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REVIEW

Nonsteroidal anti-inflammatory drugs in cats: a review

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Abstract

Objective To review the evidence regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in cats

Databases used PubMed, CAB abstracts.

Conclusions Nonsteroidal anti-inflammatory drugs should be used with caution in cats because of their low capacity for hepatic glucuronidation, which is the major mechanism of metabolism and excretion for this category of drugs. However, the evidence presented supports the short-term use of carprofen, flunixin, ketoprofen, meloxicam and tolfenamic acid as analgesics in cats. There were no data to support the safe chronic use of NSAIDs in cats.

Keywords cat, kinetics, non-steroidal anti-inflammatory drug, pain, pharmacology.

Introduction

The most widely used analgesics in veterinary, as well as human, medicine are nonsteroidal anti-inflammatory drugs (NSAIDs), which target peripheral and central nervous system (CNS) mediators of nociception (McCormack 1994; Hinz & Brune 2004). They have been found to be effective in alleviating acute and chronic pain in most species.

The acceptance of NSAIDs in small animal practice increased dramatically in the 1990s, with the realization that they could play an important role in the management of perioperative pain (Reid & Nolan 1991; Nolan & Reid 1993; Lascelles et al. 1994), and with the introduction of several new NSAIDs. Currently, several NSAIDs (aspirin, carprofen, cinchophen, deracoxib, etodolac, firocoxib, flunixin, ketoprofen, meloxicam, phenylbutazone, tepoxalin, tolfenamic acid and vedaprofen) have approval for the control of canine perioperative and/or chronic pain in various countries. However, the availability of approved NSAIDs for use in cats is very much more restricted.

There are probably multiple reasons for the relative paucity of approved NSAIDs for cats, but this is unlikely to be due to lack of conditions to treat, or lack of evidence of efficacy of NSAIDs in treating pain in cats. In the USA there are approximately 69 million cats (Wise et al. 2002) and an estimated 10 million in the UK. The majority of these undergo at least one operative procedure in their lifetime; neutering. A variety of NSAIDs have been shown to be effective ameliorators of perioperative pain in the cat (Lascelles et al. 1995a; Balmer et al. 1998; Slingsby & Waterman-Pearson 1998, 2000). Although no prospective studies have been performed, degenerative joint disease appears to be radiographically detectable in a significant proportion of the feline population (Hardie et al. 2002; Godfrey 2005), in perhaps up to 90% of cats

over 12 years old (Hardie et al. 2002). Although debated (Herzog et al. 2004), many feline patients probably do suffer pain associated with degenerative joint disease. The incidence of other painful disorders such as intervertebral disc disease (Jaeger et al. 2004) and neoplasia is unknown, but undoubtedly significant. Although NSAIDs are considered to be effective for chronic pain in the cat, there is little evidence of this presumed efficacy (Lascelles et al. 2001). The most likely reasons for the relative lack of licensed or approved NSAIDs for use in the cat are the:

- Problems assessing pain in cats and therefore knowing when NSAIDs may be required;
- Assumption by pharmaceutical companies that the market for NSAIDs in cats is not financially viable;
- Increased risks of toxicity associated with NSAID use in cats;
- Relative lack of information about NSAID use in cats.

It is widely recognized that NSAIDs should be used with caution in cats because of their low capacity for hepatic glucuronidation (Hietanen & Vainio 1973; Court & Greenblatt 2000), which is the major mechanism of metabolism and excretion for this category of drugs. However, there is a significant body of evidence in the literature regarding the use of NSAIDs in cats, which demonstrate their value and safety in this species, particularly the newer compounds. This manuscript reviews this evidence-based medicine. As the use of NSAIDs increases in cats, often based on anecdotal reports, it is timely and important to review the scientific information regarding NSAID use in cats.

Role of NSAIDs in multimodal analgesia

Together with the concept of pre-emptive analgesia (Woolf & Chong 1993; Lascelles et al. 1995b; Moiniche et al. 2002), over the last 15 years, the concept of 'multimodal analgesia' has created important advances in the approach to providing analgesia in both acute (Rockemann et al. 1996; Skinner 2004) and chronic pain (American Pain Society 2002) in humans. The basis for this multimodal drug approach stems from recent advances in our understanding of pain. Particularly important are the laboratory findings that different classes of analgesics are synergistic when combined (Penning & Yaksh 1992). Pain transmission involves a multiplicity of pathways, mechanisms and transmitter systems (Woolf & Chong 1993; Mannion & Woolf 2000; Muir & Woolf 2001) so it is expected that using several different drugs acting on multiple components of the nociceptive system would be more effective than a single therapy. No multimodal analgesic studies have been performed in cats, but clinical observations suggest that it will be effective (Robertson 2005). The most recent survey of perioperative analgesia in general veterinary practice describes significant use of both preemptive and multimodal analgesia (Williams et al. 2005). There is no published scientific evidence that multimodal drug therapy is of benefit over mono-modal therapy in veterinary patients suffering from osteoarthritis.

Pharmacology of NSAIDS

The principle therapeutic effects of the NSAIDs, including reduction of fever, pain and inflammation, derive primarily from the ability of these drugs to inhibit the production of prostaglandins from arachidonic acid by the cyclooxygenase (COX) enzymes (Lees et al. 2004a,b; Warner & Mitchell 2004). Two distinct COX isoforms (COX-1 and COX-2) have been identified that are the products of two separate genes (Warner & Mitchell 2004). COX-1 is expressed constitutively in most tissues (but not erythrocytes) leading to production of prostaglandins, important for many normal physiological functions. This includes regulation of gastrointestinal (GI) and renal blood flow as well as a role in blood clotting, through the synthesis of thromboxane A_2 in platelets (Warner & Mitchell 2004). In contrast, COX-2 is an inducible enzyme that is expressed at sites of inflammation in response to inflammatory mediators (such as interleukin-1). COX-2 is also expressed in some neoplasms in response to mitogens (such as the phorbol esters). However, this is a rather simplistic description, as COX-1 and COX-2 are known to be both constitutively expressed and inducible. For example, there is evidence that COX-1 and COX-2 are constitutively expressed in the CNS, particularly in the spinal cord, where they are involved in modulating nociceptive signaling in both neuropathic (non-inflammatory) and inflammatory pain states (Ito et al. 2001; Warner & Mitchell 2004). COX-2 is also constitutively expressed in the kidney and reproductive system.

The majority of NSAIDs act by competitive inhibition of the COX enzymes, so the effects are reversible once drug concentrations decrease when

drug dosing is discontinued. The exception to this is aspirin, which, in addition to competitive inhibition, irreversibly inhibits COX through acetylation of a serine residue near the enzyme's active site (Catella-Lawson et al. 2001). Consequently, new enzymes must be synthesized before function is restored. Platelets are unable to synthesize new enzymes, accounting for the prolonged anticoagulant effect of aspirin. The mechanism of action of acetaminophen (*contraindicated in cats*) is still unknown. Its antipyretic and analgesic effects may result primarily from COX inhibition in the CNS (Chandrasekharan et al. 2002; Davies et al. 2004; Graham & Scott 2005).

A common strategy employed in the development of novel NSAIDs has been to identify drug candidates that selectively inhibit COX-2 with minimal effect on COX-1 (Lees et al. 2004a,b; Warner & Mitchell 2004; Giraudel et al. 2005). This is based on the rationale that the therapeutic drug effects are primarily mediated via COX-2, while the unwanted drug side effects (particularly renal and GI damage, and inhibition of platelet function) result mainly from COX-1 inhibition. Consequently, various *in vitro* and *in vivo* assays have been developed to evaluate the selectivity of COX-2 *versus* COX-1 inhibition (Lees et al. 2004a), and the COX ratios reported. This ratio is calculated by dividing the concentration of a drug that will inhibit the COX-1 enzyme by a given amount (usually 50%, the IC_{50}) by the concentration of a drug that will inhibit the COX-2 enzyme by a similar amount. Larger values represent more COX-2 selectivity. Although few studies have been conducted, results from whole blood enzyme assays indicate that there may be significant species differences in the relative COX-1 or COX-2 selectivity of certain drugs. For example, while (R,S-) carprofen is somewhat COX-2 selective in dogs (COX ratio 6.5) and cats (5.5), it is essentially nonselective in horses (1.9) and may even be COX-1 selective in humans (0.02) (Brideau et al. 2001). Consequently such pharmacodynamic studies need to be performed in the species for which the drug is intended and data should not be extrapolated between species. Unfortunately, while there are substantial COX selectivity data for humans, and to a lesser extent, dogs, there are few published studies of cats. Apart from the previously referenced work, a recent study by Giraudel et al. (2005) determined COX ratios using cat whole blood for meloxicam (3.5) and S-carprofen (28) (Giraudel et al. 2005). However, aside from species differences, COX ratio values can vary with the *in vitro* system used for analysis, and the *in vivo* extrapolation of such data to drug safety is dependent on many other factors such as drug disposition and other pharmacodynamic interactions. It is also important to note that, even if COX-2 is mainly induced in one species, it may play an important constitutive role in another species. Ideally, for each species, knowledge of COX selectivity and also the normal physiology of COX *in the tissue concerned* should be known.

