AVERTING RISKS ASSOCIATED WITH UTILISING SMALL ANIMAL NSAIDS

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Catherine F Le Bars explains that despite being perceived as the “safe” option, the use of NSAIDs requires care to avoid problems such as gastrointestinal irritation and impaired renal function.

NSAIDs are a group of agents with antipyretic, analgesic and anti-inflammatory properties. A number of NSAIDs are licensed for use in veterinary medicine for the management of both acute and chronic pain.

However, although NSAIDs are often considered “safer” than other forms of analgesia, their use is not without risk.

This article will focus on the potential adverse effects associated with NSAIDs and recommendations for their use.

Mechanism of action

NSAIDs fall into various classes, depending on which enzymatic pathways of the arachidonic acid cascade they inhibit. In essence, they inhibit the breakdown of arachidonic acid by cyclooxygenase (COX) and/or lipoxygenase (LOX) into inflammatory mediators called eicosanoids, which have roles in inflammation and pain transmission, both at local and central levels.

COX products include the prostaglandins PGE2 and PGF2µ, prostacyclin (PGI2) and thromboxane
LOX products include leukotrienes, such as the chemoattractant LTB4, and bronchoconstrictors (LTC4 and LTD4). The product formed depends on a number of factors, including the nature of the stimulus and the cell type being stimulated.

For some time, it has been recognised that there are two isoforms of the COX enzyme: COX-1 and COX-2. COX-3 has been identified in the brain, although the significance of this isoenzyme is, as yet, unclear.

COX-1 is present constitutively in most tissues, including the liver, kidneys, platelets and the gastric mucosa. COX-1-derived products help maintain the integrity of gastric mucosa, preserve hepatic and renal blood flow (especially in the presence of hypotensive and/or hypovolaemic states), and aid normal platelet aggregation.

COX-2 is inducible in a variety of cells, such as monocytes, macrophages, neutrophils, endothelium, articular chondrocytes, synovial fibroblasts, peripheral nerves and the central nervous system (CNS). It is also present constitutively within the CNS and renal vasculature, as well as synovial chondrocytes in some species. COX-2-derived products are important mediators of gastrointestinal, cardiovascular and renal homoeostasis.

Traditionally, it was believed that NSAIDs provided analgesia by the inhibition of peripheral COX activity and a resultant antiinflammatory effect.

However, it is now thought that the majority of their analgesic effects occur as a result of COX activity (specifically COX-2) inhibition centrally.

**Side effects**

At therapeutic doses, NSAIDs cause few side effects, although cats appear more susceptible to toxicities because they metabolise these drugs more slowly than dogs. However, at higher doses or with inappropriate use, NSAIDs can cause serious and potentially life-threatening problems.

Adverse effects associated with the use of NSAIDs are usually related to their action on the inhibition of certain prostaglandins. The most common and serious effects are gastrointestinal ulceration and/or irritation, and impaired renal function. With the exception of aspirin, there are few effects on clotting mechanisms and bleeding times.

Prostanoids, in particular, and COX-2-derived prostaglandins (such as PGE2), have a minor role in healthy kidneys, but can cause arteriolar dilation in response to vasoconstriction caused by angiotensin-2, norepinephrine and vasopressin, thus preserving renal blood flow and protecting renal function.
Inhibition of these and other prostanoids may result in a reduced glomerular filtration rate and compromised renal function during times of hypotension or hypovolaemia.

Prostaglandins in the gastrointestinal system promote the secretion of protective mucus, preserve mucosal blood flow and help modulate gastric acid secretion. Inhibition of these protective prostaglandins may result in severe damage to, and integrity loss of, the gastrointestinal mucosa, manifesting as vomiting, haematemesis or melaena. The NSAID itself may also cause direct irritation to the gastric mucosa. Most of these effects are observed after chronic use, but may sometimes occur shortly after initiating treatment.

Although COX-2 inhibitors generally cause less gastrointestinal ulceration than non-selective NSAIDs, gastrointestinal signs still occur in approximately 10 per cent of patients. When ulceration is suspected, therapy should be discontinued since continued COX-2 inhibition can prevent angiogenesis and decrease the rate of ulcer healing.

Prostanoid production may also play a role in maintaining blood flow to the liver. Hepatotoxicity caused by NSAIDs is generally considered idiosyncratic. The administration of carprofen has been associated with an idiosyncratic, cytotoxic hepatocellular reaction. Clinical signs include anorexia, vomiting and icterus. Serum biochemistry may demonstrate elevated liver enzymes. The majority of affected dogs recover after NSAID withdrawal and supportive care.

NSAIDs such as aspirin inhibit platelet function with their effects on TxA2 production, a COX-1-mediated event. If bleeding is anticipated or present, the use of these agents should be avoided. COX-2 inhibitors should not affect haemostasis when given pre-operatively, but there is the potential for the generation of a prothrombotic state with the use of COX-2 inhibitors, due to inhibition of PGI2 production. This may be of concern in animals at risk from a hypercoagulable state (such as hyperadrenocorticism).

**Specific NSAIDs and their usage**

NSAIDs can be grouped according to their influence on particular pathways of the arachidonic pathway.

- **Non-selective COX inhibitors**
  - Aspirin (acetylsalicylic acid) is available as an oral medication for the alleviation of mild pain and the prevention of arterial thromboembolism in dogs and cats. It is not licensed for veterinary use in the UK.
  - Piroxicam is available as an oral and injectable medication for the treatment of certain tumours expressing COX receptors (transitional cell carcinomas in the bladder, prostatic carcinoma and colonic-rectal carcinoma). It is not licensed for this use in the UK.
– Flunixin meglumine is available as an oral and injectable medication for the treatment of pain caused by acute and chronic musculoskeletal disease in horses.

