

RATIONAL USE and AVOIDANCE OF ABUSE of NSAIDs – Georgina Child BVSc DACVIM (Neurology)

Non steroidal anti-inflammatory drugs or analgesics (NSAIDs or NSAIDs) are used extensively in both human and veterinary medicine and can be very effective in managing both acute and chronic pain in animals. However, adverse effects of these drugs can be life threatening and due diligence by the prescribing veterinarian in patient selection, drug and dose selection and monitoring is always indicated. Advice to the owners of treated animals regarding potential adverse effects and the clinical signs that should prompt reassessment and discontinuing drug use should always be given.

It is thought dogs and cats are more susceptible to the adverse effects of NSAIDs than people and there are species differences (humans, dogs, cats, horses and ruminants) both in the apparent effectiveness of different NSAIDs and in the adverse effects seen. The greater range of NSAIDs available and the greater tendency to prescribe these drugs has the potential to increase the number of adverse effects reported. The increased prescription rate especially in small animals is multifactorial: an increased awareness and demand to treat both acute and chronic pain in animals both by veterinarians and their owners; the increased life expectancy of pets with associated increased incidence of chronic conditions such as osteoarthritis; and the formulation and promotion of new NSAIDs by pharmaceutical companies.

NSAIDs collectively are among the most frequently prescribed medications in small animal practice. The availability of multiple NSAIDs has also increased the likelihood that patients receive multiple drugs concurrently or in a short period of time.

Unfortunately complaints by the public to the Veterinary Practitioners Board frequently include those regarding the treatment of pet animals that have had an adverse outcome, including death, where NSAIDs have been administered in the course of treatment. Recurring themes in the case histories of these animals are one or more of the following: a diagnosis as to the cause of the animal's illness had not been made but NSAIDs given as the animal was possibly painful (clients understand and empathise with "pain relief"); a dose significantly above the recommended dose of the NSAID was given on one or more occasions ("more is better" or "if some didn't work more might"); NSAIDs and corticosteroids were given concurrently or within a short period of time (close temporal association); treatment with different NSAIDs ("switching drugs") was given within a short period of time and that change may have been prompted by either lack of effect or gastrointestinal signs associated with first drug; affected patients were often old with significant risk factors (either known or not appropriately investigated) that would influence drug use or dose.

NSAIDs have analgesic, anti-inflammatory and antipyretic actions by inhibiting the production of prostaglandins (and leukotrienes) primarily by inhibiting the action of cyclo-oxygenase (COX) enzymes. Two distinct COX isoforms (COX1 and COX2) have been identified and both are responsible for the production of prostaglandins (PGs), prostacyclin and thromboxanes from arachidonic acid (AA) in phospholipid cell membranes. A third form COX3 may have a role in the CNS control of pain. COX1 converts AA to a

wide variety of prostaglandins, thromboxane and prostacyclin. COX2 activity produces a narrower spectrum of prostaglandins specifically PGE2 and prostacyclin.

Prostaglandins are important physiologically in vascular homeostasis, gastroprotection (gastric mucosal protection from gastric acid damage), renal development and blood flow, blood clotting, reproduction, bone metabolism, wound healing and immune responses. PGs are also involved in pathophysiologic processes including pain and inflammation and cancer progression and it is these processes that are targeted by NSAIDs however “side effects” are the result of interference with the important normal physiologic mechanisms mediated by PGs.

COX1 has long been considered to be most involved in physiologic functions including the cytoprotective effects on gastric mucosa, normal platelet function and maintenance of renal perfusion. COX 2 also appears to contribute to some extent to homeostasis especially in healing damaged GIT mucosa but COX2 is predominantly inducible and production is significantly increased during inflammation. COX1 expression however also has a role in the inflammatory response.

NSAIDs may inhibit COX1 and COX2 (eg aspirin, phenylbutazone, flunixin, tolfenamic acid, ketaprofen) or have a greater propensity to suppress COX2 than COX1 – so called COX2 preferential or sparing NSAIDs (eg carprofen, meloxicam) or have negligible effect on COX 1 (the so called COX 2 selective NSAIDs eg firocoxib, deracoxib robenocoxib mavacoxib). COX1 inhibitors may result in better pain relief in some species eg phenylbutazone in horses.