Nonsteroidal anti-inflammatory drugs may also interact directly or indirectly with enzymes other than COX, which may account for both additional beneficial and adverse drug effects. In particular, COX inhibition can lead to alternative processing of accumulated arachidonic acid via the 5-lipoxygenase (5-LOX) pathway to proinflammatory and gastrotoxic leukotrienes (Alvaro-Gracia 2004). Several novel NSAIDs including licofelone and tepoxalin are dual inhibitors of COX and 5-LOX (Alvaro-Gracia 2004; Agnello et al. 2005). Initial studies in humans and dogs suggest that these drugs may have very good GI safety profiles, perhaps resulting from additional 5-LOX inhibition (Bias et al. 2004; Agnello et al. 2005; Moreau et al. 2005). As yet, there are no published studies of these drugs in cats to support this contention.

NSAID disposition in cats

Most NSAIDs are cleared from the body through metabolism in the liver (often primarily glucuronidation) and then excretion of the resultant polar metabolites via the bile and/or kidney. Given the known propensity for reduced glucuronidation of drugs in cats compared with other species (Robinson & Williams 1958; Yeh et al. 1971; Davis & Westfall 1972; Miller et al. 1973; Savides et al. 1984; Wilcke 1984; Jernigan 1988; Court & Greenblatt 2000), differences in NSAID disposition between cats and other species might be expected. Table 1 compares available elimination half-life data for NSAIDs that have been studied in both cats and dogs. Aspirin, acetaminophen, and carprofen have relatively prolonged elimination half-lives in cats compared with dogs, most likely as a result of slower drug clearance via glucuronidation. In contrast, similar or even reduced drug elimination half-lives are observed in cats, compared with dogs, for drugs cleared by oxidative enzymes, including piroxicam and meloxicam. There are several exceptions, including flunixin and ketoprofen, both

Table 1 Comparison of nonsteroidal anti-inflammatory drug (NSAID) elimination half-lives in cats and dogs and relationship with clearance mechanism. This table should not be used to base dosing intervals

	Dog			Cat				
NSAID	**Half-life (hours)**	**Dose/route**	**Ref.**	**Half-life (hours)**	**Dose/route**	**Ref.**	**Species difference?**	**Clearance mechanism/s**
Acetaminophen	1.2	100 mg kg^{-1} PO	Savides et al. (1984)	0.6	20 mg kg^{-1} PO	Savides et al. (1984)	Cat > dog	Glucuronidation and sulfation
	1.2	200 mg kg^{-1} PO	Savides et al. (1984)	2.4	60 mg kg^{-1} PO	Savides et al. (1984)		
				4.8	120 mg kg^{-1} PO	Savides et al. (1984)		
Aspirin	7.5–12	25 mg kg^{-1} PO	Dittert et al. (1968)	22	20 mg kg^{-1} IV	Parton et al. (2000)	Cat > dog	Glucuronidation and glycination
				37.6	IV?	Davis & Westfall (1972)		
Carprofen	5	25 mg PO	Clark et al. (2003)	20	4 mg kg^{-1} IV	Parton et al. (2000)	Cat > dog	Glucuronidation and oxidation
	8.6	25 mg twice daily PO 7 days	Clark et al. (2003)	19	4 mg kg^{-1} SC, IV	Taylor et al. (1996)		
	7	25 mg SC	Clark et al. (2003)					
	8.3	25 mg twice daily SC 7 days	Clark et al. (2003)					
Flunixin	3.7	1.1 mg kg^{-1} IV	Hardie et al. (1985)	1–1.5	1 mg kg^{-1} PO, IV	Lees & Taylor (1991)	Cat < dog	Glucuronidation and active transport
				6.6	2 mg kg^{-1} PO	Horii et al. (2004)		
Ketoprofen	1.6 for *S*-ketoprofen	1 mg kg^{-1} PO racemic	Montoya et al. (2004)	1.5 for *S*-ketoprofen	2 mg kg^{-1} IV racemic	Lees et al. (2003)	Cat = dog	Glucuronidation and thioesterification
				0.6 for *R*-ketoprofen	2 mg kg^{-1} IV racemic	Lees et al. (2003)		
				0.9 for *S*-ketoprofen	1 mg kg^{-1} PO racemic	Lees et al. (2003)		
				0.6 for *R*-ketoprofen	1 mg kg^{-1} PO racemic	Lees et al. (2003)		
				0.5 for *S*-ketoprofen	1 mg kg^{-1} IV *S*-ketoprofen	Castro et al. (2000)		
				0.5 for *R*-ketoprofen	1 mg kg^{-1} IV *R*-ketoprofen	Castro et al. (2000)		
Meloxicam	12	0.2 mg kg^{-1} PO	Montoya et al. (2004)	15	0.3 mg kg^{-1} SC	Metacam label information	Cat < dog	Oxidation
	24	0.2 mg kg^{-1} PO, SC, and IV	Busch et al. (1998)					
Piroxicam	40	0.3 mg kg^{-1} PO, IV	Galbraith & McKellar (1991)	12	0.3 mg kg^{-1} PO, IV	Heeb et al. (2003)	Cat < dog	Oxidation

of which are known to be glucuronidated in dogs (Brady et al. 1998; Soars et al. 2001) and yet are not eliminated more slowly in cats. However, it is not yet clear to what extent glucuronidation contributes to total drug clearance of either of these compounds in dogs or cats. Elimination of unchanged flunixin through organic anion transporters into the bile has been implicated as a major mechanism determining drug clearance in cats (Horii et al. 2004). Furthermore, thioesterification is proposed as a major elimination mechanism for ketoprofen in cats (Castro et al. 2000). Consequently, the presence of alternate metabolic and nonmetabolic pathways for drug elimination may compensate for slowed glucuronidation of NSAIDs and other drugs in cats. Knowledge of the clearance of drugs in the target species is important in designing safe dosing regimens in that species.

Adverse effects of NSAIDS in cats

Nonsteroidal anti-inflammatory agents represent the largest group of drugs associated with adverse drug experiences (ADE) reported to the US Federal Drug Administration's Center for Veterinary Medicine (FDA/ CVM) (http://www.fda.gov/cvm/ade_cum.htm – accessed April 9, 2006). In dogs, the most commonly reported ADE are related to the GI (64%), renal (21%) and hepatic systems (14%) (Hampshire et al. 2004). Unfortunately, the clinical circumstances surrounding such ADE reports are not available, making this information difficult to interpret. Currently there is less published information relating to feline ADE, probably because only one NSAID is currently licensed for use in cats in the United States (Meloxicam, Metacam; Boehringer Ingelheim Vetmedica, Inc., St Joseph, MO, USA) and this has been available for <1 year. However, under the Animal Medicinal Drug Use Act of 1994 in the USA, any NSAID approved for human or veterinary use can be legally used in cats on an 'extra-label' basis.

Renal effects

Prostaglandins are important for normal renal function via their regulation of vascular tone, blood flow, salt and water balance and renin (Cheng & Harris 2005). During normovolemic conditions renal prostaglandin synthesis is low. However, when the circulating blood volume or systemic blood pressure is decreased (such as after trauma and in the perioperative period), renal prostaglandins play an important role in regulating and maintaining renal blood flow. They promote vasodilation to counteract the vasoconstrictor responses to angiotensin II and norepinephrine and the vasoconstriction resulting from sympathetic nervous stimulation. These mechanisms allow autoregulation of renal blood flow over a mean arterial pressure range from 60 to 150 mmHg (Cohen et al. 1983).

