other NSAIDs are either chondro-neutral or chondroprotective by virtue of preserving or increasing glycosaminoglycan synthesis in arthritic joints. For example, dogs with experimentally induced OA given carprofen postoperatively for 8 weeks from the time of initiation of OA had significant decreases in
the width of osteophytes and size and histologic severity of cartilage lesions versus nontreated dogs. Dogs treated with carprofen showed a decrease in postsurgical remodeling, and their subchondral bone morphology resembled that of normal dogs. The study was an encouraging indicator that carprofen did not adversely affect subchondral bone or chondrocyte metabolism at the dosages tested. However, the administration schedule is rather artificial when compared with the clinical situation, where disease is often not recognized until later on. Similar studies with other NSAIDs are needed.

Bone Healing
A relatively recent development in NSAID therapy is the reported effect of COX-2–selective NSAIDs on bone healing. Investigators at Stanford University demonstrated that bone formation in laboratory animals was suppressed by oral administration of a COX-2–selective coxib. They also suggested that COX-2 inhibitors currently taken for arthritis and other conditions may potentially delay fracture healing and bone growth. However, there are many factors that influence bone healing (e.g., weight bearing, activity level, diet, physical therapy), and assessment of progression of healing is highly subjective and variable. At present, it appears unlikely that specific COX-2 inhibitors have a clinically significant effect on bone healing in veterinary patients.

Efficacy of NSAIDs in Long-Term Therapy
The most common use of veterinary NSAIDs in North America is long-term administration to treat pain associated with OA, probably because most NSAIDs are licensed only for this purpose. This application has grown substantially in the past decade as a result of the widespread presence of canine OA (a conservative estimate is that 20% of the canine population is affected with severe OA) and the introduction of several approved veterinary NSAIDs.

Generally speaking, NSAIDs given in chronic cases of OA are very effective for treating OA-associated pain. A complete response may not take place initially because of the nervous system plasticity that occurs with chronic pain. However, as treatment continues, hypersensitization may subside and NSAID efficacy may actually increase. Conversely, as the disease progresses, noxious input to the CNS may increase or change, resulting in further CNS plasticity that makes the NSAID less effective. Thus, responsiveness to chronic NSAID treatment in veterinary medicine can be improved by adopting a multimodal approach. Such an approach ensures that the complicated “pain pathway” is interacted with in a number of different ways, thus improving overall pain control. In addition to incorporating other analgesic drugs into NSAID therapy (an area in which there is very little information in veterinary medicine), the following nondrug therapies should be considered part of a multimodal approach:

- Diet and exercise to control weight
- Physical therapy and rehabilitation
- Putative chondroprotective agents (nutraceuticals)

NSAIDs in Short-Term Therapy
Veterinarians in North America are increasingly realizing the value of NSAIDs for treating acute postoperative pain in companion animals, the application that was the driving force for acceptance of NSAIDs in Europe and other markets outside the United States and Canada. The analgesic efficacy of NSAIDs for treating acute pain is high. Moreover, NSAIDs are often more efficacious than such opioids as pethidine, butorphanol, and papaveretum in treating acute pain. This does not mean that...
NSAIDs should be used to the exclusion of opioids for acute pain relief. Their use in combination can be more effective than individual drugs used alone. Carprofen and deracoxib are currently approved for perioperative use in dogs. Carprofen is approved for soft tissue and orthopedic surgery in the United States and Canada; deracoxib is approved for orthopedic surgery in the United States (Table 1).

Several aspects of perioperative NSAID use deserve emphasis.

Preemptive Use

Prevention, not treatment, is the primary goal of pain management for several reasons. Because of pain-induced hypersensitization and neural plasticity, pain is more difficult to control once it occurs. The likelihood of postoperative pain is very high, giving added urgency to utilizing preemptive analgesia. Administration of NSAIDs before surgery maximizes and extends their efficacy, reduces the overall analgesic requirement, eases patient handling, and reduces postsurgical morbidity and mortality.

Balanced (Multimodal) Analgesia

Using NSAIDs in the context of balanced, or multimodal, analgesia is preferred because the use of drugs from two or more analgesic classes alters more than one nociceptive pathway, producing a synergistic effect. Combinations of analgesics also reduce the amount of each drug used, minimizing the risk of side effects associated with each. An example of multimodal analgesia would be preoperative administration of a parenteral NSAID and a parenteral opioid, followed by intraoperative use of an epidural or intraarticular opioid or local anesthetic, and concluding with a local anesthetic block of the wound, use of a transdermal opioid, and administration of a postoperative oral NSAID for extended analgesia after surgery.

Hemostatic and Renal Safety

When anesthesia results in relative hypovolemia, renal perfusion and glomerular filtration rate are maintained by PGs synthesized locally in the kidney by COX. Because the kidneys receive about a fifth of the cardiac output, they are particularly susceptible to ischemic injury. All NSAIDs can negatively affect kidney function because of their ability to suppress homeostatic renal PGs. Thus, it is important for clinicians to ensure patients have normal renal function and are adequately hydrated when NSAIDs are used preoperatively. In properly hydrated patients without preexisting renal compromise, approved veterinary NSAIDs can be safely given as acute therapy with little risk of inducing renal insufficiency. The margin of safety is increased if intraoperative IV fluids are given during surgeries when NSAIDs are used.