COX1 inhibition has been implicated in the cause of most NSAID side effects - especially gastric ulceration and platelet dysfunction. However COX2 preferential

or selective drugs developed to reduce some of these side effects still cause adverse events in people including renal failure, thromboembolic disease and gastric ulceration. This is also true in small animals.

The primary indication for NSAIDs in veterinary medicine is in the management of pain. The efficacy of many NSAIDs can be better than or equal to mu agonist opioids (such as morphine) and butorphanol or buprenorphine in managing postoperative pain – both orthopaedic and soft tissue. NSAIDs appear to act synergistically with opioids and may allow a reduction in the amount of opioid analgesia required in managing mild to moderate but not severe pain states (Mathews 2010). The duration (24 hours or longer) and efficacy makes them ideal for treating acute and chronic pain - predominantly post operative pain and pain associated with osteoarthritis. NSAIDs are metabolised in the liver and excreted predominantly by the kidneys in urine (some enterohepatic circulation with some drugs).

NSAIDs were first licensed in the treatment of osteoarthritis (OA) in dogs and cats. NSAIDs are also approved for the treatment of postoperative pain (mild to moderate) with effectiveness best in orthopaedic and selected soft tissue surgeries, especially those associated with significant soft tissue trauma or inflammation. The administration of NSAIDs prior to surgery so as to achieve adequate drug levels in the immediate postoperative period remains controversial primarily as untoward events during surgery or immediately post operatively that may increase the risk of adverse drug effects, such as hypotension, cannot be predicted preoperatively. An approach by some surgeons is to give NSAID 30-45 mins prior to the end of surgery. If given post operatively another

analgesic (opioid) may be given to provide analgesia in the approx 45 min period to onset of action of the NSAID. In studies looking at adverse events associated with preoperative administration of NSAIDs where intraoperative fluids were given and patient monitoring conducted adverse events did occur but were rare. Generally patients in these studies were <10 years of age, in good health and undergoing elective procedures.

Higher NSAID doses are recommended in the treatment of perioperative pain and the prescribed doses and the dosing interval and period of time that higher doses are prescribed for each drug varies from 1- 7 days. **Parenteral administration of an NSAID is recommended at a higher dose once only for the majority of drugs to be followed by oral administration.** The dose given should be tapered as pain reduces (usually within 1-3 days). NSAIDs are absorbed rapidly orally and peak concentrations reached within 2-4 hours and NSAIDs should be given orally when animals are able to eat.

For animals presented with painful conditions such as minor soft tissue trauma, inflammation or musculoskeletal pain the same recommendations are made. A higher dose is advised once only and the subsequent dose tapered depending on the drug used and given orally.

Various NSAIDs are also approved for the long term treatment of OA in dogs and some have been approved for long term use in cats (not in all countries). Recommendations are not to give above the approved dose for the particular drug and to give the lowest dose that is efficacious which may be significantly less than the recommended dose or at a longer dosing interval than recommended for shorter term use - this applies especially in cats. Guidelines on the long term use of NSAIDs in cats are available. A recent

review of the literature on NSAID drug use in dogs assessing the efficacy and safety of NSAIDs (Innes 2010) in the treatment of OA shows the balance of evidence supports long term use for increased clinical effect and that long term use was not associated with a reduction in safety. However “robust data on the safety of long term NSAID use was not available in a large population of dogs”. No specific studies in geriatric dogs or those with compromised renal or hepatic function.

In small animals GIT and renal toxicity are the most common adverse effects of NSAID use.

Both COX1 and COX2 are important in maintaining renal function. PGs normally act to increase blood flow during times of reduced renal perfusion. **Any haemodynamic compromise** such as dehydration; hypotension during anaesthesia or haemorrhage during surgery; hypotension or haemodynamic instability as result of trauma, cardiac disease or severe illness and preexisting renal disease all significantly increase the risk of ischaemic renal injury and renal failure in association with NSAID administration. **This risk applies to use in the short term treatment of acute pain (surgical or non surgical) and in the longer term treatment of animals with chronic osteoarthritis especially those with concurrent disease** (often cardiac or renal). Administration of diuretics or other nephrotoxic drugs may increase renal toxicity of NSAIDs.