There are species-related differences in susceptibility to NSAID-induced renal toxicity (Khan et al. 1998) which may be associated with the expression of COX-1 and COX-2 isoforms in the kidney (Khan et al. 1998, 2002). Khan et al. (1998) demonstrated that both isoforms are expressed in the kidney of dogs, rats, monkeys, and humans. However, there were marked differences in localization and basal expression. COX-2 is constitutively expressed in normal kidney and in addition to the importance of COX-1-produced prostaglandins, COX-2-synthesized prostaglandins also play a significant role in renal physiology. The important role played by COX-2 is most likely the reason that COX-2-selective drugs in humans have not improved the renal safety profile and must be used cautiously (Cheng & Harris 2005).

Nonsteroidal anti-inflammatory drugs impair renal autoregulation under conditions of hypovolemia and hypotension, and the resultant decrease in renal blood flow and function may lead to acute renal failure and death, as has been reported in both dogs and cats (Elwood et al. 1992; Pages 2005). Volume depletion resulted in a marked increase in COX-2 expression in rats and dogs, but not in monkeys (Khan et al. 1998), confirming that NSAID studies must be species specific. Currently, nothing is known about COX-1 and COX-2 distribution or expression under different conditions in the feline kidney.

Perioperative use of NSAIDs in humans reduced creatinine clearance and potassium output, but these transient changes in renal function were considered clinically unimportant (Lee et al. 2004). Decreased creatinine clearance has also been reported in dogs receiving NSAIDs in the perioperative period (Forsyth et al. 2000), but neither meloxicam nor carprofen altered glomerular filtration rates when administered preoperatively in healthy dogs (Crandell et al. 2004). To our knowledge similar studies have not been performed in cats. One retrospective study evaluated cats that

presented, or were referred, for acute renal failure (Pages 2005). A total of 48 cases were evaluated, and in 21, the cause was considered to be NSAID administration. Most animals (19) had been given a single dose, and the NSAIDs administered were nimesulide (16 cases), tolfenamic acid (three cases) and ketoprofen (two cases). Although nimesulide is not routinely used in cats in most countries, this study does suggest that renal toxicity caused by NSAIDs may occur relatively easily in cats. However, details of the cats' renal function prior to administration of the NSAID were not available, and the author states that acute renal failure, caused by NSAIDs, is uncommon (Pages 2005). In countries including the United Kingdom and Canada where NSAIDs such as carprofen and meloxicam have been available for use in cats for many years and are routinely administered pre-operatively, clinically detectable renal side effects appear to be rare when used in healthy cats as a single dose. However, repeated use (off-label) of meloxicam has been associated with acute renal failure in the cat, and the company's website warns about repeated dosing (http://www.bi-vetmedica.com/product_sites/METACAMINCats/reference.html – accessed April 9, 2006).

Hepatic effects

Idiosyncratic drug-induced hepatotoxicity is a rare, but potentially serious, adverse consequence associated with many classes of drugs, including NSAIDs, volatile anesthetics, antibiotics, antihypertensives, and anticonvulsants. It can occur with all NSAIDs, but is most frequently associated with diclofenac and sulindac in humans (O'Connor et al. 2003). In dogs, hepatotoxicity has been associated with repeated use (for 5–180 days) of carprofen (MacPhail et al. 1998). However, it is not yet clear whether this is specific to carprofen as no comparative studies, with different NSAIDs, have been conducted. A review of the current literature did not identify any reports of NSAID hepatotoxicity in cats, possibly reflecting the relatively smaller number of cats that are treated with these drugs compared with dogs. However, it should be mentioned that one leading hypothesis explaining NSAID hepatotoxicity is that reactive acyl glucuronide metabolites are generated that can covalently bind and haptenize hepatocyte proteins, thereby promoting an immunological response in the liver (Boelsterli et al. 1995; Boelsterli 2002; Bailey & Dickinson 2003). Under this scenario, reduced NSAID glucuronidation in cats would minimize this mechanism. Acetaminophen overdose typically results in serious liver injury in humans and dogs, but is manifest in cats primarily as methemoglobinemia and Heinz body anemia, probably because of enhanced susceptibility of feline erythrocytes to oxidative injury compared with other species (Harvey & Kaneko 1976).

Gastrointestinal effects

Several studies and reviews have suggested that a variety of risk factors may lead to GI ulceration in dogs (Stanton & Bright 1989; Sullivan & Yool 1998; Hinton et al. 2002; Lascelles et al. 2005). NSAID administration is one of the risk factors, and several reports indicate that GI ulceration can also occur in cats treated with NSAIDs (Whittle et al. 1985; Jones et al. 1992; Runk et al. 1999). Although the mechanisms are not well understood in any species, the main factor is thought to be NSAID-induced impairment of prostaglandin-dependent mucosal-protective mechanisms via inhibition of COX. In the cat, COX inhibition is an important mechanism underlying deep gastric ulceration induced by aspirin (Konturek et al. 1981a,b; Whittle et al. 1985) and where indomethacin-induced ulceration was prevented by the concomitant administration of topical prostaglandin E_2 (PGE_2), those of aspirin were only attenuated (Pendleton & Stavorski 1983), suggesting that the exact mechanism of gastric ulceration in cats may differ between compounds. Both an intravenous (IV) H_2 receptor antagonist and also IV prostaglandin I_2 significantly reduced the formation of experimental aspirin-induced gastric ulcers in cats (Konturek et al. 1981b). It has been shown that, in the cat duodenum, local prostaglandins regulate HCO_3^- transport. These prostaglandins have a similar, but less important role in the cat stomach, and the NSAID indomethacin decreases bicarbonate secretion in both sites (Smeaton et al. 1983). COX-1 inhibition is considered to be the cause of reduced bicarbonate secretion, reduced mucus formation and adverse vascular effects, all of which may lead to GI ulceration and possible perforation. However, the mRNA for COX-2 protein appears to be present in the canine GI tract (Wilson et al. 2004), although the role of COX-2 protein at this site is currently unknown. Work in rodents using acid or chemically-induced gastric ulceration has shown

that selective COX-2 inhibitors can delay or prevent healing of the ulcers (Mizuno et al. 1997; Berenguer et al. 2004), and analysis of COX-2 expression and localization indicated that COX-2 expression was upregulated during injury and was localized to reparative epithelium at the periphery of the wound. Nothing is known about the role of COX-2 in the feline gastric and/or duodenal mucosa and there is also very little information about possible risk factors for feline NSAID-associated GI ulceration. It is known that parietal cells of the feline gastric mucosa are highly sensitive to gastrin (more so than the dog or human) (Hirst et al. 1980), and cats with various degrees of renal failure have significantly higher circulating gastrin concentrations than cats without renal failure which may predispose them to ulceration (Goldstein et al. 1998). Only carprofen has been evaluated for its ulcerogenic properties in feline gastro-duodenal tissue. A single dose of carprofen was evaluated in five cats, and no erosions were detectable by endoscope 8 hours after injection (Parton et al. 2000). The concurrent administration of NSAIDs and corticosteroids led to more severe GI toxicity in dogs (Dow et al. 1990; Boston et al. 2003). Although no studies have been performed in cats, the same is considered to be true.

Clotting function

Nonsteroidal anti-inflammatory drugs affect hemostasis through effects on platelets and vascular epithelium. Platelets are activated and after activation (by exposure to arachidonic acid, collagen, thrombin, or adenosine diphosphate), their aggregation depends on formation of thromboxane A_2 from arachidonic acid within each activated platelet. COX-1, within the platelet, catalyses this reaction and COX-1 inhibition can be beneficial by preventing undesirable thrombosis, but undesirable if excessive bleeding occurs. Intact vascular epithelium produces prostacyclin, limiting the spread of a platelet plug and helping to prevent intravascular initiation of clotting. COX-2 catalyzes this reaction (Jones & Budsberg 2000), therefore COX-2 inhibition may lead to increased thrombosis, particularly if the NSAID is a highly selective COX-2 inhibitor, with no action on COX-1 (Egan et al. 2004; Das 2005).