– Phenylbutazone is available as an oral and injectable medication for the treatment of pain caused by acute and chronic musculoskeletal disease in horses.

– Ketoprofen is available as an oral and injectable medication for the treatment of pain in dogs, cats, horses, cattle and pigs.

– Tepoxalin (COX and 5-LOX pathway inhibitor) is available as an oral medication for the treatment of pain caused by acute and chronic musculoskeletal disease in dogs.

– Tolfenamic acid is available as an injectable medication for the alleviation of postoperative pain in dogs and cats, and painful conditions in cattle and pigs. It is also available in oral form for the treatment of pyrexic conditions in cats (especially upper respiratory tract disease) and chronic locomotor disease in dogs.

• Preferential COX-2 inhibitors

– Meloxicam is available as an oral and injectable medication for the alleviation of postoperative pain, and the treatment of pain caused by acute and chronic musculoskeletal disease in dogs and cats.

– Carprofen is available as an injectable medication for the alleviation of postoperative pain in dogs and cats, and as an oral medication for the treatment of pain caused by acute and chronic musculoskeletal disease in dogs.

– Deracoxib is not licensed for use in the UK.

– Firocoxib is available as an oral medication for the treatment of pain caused by acute and chronic musculoskeletal disease in dogs, and is not licensed for perioperative use.

Using NSAIDs perioperatively

The perception and processing of pain involves several components. In the presence of a noxious stimulus, peripheral nociceptors transmit the signal to the spinal cord or cranial nerve nuclei. Signals are then processed in the spinal cord or brainstem before their transmission to supraspinal structures. After further processing at supraspinal sites, the signal produces conscious perception of pain.

There is also a phenomenon where a painful stimulus can cause sensitisation of the CNS at peripheral and/or central levels. Once CNS sensitisation has occurred, stimuli may elicit an
exaggerated or inappropriate pain response. At this point, the animal appears to feel more pain, and analgesics become less effective at a given dose. When CNS sensitisation was first recognised, the theory of “pre-emptive analgesia”, and the practice of administrating analgesics pre-operatively to decrease the severity of postoperative pain gained acceptance.

Currently, the emphasis has shifted more towards the use of multimodal strategies for controlling postoperative pain, rather than focusing on the administration of a single agent (such as NSAIDs) pre-operatively.

Clinical evidence supports the perioperative use of licensed COX-2-selective NSAIDs to healthy animals undergoing routine procedures. However, the similar administration of NSAIDs to other groups of animals should be decided on a case-by-case basis. It should be stressed that the benefits of preemptive analgesia using NSAIDs are overshadowed by the risks of serious side effects, such as renal failure, if NSAIDs are used inappropriately.

In summary, vets should:

• only administer NSAIDs licensed for pre-operative administration in the perioperative period;

• only administer an NSAID pre-operatively to healthy animals undergoing routine procedures when hypotension is not anticipated, and

• not give NSAIDs to patients exhibiting signs of shock and/or hypotension until this has been corrected.

General advice

The selection of an NSAID should be based on patient requirements and that particular drug’s known safety and efficacy. Animals may vary in their response to different NSAIDs, with one drug appearing to be more effective than another in an individual. If a poor response to one NSAID is evident, it may be reasonable to trial treatment with a different NSAID. Do not use NSAIDs in combination with other NSAIDs or steroids. Add an analgesic from another drug class, such as the opioids, if the analgesic effect from an NSAID alone is insufficient.

If undesirable side effects occur, stop the NSAID and leave sufficient time for any tissue pathology to recover before initiating treatment with a different NSAID. Be aware of which NSAIDs are likely to aggravate the condition, such as gastric ulceration, and avoid using NSAIDs in patients with underlying renal, hepatic or gastrointestinal disease. If an underlying condition is suspected or the animal is old, investigate before prescribing an NSAID – the classic example is the 12-year-old dog needing “something” for its “stiff legs”. The decision on whether to treat this animal with NSAIDs should be based on the history, clinical examination and ancillary tests, such as serum biochemistry and haematology.
The effects of NSAIDs on renal perfusion parameters have been well documented. Avoid administering NSAIDs to animals that are either hypovolaemic or hypotensive, or those at risk of developing either of those states. NSAID use in these patients may lead to an irreversible deterioration in renal function.

Gastrointestinal toxicity is an extremely common side effect associated with NSAIDs, and a number of risk factors for gastrointestinal toxicity have been identified in dogs. Animals with a history of gastrointestinal ulceration or impaired hepatic or renal function, and older animals, are all at an increased risk of gastrointestinal toxicity following NSAID administration.

**Conclusion**

NSAIDs have proven valuable in the management of acute and chronic pain in animals, either singly or as part of a multimodal strategy. Although in the main safe and effective, NSAIDs should be used with care, and animals receiving medication should be monitored closely for the appearance of adverse effects. Should problems associated with the use of one NSAID occur, it might be possible to use a different NSAID after allowing for a suitable recovery period.

- References are available by request to the editor. For more published *Veterinary Times* articles on NSAIDs, visit [www.vetsonline.com](http://www.vetsonline.com)
Left: NSAIDs should be used with caution in older animals, as many of these patients have underlying diseases – which may increase the risk of adverse effects. The decision on whether to use NSAIDs should be based on the history, clinical examination and ancillary tests, such as serum biochemistry and haematology.
Right: only NSAIDs licensed for pre-operative use should be administered perioperatively, and then only to healthy animals undergoing routine procedures.
Cats and younger animals show a reduced ability to metabolise NSAIDs. Therefore, doses should be adjusted accordingly and these patients should be closely monitored.
Few NSAIDs are licensed for use in small mammals. However, many of those used in dogs and cats show similar levels of safety and efficacy in other species.