Toxicity is increased in dogs and cats with hepatic dysfunction largely due to reduced metabolism increasing the drug half life and increasing drug concentration with repeated dosing. Large NSAID overdose also causes hepatotoxicity. Rare acute hepatotoxicity has been reported after NSAID administration at approved

doses. In cats the potential for toxicity is higher with NSAIDs due to limited ability to glucuronidate NSAIDs resulting in prolonged duration of the drug. For example, in cats carprofen has double the mean half life of that in dogs and the range is highly variable (9-49 hours). Daily dosing in cats risks drug accumulation and the duration of efficacy is difficult to predict. It is approved for use in cats once only for surgical pain.

Gastric mucosal and duodenal erosion has been reported with most NSAIDs in both research studies and clinical studies. There may be some local gastric effects in some animals with oral administration but **the risk of adverse effects on the gastric and intestinal mucosa of NSAIDs is not reduced by parenteral administration.** Stress (any cause) may increase risk of GIT ulceration.

While COX2 preferential and selective NSAIDs are promoted as causing less GIT adverse effects than non selective NSAIDs all NSAIDs have the potential to cause GIT adverse effects. A recent case study (Lascelles 2005) reported 29 dogs with gastrointestinal perforation associated with administration of a selective COX2 inhibitor (deracoxib) in a 10 month period (2002-2003). Approximately half of the cases were dogs being treated for chronic pain associated with orthopaedic disease (all but two for osteoarthritis). The remainder had been treated for acute perioperative pain associated with orthopaedic or soft tissue surgery. Twenty of the affected dogs died or were euthanased due to gastric, pyloric or duodenal perforation. 55% of dogs reported had been given the NSAID at a higher than recommended dose and 59% had received another NSAID or a corticosteroid within

24 hours of deracoxib administration. In all, 90% had either received a higher than recommended dose and/or had received another NSAID or corticosteroid in close temporal association. The first clinical signs seen in dogs with GIT perforation were vomiting and generalized pain. This study specifically looked at dogs treated with deracoxib as information on affected dogs was obtained from the pharmacovigilance database of the drug company manufacturing this NSAID. **The risks associated with administration are likely not to be confined to this particular COX2 selective NSAID. Duodenal ulceration and perforation has also been reported associated with meloxicam.**

Caution is warranted with administration of NSAIDs presurgically for oral procedures including dentistry. COX1 inhibition reduces the formation of thromboxane (important in platelet activation and vasoconstriction) and in combination with fibrinolytic activators in saliva and the oral cavity predisposes to haemorrhage. It is recommended administration be delayed until surgical haemorrhage is no longer a risk.

Prolongation of bleeding times can occur after administration of any NSAID but is more severe with those which bind irreversibly to COX such as aspirin and phenylbutazone as the effect persists for the life of the platelet. NSAIDs should not be given to animals with a known coagulopathy.

Etodolac use has been associated with development of KCS (average duration of administration 8-9 months).

Acute hypersensitivity may be seen rarely with any NSAID and these drugs should not be used in animals if there is a previous history of an adverse event.

Recommendations for use of NSAIDs

1. Appropriate Indication for use

The indications for use of NSAIDs are relief of mild to moderate pain associated with osteoarthritis and other musculoskeletal disease, soft tissue inflammation or injury and post operatively after orthopaedic and some soft tissue surgeries eg ovariohysterectomy. NSAIDs may also be of benefit in the treatment of pain associated with some cancers.

For use in non surgical conditions it is important that a cause of pain be established and NSAIDs determined to be the most appropriate drug indicated. Not all animals that are unwell are painful. NSAIDs should not be used as a generic “anti-inflammatory” or as an antipyretic without a diagnosis as to the cause. NSAID use may compromise and delay treatment that is appropriate (including antibiotics, corticosteroids, exercise restriction or surgery). Diseases that are immune mediated for example polyarthritis, corticosteroid responsive meningitis, granulomatous meningoencephalomyelitis require treatment with corticosteroids. Pyrexia may be seen in animals with infection, immune mediated disease and neoplasia and the underlying cause should be treated rather than the fever.