Aspirin has been studied for deliberate use as an anticoagulant in cats (see below) and the negative effect of other NSAIDs (ketoprofen, meloxicam) on clotting has been examined in the context of surgery.

There are no published studies evaluating the effect of chronic administration of COX-2 selective drugs on the incidence of vascular thrombosis in cats.

Specific drugs

Acetaminophen (paracetamol)

Acetaminophen is one of the most commonly used drugs for mild pain and fever in humans, and is used to a limited extent in other species (off-label use). However, for several reasons, *clinical use is contraindicated in cats*. Firstly, the therapeutic index of acetaminophen in cats is very small. Acetaminophen doses as low as 60 mg kg^{-1} (one 325 mg acetaminophen capsule) resulted in severe toxicity in cats characterized by anorexia, vomiting, depression, methemoglobinemia, and Heinz body anemia (Savides et al. 1984). In contrast, more than five times this dose (300 mg kg^{-1}) was required to produce toxic effects in dogs (Savides et al. 1984). Secondly, acetaminophen elimination kinetics in cats are not linear at therapeutic doses, so drug accumulation and associated toxic effects may occur with repeated dosing. Elimination half-lives were shown to increase from 0.6 to 4.8 hours with doses from 20 to 120 mg kg^{-1} in cats, while a relatively constant half-life of 1.2 hours was demonstrated with doses of up to 200 mg kg^{-1} in dogs (Savides et al. 1984). Due to the low feline capacity to glucuronidate acetaminophen there is an increased reliance on drug sulfation for detoxification. Once the sulfation pathway becomes saturated an alternate cytochrome P450 pathway is utilized, producing the highly reactive acetaminophen metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Although normally detoxified by glutathione conjugation, excessive NAPQI overwhelms glutathione availability, leading to oxidative injury (Allison et al. 2000).

Accidental or intentional administration of acetaminophen is a common cause of toxicity in cats (Finco et al. 1975; Sundlof 1990; Jones et al. 1992; Villar et al. 1998). Clinical signs include cyanosis, depression, facial swelling, salivation, and vomiting. The main treatment is administration of the glutathione precursor, *N*-acetylcysteine, as well as symptomatic and supportive care (Gaunt et al. 1981; Villar et al. 1998).

Aspirin (acetylsalicylic acid)

Pharmacokinetics and COX selectivity

Following administration, aspirin is rapidly hydrolyzed by esterases to salicylic acid, the major circulating active metabolite (Williams et al. 1989). Aspirin is more potent than salicylic acid as it can irreversibly inhibit COX via covalent acetylation (Patrono 1989). Consequently, in most tissues COX function will need to be restored through synthesis of new enzymes. However, as platelets are unable to synthesize new enzymes, COX function is permanently inactivated in these cells. Clearance of salicylic acid is primarily via conjugation with glucuronic acid, as well as with glycine. There is also renal excretion of unchanged salicylic acid (Davis & Westfall 1972; Davis 1980). The pharmacokinetics of aspirin in cats following both oral and intravenous administration include a relatively slow salicylic acid clearance (4–5 mL kg^{-1} $hour^{-1}$) and a prolonged elimination half-life (22–45 hours) compared with other species (Davis & Westfall 1972; Davis 1980; Parton et al. 2000). As a consequence, the recommended aspirin dose is smaller and dosing interval longer in cats than in other species.

Label doses

Although no aspirin preparations have been approved by the FDA in the USA for use in cats (or any other animal), a variety of formulations intended for humans are available for extra-label use. A variety of aspirin formulations are currently marketed in the USA for use in veterinary patients with label indications that include treatment of pain, fever, and inflammation. However, it should be pointed out that none of these veterinary preparations have been specifically approved by the FDA. An oral dose of 10 mg kg^{-1} every 2 days has been recommended for pain and fever in cats, while higher doses of 10–25 mg kg^{-1} every 1–2 days could be used for inflammation with appropriate monitoring for GI toxicity (http://www.usp.org/pdf/EN/veterinary/aspirin.pdf – accessed May 23, 2006).

Evidence of efficacy

Aspirin is the NSAID that has been most studied with regard to clotting in cats. The aim was to find a dose of aspirin that would prevent thrombosis associated with cardiomyopathy and heartworm disease, but not result in toxicity. Results have been somewhat conflicting (Piegras et al. 1976; Gryglewski et al. 1978) but overall, aspirin failed to predictably prevent thrombosis associated with vascular injury in the cat unless administered in extremely high doses (Schaub et al. 1982). Greene found that 25 mg kg^{-1} of aspirin inhibited arachidonic acid-induced platelet aggregation (measured using platelet-rich plasma) for 3–5 days in the cat, and recommended that an average weight cat be treated with a 90 mg aspirin tablet twice a week to prevent thrombus formation (Greene 1985). Subsequent work has reported results that vary depending on the assay method used or the condition being treated (Piegras et al. 1976; Gryglewski et al. 1978; Schaub et al. 1982; Allen et al. 1985; Rawlings 1990; Rawlings et al. 1990; Hart et al. 1995; Behrend et al. 1996; Bright et al. 2003; Smith et al. 2003). A retrospective study examining the survival rate and recurrence of arterial thromboembolism in cats treated with high-dose aspirin (>40 mg/cat every 72 hours) and low-dose aspirin (5 mg/cat every 72 hours), showed no significant difference between groups, but fewer side effects in the low-dose group (Smith et al. 2003). Collectively, these studies demonstrated limited inhibition of platelet aggregation with aspirin, even at doses of 20–25 mg kg^{-1}. As yet, there are no published studies that have evaluated the efficacy or safety of aspirin for the treatment of pain, fever, or inflammation in cats.

Toxicity

Gastric ulceration occurs readily when aspirin is administered to cats (25–100 mg kg^{-1} daily), and the incidence appeared to have little relation to the dose administered (Bugat et al. 1976). Accidental overdose of aspirin is a relatively common cause of poisoning in cats (Sundlof 1990; Jones et al. 1992). Clinical signs of acute overdose may include depression, vomiting, hyperthermia, electrolyte disturbances, metabolic acidosis, bleeding disorders, convulsions, coma, and death (Villar et al. 1998). Treatment involves gastric lavage, urinary alkalinization to enhance excretion, and symptomatic and supportive therapy (Villar et al. 1998).

Recommended doses

For treatment of pain, inflammation, and fever, aspirin recommended doses range from 10 to

25 mg kg^{-1} administered orally every 24–48 hours (Wilcke 1984).

Carprofen

Pharmacokinetics and COX selectivity

Carprofen was one of the first of the newer NSAIDs to be studied in cats, and pharmacokinetic and limited pharmacodynamic data are available (Taylor et al. 1996; Parton et al. 2000). There is no information on pharmacokinetics following repeated dosing (in common with most other NSAIDs in the cat) and this is not generally recommended because of the very variable inter-cat pharmacokinetics; one study found that the half-life varied from 9 to 49 hours (Parton et al. 2000) (see Table 1). Carprofen is relatively slowly absorbed from the subcutaneous site, with a T_{max} of approximately 3.4 hours (Taylor et al. 1996). Carprofen is a racemic mixture, with both *R*(−) and *S*(+) enantiomers included in a 1:1 ratio. The *S*(+) enantiomer is believed to be the most active (Lees et al. 2004b). It has been suggested that carprofen causes limited COX inhibition (Taylor et al. 1996) which may explain its anecdotally good safety record following widespread clinical use in cats. One study suggested it was a preferential COX-2 inhibitor in a feline whole blood assay (Brideau et al. 2001). This study did not compare it to other NSAIDs that have been used clinically in the cat. A more recent study also found carprofen to be a preferential COX-2 inhibitor (Giraudel et al. 2005), and confirmed previous suggestions that selectivity is progressively lost at larger doses. At the dose licensed in Europe (4 mg kg^{-1}), these investigators predict 100% inhibition of COX-2, and 44% inhibition of COX-1 (Giraudel et al. 2005). These results and predictions are based on a whole blood assay of activity against COX-1 and 2 isoenzymes. Nothing is known about its ability to inhibit COX enzymes in GI or renal tissue *in vivo*, and neither is there any information on the clinical toxicity of carprofen in cats.

