NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN DOMESTIC ANIMALS: II DISPOSITION AND CLINICAL INDICATIONS

G E SWAN*, C R SHORT** and U H TUBBESING***

ABSTRACT
Most non-steroidal anti-inflammatory drugs (NSAID's) have similar absorption and disposition characteristics. Absorption after oral administration is good, extensive plasma protein binding results in a small volume of distribution, and excretion of metabolites occurs mainly in the urine after hepatic biotransformation of the active drug. The main clinical indications for use of NSAID's are anti-inflammatory, analgesic and antipyretic, and an increasing list of new indications are continually being found. The disposition, pharmacokinetics and clinical indications of non-steroidal anti-inflammatory drugs in domestic animals are reviewed.

Key words: Non-steroidal anti-inflammatory drugs, disposition, clinical indications, domestic animals


INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAID's) have a wide range of pharmacological effects that are used effectively for the treatment of a number of clinical conditions. New uses which exploit their analgesic and anti-inflammatory effects are continually being explored. Additionally, new agents are being produced which are less toxic, especially with regard to the potential for producing gastrointestinal ulceration, and are therefore potentially more useful in situations requiring administration for periods longer than a few days. The purpose of this paper is to review the absorption, disposition, pharmacokinetics and therapeutic indication of the non-steroidal anti-inflammatory drugs in domestic animals.

ABSORPTION AND DISPOSITION
With the exception of the para-aminophenols, NSAID's are weak organic acids with pKa values between 3.0 and 5.3. This characteristic is a major determinant of absorption and distribution patterns of these drugs. It may explain why these agents accumulate in an area of inflammation and produce their effects longer than would be predicted from their plasma decay.

In general, acidic NSAID's are well absorbed from the gastrointestinal tract. Although gastric absorption is favoured in monogastric animals due to a favourable pKa/pH relationship, absorption still occurs mostly from the upper small intestine because of the much larger absorptive area.

It has been shown that NSAID's absorption following per os administration to horses is markedly influenced by food in the digestive tract. This was first demonstrated for phenylbutazone* and more recently for flunixin*. Bioavailability was not reduced for either drug, but it delayed the gastrointestinal absorption of phenylbutazone and produced a biphasic absorption of flunixin. The delayed and protracted absorption could affect clinical efficacy.

Numerous NSAID's have been formulated for topical use**. The pharmacokinetics of several of these drugs in man have been recently reviewed**. In general, topical administration of NSAID's results in slower drug absorption into the systemic circulation, lower plasma concentrations, lower bioavailability (about 5%), prolonged plasma elimination half-lives and measurable drug levels in the tissues and synovial fluids in comparison to oral administration. Similar studies have not been reported in domestic animals.

Percutaneous absorption of NSAID's is dependent on the lipid solubility of the compound as well as the vehicle used***. Results of comparative skin penetration investigations among various NSAID's indicate a parabolic relationship between oil/water partition coefficients and percutaneous absorption. The optimal values for the n-octanol/water coefficient is between 2 and 2.5. Alclofenac, ketoprofen and ibuprofen were the closest to these values. Vehicles used for topical NSAID's include creams, gel and ointments. Increased penetration is achieved by minimising the particle size, use of volatile solvents e.g. isopropanol and the use of enhancers e.g. dimethylsulphoxide and hydro-
The volume of distribution of these drugs is normally quite small because of extensive plasmprotein binding. Most of these agents are more than 99% bound to albumin in plasma. Nevertheless, these drugs are distributed throughout the extracellular space and in transcgelular fluids, such as synovial fluid. The concentrations are low in comparison to plasma, but this does not lessen their effectiveness.