NSAIDs should not be used in any animals with any neurologic signs (cerebral, spinal or peripheral nerve) until a most probable or definitive diagnosis has been made as treatment with corticosteroids may be indicated or surgical treatment may be required. NSAIDs may be indicated in animals with spinal pain without neurologic abnormalities where IV disc extrusion/protrusion is the most likely cause but cage confinement/exercise restriction is more important and use may compromise treatment

if neurologic deterioration occurs. Animals with acute spinal cord injury (including IV disc extrusion) have a known increased risk of GIT ulceration that may be independent of any NSAID or corticosteroid use.

Analgesics other than NSAIDs are indicated in animals where a most probable or definitive diagnosis has not been made.

Analgesics other than NSAIDs are indicated in animals with severe pain.

2. Patient selection

NSAIDs should not be used in those animals that are haemodynamically unstable (ie any cause of hypotension). This includes all major trauma cases (these animals may also have high levels of endogenous corticosteroids), brain trauma, acute haemorrhage of any origin, major surgical cases, animals that are dehydrated or have evidence of systemic illness (eg pancreatitis, sepsis, disseminated neoplasia, DIC).

Use in surgical patients (including dentistry) generally should be restricted to patients < 10 years of age that have been in good health and are having elective procedures (not emergency). For treatment of non surgical pain the same general criteria apply (<10 years of age and in good health otherwise).

NSAIDs should not be used in animals with acute renal insufficiency or hepatic disease, suspected coagulopathy or cardiac failure (low “effective circulating volume”).

In older animals with chronic pain associated with osteoarthritis where NSAIDs are indicated doses should be reduced and/or dosing intervals increased in animals with preexisting renal, hepatic, or cardiac disease.

NSAIDs should not be used in animals with gastrointestinal disease or those that are inappetant.

Assessment of patients by CBC, biochemistry profile and urinalysis prior to administration of NSAIDs is recommended in all surgical patients. Assessment should also be extended to any non surgical patients treated for any length of time that are > 5 years of age, or at any age if there are any significant historical or clinical findings (including variation in behaviour, exercise tolerance, water or food intake, body condition, body temperature, HR, respiratory disease etc).

NSAIDs should not be used in animals with known or suspected cortisol excess (hyperadrenocorticism, stress).

For anaesthetised animals (for any reason) animals should be well hydrated and have no condition that affects gut, renal or hepatic blood flow. Intravenous fluids should be administered to maintain adequate blood pressure and ensure adequate renal blood flow. If this cannot be guaranteed, NSAIDs should not be given until the postoperative period when these criteria have been met.

NSAIDs should not be given to neonates (<6 weeks of age) and some drugs may not be approved for very young animals (firocoxib labeled for use in dogs over 10 weeks of age). NSAIDs may have an adverse effect on ovulation, implantation, the female reproductive tract and fetal circulation and should be avoided in bitches during oestrus, post mating, pregnancy and lactation.

3. Dosage

The dose of any NSAID given should be as approved for the individual drug for the clinical indication Higher doses are recommended for post operative pain than other indications. **Higher than recommended doses or administration for longer periods of time than approved for any indication should not be given as higher doses are known to be associated**

with a higher incidence of adverse side effects. Higher doses should be given for the minimum time as clinically indicated and/or approved.

There is no indication for doses higher than approved doses. Use NSAIDs at the doses and for a time period that does not exceed those labeled or referenced in veterinary texts for both the management of acute pain and in the treatment of chronic pain associate with OA. Approved doses for various drugs are different and should be heeded. **Most injectable NSAIDs are labeled for use once. Repeated parenteral administration should not be given if animals are inappetant.** Most NSAIDs should ideally be administered with food (to ensure animal is eating) however robenacoxib is labeled to be given on an empty stomach or with a small amount of food. **All orally administered NSAIDs should be withheld if animals are inappetant.**

Lack of response to therapy should prompt investigation of the cause of pain (further diagnostics) and instituting other treatment depending on the cause - for example surgery, appropriate medical therapy or adjunctive treatments for OA including weight control, exercise restriction physiotherapy etc.