Label doses

In countries where it is approved for use in cats (United Kingdom, France, Germany, The Netherlands, Italy, Belgium, Australia, and New Zealand) it is labeled for the control of perioperative pain as a single injection, and a dose of 4 mg kg^{-1}, is administered subcutaneously or intravenously.

Evidence of efficacy

In contrast to the paucity of information on the side effects (a feature common to all the NSAIDs), there are several clinical studies demonstrating its efficacy. The first reported study to evaluate carprofen in the cat (Lascelles et al. 1995a) found it to be a very effective analgesic in 30 cats undergoing ovariohysterectomy, providing profound and prolonged analgesia (for the 20 hours of postoperative assessments) compared with meperidine (pethidine). In this randomized study, using a single observer visual analog score (VAS), the cats receiving carprofen exhibited less pain postoperatively overall, with 4.0 mg kg^{-1} being the most effective dose, although in the later postoperative period, all doses of carprofen (1, 2, and 4 mg kg^{-1}) provided greater analgesia than both low- and high-dose meperidine as well as placebo (Lascelles et al. 1995a). Other studies have confirmed these findings in clinical cases undergoing ovariohysterectomy (Balmer et al. 1998), and also found carprofen to be a more effective analgesic than buprenorphine in orthopedic surgery (Mollenhoff et al. 2005) and butorphanol in ovariohysterectomy (Al-Gizawiy & Rude 2004). Subsequent clinical studies have confirmed the analgesic efficacy of carprofen (Slingsby & Waterman-Pearson 2000, 2002; Al-Gizawiy & Rude 2004; Mollenhoff et al. 2005). One study (Slingsby & Waterman-Pearson 2000) compared the efficacy of various NSAIDs in the prevention of acute pain. Forty cats, undergoing ovariohysterectomy, were assigned to carprofen (4 mg kg^{-1}, SC), meloxicam (0.2 mg kg^{-1}, SC), ketoprofen (2 mg kg^{-1}, SC), or tolfenamic acid (4 mg kg^{-1}, SC) groups. Pain was assessed using a single-observer 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 scores at 18 hours. There was no difference between groups in mechanical threshold at the incision site, measured using a finger-mounted pressure transducer (Slingsby & Waterman-Pearson 2000). In a later study (Slingsby & Waterman-Pearson 2002), 80 cats undergoing flank ovariohysterectomy were assigned to carprofen (4 mg kg^{-1}) or meloxicam (0.3 mg kg^{-1}) SC before surgery. Pain was assessed by a single observer, using a VAS over 20 hours, and there were no significant differences between groups. Two cats in the meloxicam group and one cat in the carprofen group required rescue analgesia.

Toxicity

There have been anecdotal reports of carprofen toxicity, generally associated with concurrent disease and prolonged administration of the oral formulation, and one case report describes such a scenario (Runk et al. 1999). One study found no endoscopically visible GI lesions in eight cats following a single dose of carprofen (Parton et al. 2000). Carprofen did not appear to affect renal function adversely, as measured by urea and creatinine levels (Lascelles et al. 1995a) and none of the cats developed acute renal failure as a result of the combination of surgery, anesthesia, and the analgesic regimen.

Recommended doses

From a critical evaluation of the published information available, the authors recommend using carprofen only as a single dose, pre- or postoperatively (depending on the hemodynamic status of the cat), at a dose of 1–2 mg kg^{-1} (subcutaneously or intravenously). This dose should maximize the safety margin, while maintaining clinically detectable efficacy.

Celecoxib, rofecoxib, and valdecoxib

Currently there are three different COX-2-specific drugs that have been approved by the FDA in the USA for use in humans. Rofecoxib was recently withdrawn from sale because of a possible enhanced risk of cardiovascular thrombosis with long-term use. Although not approved for use in animals, the perceived safety of these drugs in humans has led to off-label use in other species, including studies investigating their efficacy and safety in companion animals (Moreau et al. 2005). As yet, no studies have been published evaluating the efficacy, safety, or pharmacokinetics of these drugs in cats.

Deracoxib

Pharmacokinetics and COX selectivity

The pharmacokinetics of a single 1 mg kg^{-1} oral dose (compounded as an oral suspension) have been studied in healthy cats (Gassel et al. 2006) using a validated high-performance liquid chromatography assay (Cox et al. 2005). Oral bioavailability could not be calculated as an intravenous formulation was not administered for comparison. The half-life ($T_{1/2}$) reported in cats was 8.4 hours which is much longer than the 3 hours reported in dogs after a 2–3 mg kg^{-1} dose (http://www.deramaxx.com/content/ProductLabel.pdf – accessed July 21, 2006). The changes in hematological (decreased hematocrit and albumin) and biochemical values (decreased total calcium) in this study were thought to be a result of blood collection for pharmacokinetic analyses (Gassel et al. 2006).

Label doses

Deracoxib is not approved for use in the cat.

Evidence of efficacy, toxicity, recommended doses

To date, no safety or efficacy studies have been performed in cats and currently deracoxib cannot be recommended for this species.

Firocoxib

Pharmacokinetics and COX selectivity

Firocoxib was recently approved in the USA and Europe for alleviation of pain associated with osteoarthritis in dogs. There is little information about its characteristics or use in cats. In one study of COX selectivity, using 19 experimental cats (McCann et al. 2005), it was administered at 2 mg kg^{-1} IV, or 3 mg kg^{-1} orally and using a whole blood assay, was found to be a selective COX-2 inhibitor. Its half-life was determined to be 8.7–12.2 hours.

Label doses

Firocoxib is not approved for use in the cat.

Evidence of efficacy

Doses of 0.75–3 mg kg^{-1} attenuated fever when administered to cats 1 or 14 hours before challenge with lipopolysaccharide (LPS) (McCann et al. 2005). Given its relatively short half-life, and its efficacy against LPS-induced fever, the authors concluded that it may be a suitable anti-inflammatory drug for once daily dosing in cats.

Toxicity

There is no information on toxicity.

Recommended doses

Given the current sparse information on firocoxib, the authors cannot recommend its clinical use in cats.

Flunixin

Pharmacokinetics and COX selectivity

Flunixin is well absorbed from the GI tract and undergoes enterohepatic circulation, resulting in a bioavailability >100% (McKellar et al. 1991; Taylor et al. 1994). The T_{max} after oral dosing is approximately 1.3–2 hours (Taylor et al. 1994). The elimination half-life has been found to be 1–1.5 hours, using an assay with a limit of detection of 0.25 μg mL^{-1} (Taylor et al. 1991, 1994). More recent studies, using an assay with a limit of detection of 0.046 μg mL^{-1}, determined the elimination half-life to be 6.6 hours after 2 mg kg^{-1} IV (Horii et al. 2004). The long half-life could be reduced if a drug was given to block active enterohepatic recirculation. Flunixin is actively transported into liver cells and then excreted into bile. Renal tubular secretion is a minor pathway of excretion. In a study in which flunixin 1 mg kg^{-1} PO was administered every 24 hours for 7 days, there was no accumulation of drug (Taylor et al. 1994). In fact, the maximal concentration and the AUC_{0-24} 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 for only 2 hours on day 7. Alanine aminotransferase (ALT) increased from 11.4 to 21.3 IU L^{-1}, suggesting that liver toxicity may be a problem with chronic administration.

Label doses

Flunixin is not approved for the cat.

Evidence of efficacy

There is only one study that has examined the effect of flunixin (1 mg kg^{-1} IV) in 40 cats undergoing a variety of surgical procedures. The study used three observers and a VAS, and found no significant differences in analgesia between flunixin and meperidine, except at 15 minutes, when the cats given meperidine were in less pain. The cats given flunixin were less sedate from 30 to 90 minutes (Fonda 1996).

Recommended off-label doses

The recommended dose is 0.5–1 mg kg^{-1} IV or PO, once.

Ketoprofen

Pharmacokinetics and COX selectivity

Ketoprofen is a chiral molecule that has different pharmacokinetics for the two mirror-image, entantiomeric, *R*(−) and *S*(+) forms. The drug is highly bioavailable in cats after oral dosing and similar pharmacokinetic differences were noted for the two enantiomers with IV and oral dosing of the racemic mixture (Lees et al. 2003). There are no published data on the relative inhibition of COX-1 or COX-2 by ketoprofen in the cat.