Many of the available NSAID’s are racemates - that is, they are an even mixture of optical isomers. This is especially true for 2-aryl propionic acids, the commercial products of which are all racemates, except for naproxen. The S(+) form has generally been found to be much more effective as an inhibitor of eicosanoid synthesis than the R(-) antipode. The effectiveness of the drug could be dependent on differential distribution and elimination of the enantiomers. In this regard, it has been shown in laboratory species, that some arylpropionic acids undergo chiral inversion from the R(-) to S (+) enantiomer. Lee and co-workers showed this not to be the case for carprofen in the horse, where 24 and 48 h after administration, 82% of the drug in plasma was in the R(-) form. Ketoprofen, however, was demonstrated to change in the opposite direction in the same species. In the case of carprofen, this conversion does not appear to have a negative impact, as it is only a weak inhibitor of cyclo-oxygenase, which, nevertheless, retains a potent anti-oedema effect by some unknown action. However, for other chiral agents, such as ketoprofen, this change in predominant form could certainly have an impact on clinical effectiveness. The concentration of the more active enantiomer at its site of action, in turn, is a product of its specific affinity for plasma albumin, its rate of metabolism, its ability to penetrate barrier-restricted tissues and its renal and/or biliary excretion, relative to the less active enantiomer. The disposition of specific isomers of chorialy active drugs is an area of active investigation and there are many questions to be answered.

Pharmacokinetic parameters have been described for phenylbutazone, aspirin, and flunixin, as well as for some of the newer agents being developed for veterinary use, including carprofen and ketoprofen, eltenac, miloxicam, piroxicam, tolfenamic acid and others. While there is very little work to date which profiles the kinetics of individual enantiomers of chiral drugs, there is substantial evidence to show that large species variations in the disposition of total drug. For example, aspirin has a half-life of about 1 h in the horse, 8.6 h in the dog and 21.8 h or longer in the cat. Likewise carprofen has a half-life of up to 21.9 h in the horse, 8 h in the dog and up to 57.8 h in cattle. Lees et al. have published a summary of species differences in the half-lives of NSAID’s. In contrast to elimination half-life, there is a high degree of consistency in volume of distribution for these agents. Distribution volumes range from approximately 0.15 - 0.30 l/kg for the different drugs, regardless of the species under consideration.

The duration of pharmacological effect of NSAID’s such as phenylbutazone, flunixin meglumine and miloxicam exceeds their biological half-life. This phenomenon has been explained as increased intracellular concentrations of acidic NSAID’s at locations where the pH of extracellular fluid decreases, such as may exist at sites of inflammation. Greater drug levels in sites of inflammation have also been attributed to increased blood flow, increased vascular permeability and increased protein passage into these sites. Most NSAID’s cross the blood-brain barrier poorly. Para-aminophenols, on the contrary, distribute fairly well into the central nervous system (CNS), where they appear to have their main effects viz. antipyresis and analgesia. It must be noted, however, that other NSAID’s, such as salicylic acid and dipyrone penetrate well enough to produce therapeutics effects.

Both hepatic metabolism and renal and/or biliary excretion are involved in terminating the action of NSAID’s. In some instances, the metabolites are themselves anti-inflammatory, analgesic and/or antiptetic. The metabolism of aspirin to salicylic acid and of phenylbutazone to oxygenphenthazone are excellent examples, and are additional causes of discrepancies between plasma concentrations of the parent drug and effect. Furthermore, metabolism may be chiralselective, the S(+) enantiomer being more or less favoured as a substrate, with the result again being a lack of correlation between total drug concentration and effect.

The kidneys are primarily responsible for excreting unchanged drug and metabolites. Elimination is largely a function of glomerular filtration and is normally slow, due to extensive plasma protein binding. Some NSAID’s also undergo active proximal tubular secretion, as has been demonstrated for phenylbutazone, but not flunixin meglumine. Urinary pH changes can theoretically cause substantial change in the rate of excretion of NSAID’s. It is probably interspecies variation in metabolism, however, which is primarily responsible for differences in plasma half-life. Non-renal excretory pathways may be important in some species, such as equines. Excretion in bile, for example, could enhance ulcerogenicity of NSAID’s by causing high concentrations in the small intestine. It is thought that duodenal reflux of prostaglandin synthetase inhibiting NSAID’s excreted in bile, may increase the occurrence of gastric ulcers in humans, and this rationale could apply to some domestic species as well.