For both acute and chronic use of NSAIDs reduction of the given dose should be made based on clinical response. The dose required may be significantly less than the recommended dose or at a longer dosing interval. In older animals and cats doses that are effective can be very much lower than the labeled dose and every other day dosing may be adequate to maintain adequate drug levels due to reduced metabolism and drug excretion which may result in accumulation of the drug and much longer duration of action (see referenced guidelines treated long term for osteoarthritis in cats).

Dosage should be made on ideal body weight as overdosage can occur in obese animals.

4. Use of multiple NSAIDs and /or Corticosteroids

The incidence of adverse effects is increased in animals that have received multiple NSAIDs within a short period of time or have received corticosteroids either concurrently or within a short period of time of a NSAID.

The half life of NSAIDs varies between drugs and in individual animals and concurrent use of different drugs increases possible adverse effects. **A safe “wash out” period has not been determined for any NSAID.** It has been recommended that switching between NSAIDs be done cautiously and the cumulative effects of all NSAIDs being administered should be considered. In one study a change to a second NSAID was not associated with a significant increase in adverse effects when an interval of 1-7 days (majority > 2days) was allowed between treatments. A period of 24 hours is a minimum and dependent on drug or drugs used.

The major reported adverse effects of NSAIDs are gastrointestinal with vomiting and inappetance the predominant clinical signs. Vomiting and inappetance should not be ignored. Local gastric irritation may be a cause of GIT signs but this is indistinguishable from a more sinister cause such as ulceration, GIT perforation, renal failure or hepatotoxicity. **Any “switch” to another NSAID should only be made after an appropriate time for clearance of the initial NSAID and it has been determined that the animal is eating and in good health.**

There is potential for a significant increase in GIT pathology when an “**intolerance**” (vomiting or inappetance) is a reason prompting a change in drug therapy (rather than efficacy) as GIT clinical signs may reflect existing GIT pathology and GIT ulceration is likely to continue if the patient is switched to another drug.

Corticosteroids are known to increase gastric erosion in dogs receiving NSAIDs and no information is available on the preferred or safe wash out period between corticosteroids and NSAIDs. NSAIDs are heavily protein bound and may displace other protein bound drugs including corticosteroids and potentiate their effects. Concurrent or close temporal administration with corticosteroids increases the risk of gastric pathology. **At least 2 days “washout” in dogs has been recommended between the use of NSAIDs and corticosteroids however this is arbitrary – it may not be long enough and adverse cumulative effects may be dependent on the time animals have been treated, individual drugs, the doses given and other factors including the underlying disease, stress etc.**

Three to five days between drug treatments has been recommended in cats and >7 days if aspirin has been used.

NSAIDs may also affect the efficacy and concentration of other drugs given that are protein bound including ACE inhibitors.

5. Monitoring

Advice re the potential adverse effects of NSAIDs should be given to the owners of all animals receiving NSAIDs. Any clinical signs of unwellness including inappetance, vomiting, diarrhoea, melaena and/or pain should prompt reassessment of both the original diagnosis and possible adverse drug

effect in both outpatient and post surgical patients.

As a group NSAIDs are not reversible and it is imperative that general health be considered prior to prescribing NSAIDs – this may include baseline CBC, biochem and UA in animals, especially older animals, where longer term therapy is instituted and where long acting NSAIDs (mavacoxib) are given. A concern with the administration of a long acting NSAID is that alteration of PG activity may be seen for up to 2 months after a single tablet and treatment may complicate other treatment or health in unforeseen situations (trauma, illness).

Adverse effects associated with any NSAID use can be seen in both therapeutic and overdose.

All animals receiving NSAIDs chronically should be monitored for gastrointestinal abnormality including melaena. Physical examination, PCV, hepatic and renal function should be monitored periodically in animals on long term NSAID therapy.

Ongoing monitoring for early signs of toxicity is imperative as adverse drug effects are typically treatable if recognised early, the NSAID is discontinued and appropriate supportive treatment is given.

Other recommendations

- Doses should be prescribed and measured accurately.
- Large animal preparations should not be used for small animals as small variations in dose may result in a relatively large overdose. Similarly appropriate preparations should be used for cats and small dogs.
- **Flavoured chewable tablets are attractive to animals and small children and must be dispensed in child proof containers and owners advised to store securely to prevent accidental poisoning.**

References

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