Label doses

Ketoprofen is not approved for the cat in the USA but in Europe, Australasia, and Canada, the labeled doses are: PO: 1 mg kg^{-1} daily for up to 5 days, and SC: 2 mg kg^{-1} daily for up to 3 days.

Evidence of efficacy

Administration of ketoprofen did not affect the wheal volume produced by intradermal carageenan injection, but skin wheal temperature was reduced in cats given 2 mg kg^{-1} IV at some time points during the 12 hours after treatment (Lees et al. 2003). In cats with clinical pyrexia above 39.3 °C, randomly assigned to antibiotics or antibiotics plus ketoprofen (2 mg kg^{-1} SC once, followed by 1 mg kg^{-1} orally for 4 days) those given ketoprofen recovered faster from pyrexia, inappetance, and depression (3 days) than cats given antibiotics alone (5 days) (Glew et al. 1996). The antipyretic effect of ketoprofen was rapid and lasted for >8 but <24 hours.

In a large study, Slingsby (1997) examined 100 cats undergoing flank ovariohysterectomy, randomly assigned to meperidine, buprenorphine, ketoprofen, carprofen, or control groups. The dose of ketoprofen was 2 mg kg^{-1} SC, administered at extubation. Pain was assessed using a VAS. Until

1–2 hours after surgery the lowest pain scores were in the two opioid groups. Scores at 4 and 8 hours, and the next morning were lower in NSAID groups. Significantly less rescue analgesia was administered to cats in NSAID groups (Slingsby 1997). In a study of 60 cats undergoing flank ovariohysterectomy (Slingsby & Waterman-Pearson 1998), patients were randomly assigned to control, meperidine, buprenorphine, or ketoprofen (2 mg kg^{-1} SC, given at extubation) groups. The single-observer VAS score for pain was lower for the ketoprofen group compared with the control group at 4, 8, and 18 hours, compared with the meperidine group at 2, 4, and 8 hours, and compared with the buprenorphine group at 8 hours. Overall clinical score and need for intervention was significantly lower in the ketoprofen group compared with the control and both opioid groups (Slingsby & Waterman-Pearson 1998). Ketoprofen was equally as effective as carprofen, meloxicam, and tolfenamic acid (see Carprofen above) (Slingsby & Waterman-Pearson 2000).

There is one reported study that assessed the effect of ketoprofen for 5 days on chronic pain (Lascelles et al. 2001). Both the cats that received meloxicam ($n = 43$; 0.3 mg kg^{-1} day 1 followed by 0.1 mg kg^{-1} daily) and those that received ketoprofen ($n = 26$; 1 mg kg^{-1} PO daily for 5 days) improved in demeanor, feed intake, weight bearing and lameness. Pain on palpation and inflammation decreased but there was no control group and there were no significant differences between groups (Lascelles et al. 2001). The doses used in this study were those used, clinically, in cats for chronic pain.

Toxicity

Inhibition of platelet COX-1, measured by *ex vivo* thromboxane synthesis in feline blood, lasted for 72 hours after administration of 2 mg kg^{-1} ketoprofen IV, and for 24 hours after 1 mg kg^{-1} orally (Lees et al. 2003). However, no excessive bleeding (from direct observation, with 'excessive' meaning any bleeding from the wound postoperatively) was noted in a study of 60 cats comparing meperidine, buprenorphine, and ketoprofen administered after ovariohysterectomy (Slingsby & Waterman-Pearson 1998). Pages (2005) reported two cases of renal insufficiency following ketoprofen administration, but one cat had received a dose 15 times higher than that normally used.

Recommended off-label doses

After critical evaluation of the available published information, the authors recommend 1 mg kg^{-1} daily (PO or SC) for up to 5 days, or 2 mg kg^{-1} SC as a single injection.

Meloxicam

Pharmacokinetics and COX selectivity

Meloxicam is nearly 100% bioavailable after SC injection to cats, with a T_{max} of approximately 2.2 hours, and the terminal elimination half-life in cats is 15 hours after a single 0.3 mg kg^{-1} dose by this route. *In vitro* studies using standardized whole blood assays demonstrated 43% inhibition of COX-1 and 90% inhibition of COX-2 at a plasma meloxicam concentration of 3.95 μM, which would be the maximum concentration achieved with the label dose. Any meloxicam concentration producing COX-2 inhibition always caused at least 20% COX-1 inhibition as well. At plasma concentrations of meloxicam producing more than 80% inhibition of COX-2, a reasonable therapeutic target, COX-1 inhibition was >40%. If an IC_{50} of COX-2 was chosen as a therapeutic target, the extrapolated dose was 0.11 mg kg^{-1} every 24 hours. If an IC_{80} of COX-2 was chosen as a therapeutic target, the extrapolated dose was 0.17 mg kg^{-1} every 24 hours. For the label dose, the time above IC_{50} for COX-2 was 23 hours, while the time above IC_{80} was 8.8 hours. The time above IC_{10} for COX-1 was 109.5 hours, while the time above IC_{20} was 64 hours. If COX-1 inhibition, above a certain minimal amount, may result in GI side effects, then the label dose would be likely to cause toxicity, if given more than once (Lees et al. 2004a; Giraudel et al. 2005).

Label doses

Meloxicam is approved (Europe, Australia, New Zealand, USA) at a dose of 0.3 mg kg^{-1} SC once, prior to surgery. There are currently no approved dosing schedules for repeated dosing, although chronic dosing recommendations for cats are available in the US Pharmacopoeia (http://www.usp.org/pdf/EN/veterinary/meloxicam.pdf – accessed February 8, 2006) based primarily on the work of Lascelles et al. (2001).

Evidence of efficacy

The effect of meloxicam on fever was studied *in vivo*, using a single intravenous dose of 0.1, 0.3, or 0.5 mg kg^{-1}, given 30 minutes before endotoxin challenge (Justus & Quirke 1995). Body temperature was measured for 300 minutes after the administration of endotoxin and a dose-related prevention of fever was demonstrated. The degree of fever prevention gained by increasing the dose from 0.3 to 0.5 mg kg^{-1} was minimal, compared to that gained by increasing from 0.1 to 0.3 mg kg^{-1}. This study is the justification for the label dose of 0.3 mg kg^{-1}, administered once (Justus & Quirke 1995). In another study (Engelhardt et al. 1996), cumulative intravenous doses of 4 mg kg^{-1} of meloxicam were administered to cats under IP chloralose-urethane anesthesia. Minimal effects on arterial blood pressure were noted. There was no effect on the blood flow in the carotid artery, heart rate, ECG tracings, or respiratory minute volume (Engelhardt et al. 1996).

Two studies have compared meloxicam with carprofen and other NSAIDs (for results see Carprofen above) (Slingsby & Waterman-Pearson 2000, 2002).

Recently, a study was performed in which 64 female cats and 74 male cats were assigned to receive meloxicam ($n = 72$; 0.3 mg kg^{-1} SC) or butorphanol ($n = 66$; 0.4 mg kg^{-1} SC) prior to onychectomy (Carroll et al. 2005). There was no control group. Cats in the meloxicam group were less lame, had lower pain scores, and fewer required rescue analgesia, as assessed on palpation, a subjective gait score, and visual observation. Plasma cortisol concentrations were significantly higher at extubation and lower at 3, 5, 12, and 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. Hematocrit and blood urea nitrogen (BUN), decreased in both groups, while glucose decreased after surgery in the meloxicam group (Carroll et al. 2005).

There is one reported study assessing the effect of meloxicam on chronic pain (see Ketoprofen for details) (Lascelles et al. 2001).

Toxicity

There are no published reports primarily evaluating the clinical toxicity of meloxicam in cats. The manufacturer's package insert suggests the safety margin is narrow (http://www.bi-vetmedica.com/product_sites/METACAMINCats/documents/Metacam_Inj_cats_label.pdf – accessed July 31, 2006), and this has also been suggested from work evaluating the pharmacokinetics and pharmacodynamics of COX-1 and COX-2 inhibition (Giraudel et al. 2005). As discussed above, in clinical studies primarily evaluating efficacy, clinical *short-term* toxicity has been evaluated following single doses of meloxicam. In a total of 40 cats administered meloxicam, BUN decreased and asparate aminotransferase increased 24 hours after surgery (Slingsby & Waterman-Pearson 2002), but there were no changes in creatinine or ALT. In a study of 138 cats administered a single dose of meloxicam, or butorphanol, there was no difference in buccal mucosal bleeding time between the groups; hematocrit and BUN were decreased in both groups 24 hours after surgery, while glucose decreased after surgery in the meloxicam group (Carroll et al. 2005).