**CLINICAL INDICATIONS**

**Anti-inflammatory**

NSAID’s are classically indicated for the treatment of many acute and chronic musculoskeletal inflammatory conditions, particularly in equine practice. Specific anti-inflammatory treatment may include osteoarthrosis, a variety of skeletal muscle and tendon inflammatory diseases, severe cellulitis associated with septic wounds, snakebites, tickbite necrosis and other inflammatory conditions affecting soft tissues. The major use of NSAID’s in small animals is musculoskeletal disorders, where the anti-inflammatory and analgesic properties are of benefit. The use of NSAID’s for anti-inflammatory purposes in osteoarthrosis, however, is controversial. Some of these agents e.g. aspirin, phenylbutazone, indomethacin, ibuprofen, and naproxen have been found to promote osteoarthrosis in genetically predisposed mice. Others, e.g. diclofenac may be chondroprotective. While the application of these findings to any domestic animal is tenuous, there is concern that proteoglycan synthesis in cartilage may be impaired, leading to degeneration, in the face of long-term therapy.
The classic signs of inflammation - erythema, swelling, heat and pain - are all suppressed by NSAID's. The first 3 are often poorly discernable in chronic inflammatory processes, so that effective therapy is usually expressed as pain relief in these situations e.g. degenerative joint disease, laminitis.

Since Vane in 1972 described that the anti-inflammatory potency of NSAID's was directly proportional to cyclo-oxygenase inhibiting capacity, the latter was taken as the mechanism of action of all of these drugs. The degree to which specific NSAID's inhibit distinct signs of inflammation, however, has recently been shown to vary. For example, carprofen and paracetamol are poor inhibitors of cyclo-oxygenase, but have demonstrated antipyretic, anti-oedematous and analgesic actions.

The anti-inflammatory drugs have seen wide application in ophthalmology, with NSAID's receiving increasing attention. In this regard, they have been applied topically for episcleritis, scleritis, cystoid macular oedema and uveitis. Following topical application they apparently do not inhibit re-epithelialisation of the cornea either by corneal epithelial cells or by conjunctival epithelial cells. Flunixin and phenylbutazone have also been administered systemically to control both inflammation and pain in non-ulcerative kerato-uveitis and corneal ulceration in horses.

Additional anti-inflammatory applications of NSAID's include topical use in the treatment of eczema, dermatitis and mild sun burns, and use in abdominal surgery to reduce the development of adhesions. NSAID's have been employed widely for reduction of adhesions, with ibuprofen, indomethacin, and oxyphenbutazone being studied most. Ibuprofen has been shown to be approximately equivalent to dexamethasone in reducing the fibroproliferative response to serosal abrasion in a laboratory species model. Unfortunately, controlled studies with phenylbutazone, flunixin or newer NSAID's are lacking.

**Analgesia**

As a general rule, opioid analgesics are used for acute and intense pain associated with severe trauma and certain surgical procedures. NSAID's are indicated more for the treatment of chronic and lower grade pain associated with joint and musculoskeletal disease, or colic in horses. The conventional view has been that the relief of pain results from reduction of inflammation. More recently, however, it has been shown that NSAID's may have a central component for pain relief. Malmberg & Yaksh have shown that NSAID's injected intrathecally attenuated the pain response in rats. They were further able to show a direct spinal action that partially blocked hyperalgesia induced by the activation of spinal glutamate and substance-P receptors. Jurna et al. have also shown that aspirin, salicylic acid and indomethacin administered intrathecally, depress C-fibre-evoked activity in rats. These findings demonstrate that the analgesic effects of NSAID's may be dissociated from their anti-inflammatory actions. There are also indications that NSAID-evoked analgesia is not necessarily mediated through cyclo-oxygenase inhibition. In this regard, it has been shown that paracetamol, carprofen, salicylic acid and R(-)-flurbiprofen, which are all practically devoid of prostaglandin synthesis inhibition in vitro, do exert analgesic activity in different models of pain and nociception. They therefore lack ulcerogenic potential for the gastro-intestinal tract while retaining analgesic properties. Of these 4 NSAID's, only carprofen has anti-inflammatory (anti-oedema) activity. All of these agents, and perhaps the pure R(-) enantiomers of other chiral NSAID's, offer the potential for pain relief with a much reduced risk of gastrointestinal ulceration.