Platelet coagulation and clotting activity are regulated by COX-1 synthesis of thromboxane, whereas antithrombotic activity is regulated by COX-2 synthesis of prostacyclin. Because prolonged bleeding is a potential risk with NSAIDs that inhibit COX-1 (e.g., aspirin), they should be avoided preoperatively. Meloxicam, tepoxalin, and carprofen are three US-approved NSAIDs that have been evaluated for their effect on bleeding times in dogs.
undergoing surgery, although meloxicam and tepoxalin were administered in a manner not yet approved in the United States (i.e., for perioperative pain). None was found to have any clinically significant effect on bleeding.14–17,34,35

■ SCREENING AND MONITORING

Because NSAIDs have potentially lethal side effects and because they can affect the obligate liver and kidney functions, they should not be used in any animal that has not undergone adequate screening and posttreatment monitoring, particularly in cases of long-term therapy. Adverse event reports related to NSAIDs appear to be disproportionately associated with older animals,9 so it is recommended that dogs 6 years and older be carefully evaluated for concurrent diseases and overall suitability. Although idiosyncratic reactions can always occur without an evident causal relationship, screening and monitoring will identify most high-risk patients and ensure successful use in the great majority of cases. A suitable approach to screening could include the following four steps:

1. **Conduct a physical examination and obtain the patient’s history:** A thorough physical examination, including the patient’s history and identification of any previously administered medications, enables assessment of an animal’s overall health and the possibility of drug interactions.

2. **Identify preexisting diseases or conditions:** NSAIDs should be used with caution or not at all in animals with a history of NSAID-associated adverse reactions. Other NSAID contraindications include the following:1:
   - Patients with renal or hepatic insufficiency, dehydration, or hypotension
   - Conditions associated with low effective circulating volume (congestive heart failure, ascites, use of diuretics)
   - Coagulopathies
   - Evidence of gastric ulceration (e.g., melena) or GI disorders of any kind
   - Trauma cases until adequate fluid intake and absence of internal hemorrhage and shock have been confirmed (however, the use of injectable NSAIDs is an extremely valuable therapeutic tool in providing pain relief for trauma patients)
   - Pregnant animals

3. **Perform hematologic and clinical chemistry evaluations:** It is important to determine hematologic and serum biochemistry baseline values before initiating treatment and periodically thereafter for any animal undergoing chronic therapy with NSAIDs (or any medication, for that matter). If clinical chemistry levels reveal renal or hepatic compromise, more frequent monitoring is essential if NSAIDs are used. There is no consensus on frequency of monitoring, but a baseline blood panel followed by a renal and liver panel 2 weeks after initiating treatment is advisable. Thereafter, monitoring clinical chemistry values every 6 to 12 months in young, healthy animals and every 2 to 3 months in older dogs is a reasonable approach.

4. **Determine concurrent drug use:** Because NSAIDs are highly plasma protein bound, they should be used with caution with other drugs that are also highly protein bound. Displacement of other protein-bound drugs (e.g., phenobarbital) from their binding sites by NSAIDs could alter their metabolism and result in adverse effects. Concurrent use of NSAIDs with the following drugs is contraindicated or should be done with caution:
   - Drugs that may be toxic to the kidney (e.g., the chemotherapeutic drug cisplatin)
- Drugs that may be toxic to the liver
- Drugs that modify renal PGs (diuretics, angiotensin-converting enzyme inhibitors, aminoglycosides)
- Corticosteroids

**SWITCHING PATIENTS FROM ONE NSAID TO ANOTHER**

When a poor individual response or an adverse reaction to an NSAID occurs, the affected animal will often respond normally to another NSAID. Fortunately, veterinarians have several approved NSAIDs at their disposal. If an animal experiences adverse effects from two different NSAIDs, the assumption should be that the animal is NSAID intolerant and should not be treated with drugs in this class. If there is an inadequate analgesic response to an NSAID in treatment of chronic pain, use of another NSAID or another NSAID in the context of multimodal therapy should be considered.

In cases in which an animal is switched from one NSAID to another or has been treated with corticosteroids, there should be a washout period before initiating therapy with a different NSAID to avoid adverse drug interactions. Aspirin has an irreversible effect on platelet function that persists until the platelets are replaced. In dogs, after a single dose of aspirin, functional platelets enter the circulation slightly more quickly than in humans, but normal coagulation function is not restored until about 6 days. Thus, it is particularly important to schedule an appropriate washout period (7 to 10 days) for an animal that has been treated with aspirin and is scheduled for surgery or long-term treatment with an NSAID.