Recommended off-label doses

After critical evaluation of the available published information, the authors recommended 0.1–0.2 mg kg^{-1} PO or SC as a single dose for perioperative pain, followed by 0.05 mg kg^{-1} for 4 days. For chronic conditions, they recommended 0.1 mg kg^{-1} PO or SC on day 1, followed by 0.05 mg kg^{-1} for 1–4 days; then to reduce it rapidly to the lowest effective dose (0.025 mg kg^{-1} every 24 or 48 hours); monitoring closely for side effects.

Phenylbutazone

Pharmacokinetics and COX selectivity

The clearance mechanism or pharmacokinetics of phenylbutazone in cats has not been reported. According to the US Pharmacopeia, phenylbutazone is rapidly converted to the active metabolite oxyphenylbutazone, which is very slowly eliminated by the cat (http://www.usp.org/pdf/EN/veterinary/phenylbutazone.pdf – accessed May 23, 2006). In all species evaluated to date, clearance of phenylbutazone occurs primarily via metabolism in the liver and excretion of metabolites in urine and bile (Tobin et al. 1986; Mills et al. 1995). In humans, the majority of a phenylbutazone dose is cleared via glucuronidation (Dieterle et al. 1976; Aarbakke 1978). However, the role of glucuronidation in

phenylbutazone clearance in other species is unclear, although it may be substantial. There is no information on relative COX-1 or 2 inhibition in the cat.

Label doses

Phenylbutazone was approved for use in the cat in the UK at a dose of 25 mg/cat, once or twice daily for 7 days, reducing to 25 mg/cat daily or every other day thereafter. The license has recently been withdrawn. Recently, the license in Australia for phenylbutazone use in cats was not renewed (1999).

Evidence of efficacy

No studies supporting the efficacy or safety of phenylbutazone use in cats have been published to date.

Toxicity

Phenylbutazone is approved by the FDA in the USA for anti-inflammatory treatment of musculoskeletal disorders in horses and dogs. Although there is significant extra-label use in other species, use in cats is limited by toxicity concerns, although published data on this are limited. In one experimental study all five cats treated with phenylbutazone at a dose of 44 mg kg^{-1} daily (about twice the dose used in dogs) showed anorexia within 3 days, and four of the cats died within 3 weeks, with the fifth being killed *in extremis* after 7 weeks (Carlisle et al. 1968). Toxicity primarily manifested as bone marrow suppression as well as GI, renal, and liver injury (Carlisle et al. 1968).

Recommended off-label doses

Given the current sparse information on phenylbutazone, the authors cannot recommend its clinical use in cats at the present time.

Piroxicam

Pharmacokinetics and COX selectivity

Single-dose pharmacokinetics for oral and intravenous doses of 0.3 mg kg^{-1} have been determined in the cat (Heeb et al. 2003). There are no reported pharmacodynamic studies, nor has the COX-1/COX-2 selectivity been determined for the cat. The median elimination half-life is 12 hours for the intravenous dose and 13 hours for the oral dose. This is shorter than in the dog, in which elimination half-lives of 37 and 40 hours have been measured (McKellar et al. 1991). The T_{max} following oral administration is 3 hours (Heeb et al. 2003). Multiple-dose pharmacokinetics and acute safety have been evaluated for piroxicam administered at 0.3 mg kg^{-1} daily for 10 days, with and without concurrent cimetidine administration (Heeb et al. 2005). The mean half-life increased from 11 hours on day 1 to 14 hours on day 10. Cimetidine reduced the half-life of piroxicam, but not significantly (Heeb et al. 2005).

Label doses

Piroxicam is not approved for use in the cat.

Evidence of efficacy

There are no studies of its analgesic efficacy in the cat. Piroxicam has been used mainly in the treatment of epithelial neoplasia, although there appears to be little rationale for this treatment, as feline tumors have not been shown to over-express COX enzymes (Beam et al. 2003).

Toxicity

There is no information on the toxicity of piroxicam in the cat, but unpublished work by one of the authors (BDX Lascelles, personal communication, 2006) suggests daily dosing can lead to a significant decrease in hematocrit in 30% of cats after 7–14 days. In one study, serum BUN, creatinine, alkaline phosphatase, and ALT all remained within their reference ranges. Four of seven cats receiving piroxicam developed mild to severe gastric erosions; however, they remained clinically asymptomatic. Two of seven cats receiving both piroxicam and cimetidine (15 mg kg^{-1} PO every 12 hours) developed mild erosions (Heeb et al. 2005).

Recommended off-label doses

Doses of 0.3 mg kg^{-1} PO every 24–48 hours have been used in the treatment of neoplasia but it is not known whether this dose provides anti-inflammatory or analgesic effects.

Tepoxalin

Pharmacokinetics and COX selectivity

Tepoxalin is classified as a dual inhibitor and has inhibitory activity against COX-1, COX-2, and 5-LOX in dogs (Agnello et al. 2005). There is no information about its selectivity or action in cats.

Label doses

Tepoxalin is not approved for use in the cat.

Evidence of efficacy

There is no published information on efficacy of tepoxalin in cats.

Toxicity

There is no information on safety or toxicity of tepoxalin in the cat.

Recommended off-label doses

There are currently no safety data for cats, and the optimal dose, dosing interval, and formulation have not been established.

Tolfenamic acid

Pharmacokinetics and COX selectivity

There are no data available describing the pharmacokinetics for this drug in cats. *In vitro* assays using a canine monocyte/macrophage cell line show that it preferentially inhibits COX-2 over COX-1 (Kay-Mugford et al. 2000), but other authors suggested that it is a preferential COX-1 inhibitor (Vane & Botting 1995). Newly available feline-specific assays will provide a robust method for determining NSAID selectivity in this species, but tolfenamic acid has not been tested using this system (Giraudel et al. 2005).

Label doses

This drug belongs to the fenamate group of NSAIDs and is licensed for use in cats in many countries including Canada, Australia, New Zealand, and most members of the European Union, but not the United States. It is the most popular NSAID used in France (Hugonnard et al. 2004). In cats, tolfenamic acid is labeled for oral and/or injectable use (for example: 4 mg kg^{-1} – product packet insert; Vétoquinol Inc., Lavaltrie, Quebec, Canada) for 3–5 days, depending on the country of license, for the treatment of upper respiratory disease and as a symptomatic treatment of fever (product packet insert).

Evidence of efficacy

There are few published reports on the clinical use of tolfenamic acid in cats. However, Slingsby & Waterman-Pearson (2000) compared it with other NSAIDs and found it to be equally as effective as carprofen, ketoprofen, and meloxicam (see Carprofen for details).

Toxicity

There is little information on the toxicity of tolfenamic acid in the cat. In a study of 63 cats treated with a placebo ($n = 32$) or tolfenamic acid ($n = 31$) (4 mg kg^{-1}) for 3 days, for fevers of various etiologies, the incidence of side effects (seven cases in each group: vomiting, diarrhea, polyuria, polydypsia, and aggressiveness) was similar in both groups (Thomas et al. 1993). It is suggested that when the injectable formulation is used in cats undergoing general anesthesia, tolfenamic acid should not be administered until they are fully recovered (http://www.vetoquinol.co.uk – accessed July 21, 2006). However, it has been administered at endotracheal extubation without any untoward side effects (Slingsby & Waterman-Pearson 2000).

Recommended doses

Recommended doses are the same as the label doses (4 mg kg^{-1} PO once daily, for 3 days; or, 4 mg kg^{-1} every 24 hours for a maximum of two doses).

Vedaprofen

Pharmacokinetics and COX selectivity

Vedaprofen is an NSAID licensed in the Netherlands and the UK for use in the dog for the control of musculoskeletal pain. It has been described as a preferential COX-2 inhibitor, but there is no infor-

mation on COX selectivity in the cat, nor on its pharmacokinetics in this species.