There is currently a resurgence of interest in the NSAID's as analgesics in surgery because they do not produce sedation or ataxia and allow more rapid recovery from anaesthesia. The latter is especially important in horses, as it is desirable that they stand up soon after surgery has been completed. Post-operative pain is not primarily of inflammatory origin and thus also serves as a good model for studying the intrinsic analgesic effects of the NSAID's. When the use of carprofen, phenylbutazone and flunixin was compared in horses recovering from surgery, there were no differences in pain scores (analgesia) between the 3 drugs, but phenylbutazone had to be given more frequently than flunixin, with the dosing interval for carprofen being intermediate between the 2. However, those that received butorphanol during surgery, required less NSAID's than those that didn't receive it, implying that the analgesic effect of the opioid predominated, over that of the NSAID's. In contrast, however, carprofen was judged to produce analgesia equivalent to, and of longer duration than papaveretum (a morphine containing mixture of opium alkaloids) when used post-operatively in dogs. Carprofen has also been shown to be a more effective analgesic than flunixin when tested in horses using a model where heat is applied to the skin. Another new NSAID, eltenac, has been shown to be effective in relieving both pain and swelling, following castration of horses.

The systemic administration of analgesics is the most common means of treating colic in horses. Flunixin meglumine has been the drug of choice for reducing acute abdominal pain for nearly 2 decades. Detomidine, a relatively new α₂-agonist analgesic and sedative, also produces excellent results and it is usually considered to be more effective than xyloproxyne or butorphanol. Flunixin is considered to be more effective than phenylbutazone, dipyrone, meclofenamic acid, naproxin, and ibuprofen while ketoprofen has recently been found to be equally effective. The analgesia produced, is thought to be mediated through cyclo-oxygenase inhibition, although it is now clear that an intrinsic analgesic mechanism, apart from an effect on prostanoid concentrations, could also play a role. It should be noted that many clinicians, especially those with access to adequate surgical facilities, do not recommend the use of potent analgesics because they may mask a requirement for surgical intervention.

**Antipyresis**

Fever responses serve a beneficial purpose in combating infectious diseases by retarding bacterial growth and viral replication. A drop in body temperature as a result of anti-bacterial therapy is a valuable clinical sign in the assessment of therapeutic response. Body temperature above 41°C for a prolonged period, may result in permanent brain damage. The therapeutic value of NSAID's which are antipyretic, lies in the prevention of irreversible pathology.

The hypothalamus regulates a set point at which body temperature is maintained. The set point is elevated in fever, and certain aspirin-like...
NSAID's promote its return to normal. Pathologic conditions that produce an elevation in set point, induce the synthesis of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in the preoptic hypothalamus. The aspirin-like drugs that cross the blood-brain barrier and inhibit PGE<sub>2</sub> synthesis, suppress fever induction. Reduction of PGE<sub>2</sub> levels cause a reversal of interleukin-1 (IL-1) induced elevation in the hypothalamic set point. Heat production decreases while heat loss increases, and body temperature drops. Examples of antipyretic drugs include aspirin, salicylic acid, diflunisal, dipyrone and other pyrazolones, ibuprofen, paracetamol and related drugs.

Prophylaxis of thromboembolism and thrombophlebitis

Thrombosis and thromboembolism in the dog and cat are usually the result of an underlying disease such as feline cardiomyopathy, bacterial endocarditis, inflammatory disorders, amyloidosis, nephrotic syndrome, Cushing's disease and polycymia. In horses, thrombotic disease is associated with conditions such as laminitis, verminous colic, disseminated intravascular coagulation (DIC) and endotoxemia. In addition, the use of venous catheters inserted chronically, can damage vessel endothelium and initiate thrombus formation. The latter can be greatly exacerbated if the catheter becomes infected. Prophylactic therapy should also be considered in patients scheduled for angiographic procedures, another predisposing factor to thrombus formation.