Determining the washout period for other NSAIDs has been based on their half-lives. Some consider that it is usually safe to assume that drug interaction will be minimal and clinically insignificant after expiration of three or four half-lives. However, NSAID half-lives are particularly variable. This variability in conjunction with the fact that a drug’s tissue effects are not necessarily linked with its serum half-life means that basing a washout period solely on pharmacokinetic variables should be done with caution. The unpredictability of drug activity and interactions at the cellular level suggest that a conservative approach (discussed below) to establishing a washout period is warranted.

A washout period appears to be important in avoiding suppression of aspirin-triggered lipoxin (ATL) in patients given COX-2–selective NSAIDs. ATL is a lipid mediator synthesized by COX-2 that aids in gastric protection. In subjects that have been treated with aspirin for extended periods, ATL is upregulated as a compensatory mechanism to protect the GI tract. Thus, prior treatment with even low doses of aspirin should be taken into account before prescribing COX-2–selective NSAIDs. Suppression of ATL may explain anecdotal accounts of GI toxicity in animals previously treated with aspirin and switched to COX-2–selective NSAIDs without an adequate washout period.

Clinicians often ask if it is safe to shift a dog from one NSAID to another within a 24- or 48-hour period. There are no definitive studies on what constitutes an adequate washout period when an animal is switched from one NSAID to another. A recent, as yet unpub-

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*It is an oversimplification to consider COX-2 selectivity or COX-1 sparing to be the sole factor in NSAID safety.*
lished pilot study evaluated the effect of sequential NSAID therapy on gastric lesions. The study evaluated injectable carprofen followed by oral carprofen or oral deracoxib for 4 days, with appropriate control groups. Lesions (erosions) in the fundic, antral, and lesser curvature regions worsened in both the carprofen–carprofen and the carprofen–deracoxib groups, but the clinical significance of these results is unclear.

Based on current opinion leaders’ recommendations, a minimum washout period of 5 to 7 days would be appropriate for an animal that has been treated with a nonaspirin NSAID or a shorter-duration corticosteroid (e.g., oral prednisone, dexamethasone). Particular care should be taken when considering animals given corticosteroids, in which case a longer washout period (consistent with the duration of action of the extended-effect corticosteroid) is required. Aspirin deserves special consideration because of its profound effect on platelets. In cases of extended treatment with aspirin or doses exceeding 10 mg/kg, a washout period of at least 7 days is advisable. These guidelines may appear conservative, but until definitive information is published, the authors consider this approach to be appropriate.

CLIENT PARTICIPATION IN MONITORING PATIENT RESPONSE

The likelihood of safe and efficacious use of NSAIDs can be greatly increased if veterinarians counsel clients on potential adverse effects and proactively ask for feedback on safety and efficacy. Is the drug working? Does the animal’s behavior indicate that the NSAID is providing adequate pain relief? Are there behavioral or physiologic indications of adverse effects, such as vomiting, melena, or anorexia? Answers to these questions provide valuable information on the performance of prescribed NSAIDs.

When NSAIDs are prescribed, it is critical that clients be informed of potential adverse effects that characterize all drugs in this class. Pet owners need to be told what the possible side effects are and their clinical signs. Manufacturers are required by the FDA to provide client information sheets expressly to help ed-

The exact mechanism of NSAID-induced renal toxicity is unknown and may actually have little to do with COX selectivity.

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The exact mechanism of NSAID-induced renal toxicity is unknown and may actually have little to do with COX selectivity.
ASSESSING PRODUCT SAFETY AND EFFICACY

The single most misleading claim or inference about the newer NSAIDs approved for use in dogs is that one NSAID is totally safe or much safer than others based on its pharmacology. COX-2 selectivity may have a favorable effect on GI toxicity and to a lesser extent on coagulopathies. However, renal safety, idiosyncratic hepatopathies, and efficacy appear to be poorly correlated with COX selectivity. Because all NSAIDs have toxic potential, veterinarians and pet owners should never consider any NSAID to be completely safe.

A product’s package insert is the foundation document containing much of the developmental data that regulatory agencies consider when licensing a product. Package inserts should be examined for prelicensing studies that describe toxicity tests to assess safety at elevated dosages; long-term usage studies that evaluate incidence of adverse effects over time; the number and type of postlicensing adverse events reported (postlicensing data are much more extensive than prelicensing data and will give a truer perspective of an NSAID’s safety profile); and the effective publication date of the package insert information to determine temporal relevancy. A review of package inserts may reveal considerable variances among NSAIDs in these areas of comparison. However, because of differences in the way individual companies present data and the inevitable “guesstimates” of the number of animals treated with various NSAIDs, systematic client feedback will, over time, provide an emerging profile of the risks and benefits of a particular NSAID. Monitoring patients will complement client feedback by providing objective data on physiologic functions in treated animals. Veterinarians should try to avoid relying on a single adverse experience with a given NSAID as an indication of that product’s performance in general (i.e., the “n = 1 experience”). Every clinician has treatment failures. Cumulative personal experience balanced against available, credible data is a sound approach for assessing the merits of an NSAID.

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