Label doses

Vedaprofen is not approved for use in the cat.

Evidence of efficacy

Vedaprofen (0.5 mg kg^{-1}) has been found to provide analgesia following ovariohysterectomy in the cat (Horspool et al. 2001). Cats were treated with oral vedaprofen gel (0.5 mg kg^{-1}; $n = 142$) or placebo ($n = 160$), daily for 3 days, and behavior and appetite were assessed. Detailed information is lacking, but the authors indicated that the cats receiving vedaprofen returned to normal behavior and appetite more quickly than those treated with placebo. They indicated the incidence of side effects (undefined GI signs) were the same in each group, 7% and 5%, respectively (Horspool et al. 2001).

Toxicity

There is no published information on safety or toxicity of vedaprofen in the cat.

Recommended off-label doses

There are no safety data for cats at this time, and the optimal dose and dosing interval have not been established. Vedaprofen cannot yet be recommended for use in the cat.

The role of NSAIDS as anti-neoplastic agents

There is growing evidence from experimental, epidemiological, and clinical trials that NSAIDs and, in particular, the COX-2 selective drugs may have a role in prevention and treatment of some types of tumors (Thun et al. 2002). COX-2 has been identified in many human and dog carcinomas, and its upregulation and overexpression result in high concentrations of prostaglandins, most notably PGE_2 (Mohammed et al. 2004).

In dogs, COX-2 is expressed in many neoplasms (47–100% of squamous cell carcinomas, transitional cell carcinomas, and prostatic adenocarcinomas) (Khan et al. 2000; Kleiter et al. 2004; Mohammed et al. 2004). Strong COX-2 expression in appendicular osteosarcomas has been associated with a significantly shorter survival time compared to dogs with no, or poor to moderate COX-2 expression in the tumor (Mullins et al. 2004). Beam et al. (2003) performed immunocytochemistry studies on a variety of feline neoplasms to determine COX-2 expression. In contrast to canine tumors, only 37% of feline transitional cell carcinomas and 9% of oral squamous cell carcinomas expressed COX-2. No COX-2 immunoreactivity could be found in feline cutaneous squamous cell carcinomas, adenocarcinomas (mammary, intestinal, and pulmonary), or vaccine-related sarcomas (Beam et al. 2003). The authors suggest that there is a species difference in COX-2 expression between canine and feline neoplasms, and that NSAIDs may have little application in the treatment of tumors in cats. Their work needs confirmation, especially as the antibodies were not specific for the cat. As yet, there are no published studies of NSAID effectiveness as anticancer agents in the cat.

Owner compliance

Administration of medications to cats is a problem for some owners. There is only one study that has examined (as a secondary outcome measure) the ease of NSAID administration to cats, in which meloxicam drops were found to be easier to administer than ketoprofen tablets (Lascelles et al. 2001). Accurate dosing, using formulations designed for dogs or humans, can be a problem with drugs that are not approved and marketed for cats. A pill splitter or razor blade can be used to cut tablets, but split tablets do not always contain the intended dose (Teng et al. 2002). Alternatively, liquid formulations designed for injection have been administered as oral drops. There are no data showing that appropriate blood levels are achieved when cats are treated with NSAIDs in this fashion, but the high bioavailability of most NSAIDs suggests that this may be a reasonable strategy. The taste preferences of cats are understood (Thombre 2004) and compounding pharmacies will create flavored liquids and pastes for cats; however, the stability of the product in these formulations is unknown. There is a great deal of interest in developing methods for transdermal administration of NSAIDS, but the precise formulation and design of the transdermal patch or gel appears critical in achieving reliable absorption of the drug (Takahashi et al. 2002; Swart et al. 2005).

Responsible use of NSAIDS in cats

Responsible use of NSAIDs includes administering products that are licensed for use in cats and for the labeled indications where possible, because this means that there exists a body of evidence-based medicine to support this use. The reader should be aware that licensing varies widely between countries. If NSAIDs are used off-label the owner should be made aware of this fact. In all cases, they should be informed of the possible side effects in their pet both verbally and in writing. This should include what clinical signs to look for (e.g., vomiting, inappetance, bloody stool) that would warrant calling their veterinarian and stopping treatment.

Acute and perioperative use

Nonsteroidal anti-inflammatory drugs are effective in cats for the alleviation of surgical pain and for the treatment of upper respiratory diseases and fever. Carprofen and meloxicam are labeled for preoperative use but should not be used if there is preexisting hypovolemia, dehydration, or hypotension. If substantial blood loss is predicted, their use should be reserved for the postoperative period when fluid replacement has been adequate and normal cardiovascular and circulatory function is restored. Because ketoprofen has been shown to affect platelet function *ex vivo* in cat blood (Lees et al. 2003), it is recommended that its use is reserved for the postoperative period. The authors highly recommend administering perioperative fluids to cats when using NSAIDs for the relief of perioperative pain. NSAIDs should not be used in combination with corticosteroids because both act on the arachidonic acid pathway; their use together increases the risk of adverse side effects, especially in the GI tract.

Pre-administration hematological examination may detect animals unsuitable for NSAID treatment (e.g., those with renal disease or significant liver disease) and provide an historical baseline if there is an unexpected complication following administration. Preoperative blood work should include measurement of BUN and creatinine. A baseline hematocrit and total plasma protein should also be recorded. Although it is usually stated that animals with hepatic disease should not receive NSAIDs, this is more controversial than the more clear-cut issue of renal disease. Hepatic function is not reflected by measuring hepatic enzymes. If hepatic disease is suspected, liver function tests such as measurement of fasting serum bile acids should be undertaken before a decision is made to use an NSAID.

Repeat dosing of NSAIDs should be undertaken with particular care in cats, because of the variable and sometimes long half-lives (e.g., carprofen 20.1 ± 16.6 hours). Subsequent treatments should be administered at a reduced dose or increased dosing interval. For the majority of drugs, there is little evidence to guide dosing recommendations. Tolfenamic acid or ketoprofen can be used for several days where appropriate licensing is present, but even then the labeled indication does not include postoperative pain.

There is little information on appropriate washout periods between different NSAIDs in dogs, and none in the cat. It is therefore recommended that any treatment using NSAIDs is completed using the same drug as used initially. If further doses of that drug are considered inappropriate, other treatment options that do not include NSAIDs should be considered.

Chronic administration

Tolfenamic acid and ketoprofen are labeled for up to 5 days' use in some countries, but unlike dogs, no NSAIDs are intended for long-term use in cats. Despite this, many cats have benefited from treatment with NSAIDs for months and sometimes years. The most commonly used drug for this purpose is oral meloxicam (authors' personal experience) although this is off-label use of the product. In our opinion it is important to reduce the dose to the lowest level that produces the desired result. For example, in cats with degenerative joint disease, sufficient comfort may be achieved with as little as 0.025 mg kg^{-1} every other or every third day. There are no established guidelines for type or frequency of testing that should be performed in cats receiving long-term therapy. However, a thorough physical examination should be performed and a complete blood count and chemistry panel (at least BUN, creatinine, total plasma proteins, albumin, liver enzymes, and electrolytes) evaluated prior to a course of any NSAID. Elevations in BUN and creatinine occur relatively late in renal disease, therefore screening urine for protein has been recommended as this can detect disease earlier. Several tests including urine dipsticks, microalbuminuria assays, and sulfosalicylic acid precipitation tests are available. Any positive test should be followed by measurement of urine protein:creatinine

ratio to assess the patient fully. Baseline evaluation should be repeated 1 week after the start of treatment. The implications of increased liver enzymes at any point before or during treatment are difficult to determine. A moderate increase may be expected with any chronic drug administration, and, as previously stated, liver enzymes are not a good measure of hepatic function. If there are concerns about hepatic function, liver function tests should be conducted. Suggested intervals for repeating blood work and urine analysis are arbitrary. However, every 1–2 months is suggested for cats, as many of these are likely to be older and in an age range where chronic renal failure is most likely to occur. Early detection of problems will allow quicker intervention, and hopefully resolution, or at least stabilization of the patient. In some cases, after discussion with the owner, it may be decided that the benefits to the cat's welfare of continuing therapy with NSAIDs outweigh the potential risks and this reinforces the importance of communication with owners and the value of informed consent.

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