Damage to vascular endothelium from any of the above causes, results in platelet aggregation, leading to thrombus formation and sometimes vessel occlusion. When platelets are activated they produce, via the action of a cyclo-oxygenase, the pro-aggregatory and vasoconstrictive eicosanoid thromboxane A<sub>2</sub> (TXA<sub>2</sub>). Experimentally, this is measured as the stable metabolite TXB<sub>2</sub>. Most of the NSAID's used in practice today will inhibit the activity of this cyclo-oxygenase. NSAID's which are poor cyclo-oxygenase inhibitors, such as carprofen are exceptions. Because the inhibition is reversible, NSAID's must be given daily or every other day in order to maintain an anti-coagulant effect. This is usually inadvisable because of the potential for toxic effects, as described below.

Aspirin (but not salicylic acid), however, causes an irreversible inhibition of platelet cyclo-oxygenase. A single I.V. dose of 19 mg kg<sup>-1</sup> given to horses has been shown to produce complete blockade of serum TXB<sub>2</sub> for 7 d with 74% inhibition still present after 24 h. Even though the half-life of aspirin is very short (0.11 h) in the horse, platelet cyclo-oxygenase is apparently acetylated and inactivated for the life of the platelet. The enzyme cannot be regenerated within the platelet so that the generation of new platelet is necessary for TXA<sub>2</sub>/TXB<sub>2</sub> production. Aspirin has also been shown to prolong bleeding time, but the effect only lasts for 24 to 48 h in horses. Similar studies in cats indicate that an anti-thrombotic dose of aspirin would be 5-10 mg kg<sup>-1</sup> given on alternate days, or 25 mg kg<sup>-1</sup> once weekly. Theoretically, the dose of aspirin employed must be kept small enough to prevent inhibition of PGI<sub>1</sub> (prostacyclin) formation in vascular endothelial cells by the salicylic acid produced from aspirin. PGI<sub>1</sub> is a disaggregator and vaso-dilatory eicosanoid that counters the effects of thromboxane.

Glomerulonephropathies

In some glomerulonephropathies, immune complexes lead to complement activation, inflammation and the activation of the clotting mechanism. NSAID's, especially indomethacin and aspirin, are thus often prescribed for their anti-inflammatory effects as well as for their inhibitory effects on platelet aggregation and adhesion. Therapeutic response is noted as reduction in urinary protein loss. However, it is important to remember that renal prostaglandins play an important part in normal renal function (maintenance of glomerular medullary perfusion, glomerular filtration rate as well as sodium and water clearance). In certain major clinical circumstances (extracellular volume depletion, congestive heart failure, hepatic disease, and many glomerulonephropathies) vasoconstrictor hormones increase to maintain cardiovascular homeostasis. In these conditions, renal prostaglandin synthesis is augmented to maintain renal perfusion and renal function becomes prostaglandin-dependent. It is therefore obvious that treatment with NSAID's will potentiate renal vasoconstrictory hormones and may result in either acute or chronic renal failure under these circumstances.

Treatment and prophylaxis of endotoxaemia

Endotoxaemia occurs in cases of septic shock, equine colic and its sequelae, gram-negative bacterial sepsis, parvovirus enteritis, endo­metritis, coliform mastitis and endometritis in cattle, and gastric dilatation-volvulus in dogs. Endotoxin is a lipid constituent of the cell wall of enteric gram-negative bacterial organisms and is normally restricted to the intestinal lumen by mucosal cell barrier mechanisms. Gram-negative endotoxins exert their adverse effects on haemodynamic, haematologic, and immunological mediation through a variety of host-derived mediators. Those that have been implicated include products of cyclo-oxygenase (prostaglandins E<sub>2</sub>, F<sub>2α</sub> and I<sub>2</sub> and thromboxane A<sub>2</sub>) and lipoygenase activity, as well as interleukins, platelet activating factor (PAF), tissue necrosis factor (TNF) and other cytokines. The macrophage-derived cytokine, TNF, is an early mediator of endotoxaemia, and in fact, monoclonal antibodies against TNF have improved survival of animals with endotoxaemia and septic shock.

The effects of the eicosanoids can be summarised briefly as intense vasoconstriction mediated by PGE<sub>2</sub> and TXA<sub>2</sub>, vasodilation mediated by PGE<sub>2</sub> and PGI<sub>2</sub> (prostacyclin), abdominal pain and diarrhoea produced by PGE<sub>2</sub>, a prothrombotic action mediated by TXA<sub>2</sub>, and chemotaxis enhanced microvascular permeability, airway and pulmonary vasoconstriction produced by the leukotrienes. A basis for the use of NSAID's in the prevention and treatment of endotoxaemia, was provided by the finding that plasma TXB<sub>2</sub> increased markedly in consonance with the early vasoconstrictive phase, and that the subsequent peripheral vasodilation correlated with a similar decrease in plasma prostacyclin concentrations. Furthermore, it was shown that when potent NSAID's were administered before or immediately after the onset of endotoxaemia in horses, nearly all of the early clinical responses to endotoxin were prevented.

Although it might be assumed that many NSAID's would have an effect in the prevention of the clinical signs of endotoxaemia, flunixin has been preferred as being the most effective, at least until recently. The availability of dual inhibitors, of both cyclo-oxygenase and 5-lipoxygenase, such as...
as ketoprofen, might be even more effective in preventing the early signs of endotoxaemia. Recent work has shown that an experimental dual inhibitor reduced the endotoxin-induced release of TNF from equine peritoneal macrophages. However, other potent lipooxygenase inhibitors apparently do not block endotoxin-induced TNF synthesis. Thus if dual blockers do act to reduce TNF production, it is probably through an as yet undescribed mechanism.

Flunixin meglumine at the recommended dosage of 1.1 mg kg⁻¹ has been shown to alleviate the physical signs of endotoxaemia in the equine 18-19. Low doses of flunixin (0.25 mg kg⁻¹) also inhibit eosinoid production in experimental endotoxaemia in horses, but without masking all the physical signs 20. This has the advantage of accurate clinical evaluation of the horse’s status as well as averting or delaying the onset of the toxic effects of NSAID’s. Studies with low doses of other NSAID’s, e.g. ibuprofen and aspirin, have also been shown to be effective against lethal endotoxic shock in rats 21-22. Ibuprofen at 15 mg kg⁻¹, just prior to Pasteurella haemolytica endotoxic infusion, followed by a continuous infusion of a maintenance dose of 86.6 μg kg⁻¹ min⁻¹ of ibuprofen, effectively suppressed the endotoxic effects in sheep 23. Phenylbutazone at the recommended dosage was not fully effective in combating the changes associated with equine endotoxic shock 24.

Various NSAID’s have been shown to have beneficial effects in the treatment of both canine sepsis and rat peritonitis 25-26. In the treatment of acute lethal peritonitis in the dog, flunixin meglumine at a dose of 1.1 mg kg⁻¹ increased the survival time of dogs by delaying the onset of cardiovascular collapse, allowing for more time for the actions of the body’s defense mechanisms and for antibiotic therapy 27. Appropriate antibiotic therapy is essential in these cases. A possible synergistic action between NSAID’s and gentamycin sulphate has been suggested 28, but the reduction of bacterial numbers alone will improve survival if the cardiovascular system can be maintained.

The role of prostaglandins in the pathogenesis of bovine mastitis induced by E. coli endotoxin has been described 29. NSAID’s were therefore used during the treatment of acute and peracute cases of coliform mastitis. In a study of the treatment of endotoxin-induced bovine mastitis, multiple doses (7) of flunixin meglumine at 1.1 mg kg⁻¹ were shown to be effective in reducing fever and mammary inflammation, and laboratory indicators of inflammation in milk were not altered. The lack of effect on somatic cell count (SCC) in milk may be desirable because of the function of the neutrophil in elimination of coliform organisms from the mammary gland in naturally occurring cases of the disease.

Other indications for the use of NSAID’s

Nephrogenic diabetes insipidus is a condition where the renal collecting duct is unresponsive to antidiuretic hormone (ADH). By removing the inhibitory effect of prostaglandins, NSAID’s (e.g. indomethacin) potentiate the effect of ADH leading to reduced free-water clearance and medullary hypertonicity with resultant water retention.

Prostaglandin E acts as a feedback inhibition on cellular immune responses. Inhibition of prostaglandin E by indomethacin or aspirin, increases both humoral and cellular immune response and natural killer cell activity. Immunological diseases such as systemic lupus and rheumatoid arthritis show a good response to treatment with NSAID’s, due to their anti-inflammatory effects. Research seems to indicate a more direct effect of NSAID’s in these diseases by stimulating T-suppressor cells in their action against T-helper cells and auto-antibody-producing B cells 30.

Pre-operative aspirin treatment (30 mg kg⁻¹ every 8 h for 40 h) for intra-ocular surgery in the dog, may be of value in minimising the post-operative increase in protein content of the aqueous humour. Krohne & Verste 31 found that flunixin meglumine plus dexmethylxazone had a greater inhibitory effect on post-operative aqueous protein increases than dexmethylxazone or flunixin alone.

Aspirin has been used with varying success in human paediatrics for the treatment of patent ductus arteriosus. This application has been reported in the veterinary literature and some success was obtained with this treatment 32.

There are several other applications of NSAID’s in humans that may not have any direct application in veterinary medicine. These include the use of NSAID’s in the treatment of migraine headaches, the use of aspirin in the prevention of ischaemic stroke and myocardial infarction, and the use of several anti-inflammatory drugs in the treatment of adult respiratory distress syndrome.

Future developments

The applications of the NSAID’s depend largely on their pharmacodynamic and pharmacokinetic properties. At present, their uses depend on whether they distribute into the CNS to affect cyclo-oxygenase and produce antipyresis and analgesia, and to what extent their application is limited by toxicity.

It is now appreciated that the cyclooxygenases differ, and it may therefore be possible to synthesise drugs which will block the activity of one enzyme (the useful effect) without affecting an enzyme which would lead to a toxic effect, e.g. gastrointestinal ulceration. One avenue of research leading to less toxic and more useful NSAID’s is the selective effect of enantiomers of racemic drugs, such as flurbiprofen, the R(-) isomer of which has no coxiceptive properties, but little effect on gastrointestinal cyclo-oxygenase involved in mucosal protection. We can also expect to see the development of additional drugs with the properties of carprofen, where the anti-oedema effect is apparently independent of the ability to inhibit cyclo-oxygenase.

We may also expect to see the development of additional drugs which are blockers of both cyclo-oxygenase and lipooxygenase synthesis. Interest in this area, however, will depend to some degree on the effectiveness of currently available agents which are claimed to be dual blockers.

We may also expect to see additional drugs which produce a higher degree of analgesia independent of general anti-inflammatory activity. These agents, while structurally and functionally classified as NSAID’s, will be used primarily as analgesics in the manner of paracetamol, aspirin and similar drugs. They may however, be employed for local or regional pain-reduction rather than general centrally-mediated analgesia.

Two additional areas of research currently underway, deserve mention. One is the use of drugs which block the effects of inflammatory mediators at their various receptors, rather than inhibiting their synthesis. In this regard, there is already good progress.

in classifying prostaglandin receptors, and there are several experimental drugs being tested for their ability to reduce specific parameters of inflammation through competitive blockade. Secondly, there are also experimental agents which block other mediators of inflammation, such as platelet activating factor (PAF). Blockade of the synthesis or action of pro-inflammatory cytokines may prove very useful in the prevention of a variety of inflammatory diseases.

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