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NSAIDS IN EQUINE MEDICINE:
BEST PRACTICES

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BACKGROUND

Eicosanoids are derived from 20-carbon essential fatty acids, with arachidonic acid being the most common precursor. Perturbations of cell membranes, whether chemical, physical or immune-mediated, releases phospholipids, which are rapidly converted to arachidonic acid by phospholipase A2 and other acylhydrolases. Once released arachidonic acid and its congener form the substrates for a number of enzyme systems. Products that contain ring structures (prostaglandins and thromboxanes) are the result of metabolism by the cyclooxygenase (COX) enzymes, while the hydroxylated derivatives of straight-chain fatty acids (leukotrienes) result from the action of various lipoxygenases.

In many organ systems prostaglandins (PGs) and thromboxanes (TXs) are produced constitutively and serve numerous homeostatic roles. For example, in the gastrointestinal (GI) tract PGs of the E series, primarily PGE2, have been shown to protect the gastric mucosa from damage secondary to a multitude of insults, including acids, alcohol and hypertonic solutions. In the kidney, PGs serve a similar protective role. It has been proposed that a balance between the production of PGI2, which inhibits platelet aggregation, and TXA2, which induces platelet aggregation, regulates platelet-vessel wall interactions and the formation of hemostatic plugs and thrombi.

In addition to homeostatic functions, PGs are the key to the development of the inflammatory response. PGE2, for example, produces long lasting vasodilatation, which can counteract the vasoconstrictor effects of norepinephrine and angiotensin II. In addition, PGE1, PGE2 and PG2 increase vascular permeability and can produce edema in the absence of other mediators. There is also evidence that PGs act synergistically with other mediators, such as bradykinins, to produce inflammatory responses and are important mediators of the pain associated with injury or inflammation. PGs are also important in the regulation of body temperature. For example, bacterial endotoxins induce fevers by stimulating the biosynthesis and release of endogenous pyrogens from leukocytes.

MODE OF ACTION FOR NSAIDs

All NSAIDs, by definition, inhibit COX enzymes to some degree. This prevents the metabolism of AA to the unstable endoperoxide intermediate, PGG2. Currently two isoforms of the COX enzyme, known as COX1 and COX2, have been described. In addition, the existence of a COX3 isoenzyme has been proposed, but it is unclear whether this is actually a functional enzyme or a aberrant splice variant of the COX1 gene.

The COX1 enzyme is produced constitutively in many tissues and this isoform is responsible for the production of PGs involved in the homeostatic functions in platelets, gastrointestinal mucosa and to some extent the kidneys. In contrast, in most tissues the constitutive production of the COX2 enzyme is limited. COX2 production, however, can be induced in many cells, including those primarily associated with the inflammatory process. For example, in quiescent unstimulated rat macrophages, COX1, but not COX2, can readily be detected. COX2 expression is dramatically increased when the macrophages are exposed in vitro to bacterial lipopolysaccharides, while COX1 levels remain unchanged. Many NSAIDs, such as aspirin and indomethacin, are more effective at inhibiting COX1 than COX2. Other NSAIDs, such as ibuprofen and meclofenamic acid, are equipotent at inhibiting the COX1 and COX2 isoforms. It has been proposed that this inhibition of the constitutively produced COX1 isomers is responsible for many of the adverse effects of NSAIDs including gastric ulceration, renal function impairment and platelet dysfunction.

A NEW VIEW OF COX2

As discussed above initially the COX2 isoenzyme was believed to be strictly produced in inflammatory settings. It is now apparent that this simplistic view was incorrect. COX2, for example, appears to play an important homeostatic role in some organ systems. For example, when normal dogs were administered the COX2 selective agent nimesulide, renal blood flow decreased by 16%, but glomerular filtration rate was not affected. In the presence of low sodium intake, however, the effects were even more pronounced with nimesulide decreasing renal blood flow by 31% and glomerular filtration rate by 34%. The respective roles of COX1 and COX2 in the renal function of most veterinary species remains to be determined, and veterinarians should use human COX2 selective agents with care in these patients. In addition, there is some evidence that COX2 may play a physiological role in the cardiovascular system. Although extremely controversial, in some studies individuals taking COX2 selective inhibitors, such as rofecoxib and celecoxib, appeared to be at higher risk for a myocardial infarction (MI) than individuals taking nonselective COX inhibitors. One explanation, for these results may be that nonselective agents are actually protective against MIs because of their inhibitory effects on platelet aggregation. Regardless, as MIs are very rare in veterinary species, this particular side effect is of less concern to veterinarians than MDs. COX2, however, may also play a role in mucosal repair in the gastrointestinal tract. Although the risk of gastrointestinal side effects appears to be less with selective COX2 inhibitors, than with nonselective agents, it is not insignificant. COX2 is also constitutively produced in the CNS, although its role in that system has yet to be elucidated. Undoubtedly, as research continues and as their use increases in both humans and veterinary patients additional roles for the COX2 isoenzyme may come light.

COX2 SELECTIVE INHIBITORS

In human medicine the use of agents that selectively inhibit COX2 versus COX1 at therapeutic doses has become the rage for treating osteoarthritis. In veterinary medicine there are now several NSAIDs approved for use in dogs that are marketed as selective COX2 inhibitors. The assumption is that because these agents do not significantly inhibit COX1 at therapeutic doses they should be much safer in terms of gastrointestinal complications than nonselective agents. However, as discussed above, reality is not so straightforward. First, selectivity itself is species specific. Therefore, what is a selective COX2 inhibitor in humans may not be selective in another species. In some cases selectivity itself is hard to determine. For example, in one study carprofen did not inhibit COX2 activity in equine blood,
in other studies it was shown to be a weak nonselective COX inhibitor. Regardless, in numerous species carprofen has been shown to be a fairly good analgesic although its mechanism of action remains debatable. In addition, in humans the role of COX2 in non-inflammatory pathways appears to have been underestimated. As we know very little about COX2 expression and regulation in other species, such as the horse, care should be used when administered so-called “selective” COX2 inhibitors to horses.

NEW ADVANCES IN NSAID THERAPY FOR HORSES
Topically Applied Products
Veterinarians commonly use nonsteroidal anti-inflammatory drugs (NSAIDs) to treat pain and inflammation associated with any number of diseases in horses. Most commonly, the use of NSAIDs has been limited to systemic administration, either orally or parenterally, even if the site of inflammation is localized. Common side effects observed following systemic administration of NSAIDs include gastrointestinal ulceration, renal toxicity, and injection site reactions. In contrast, topical administration of NSAIDs is associated with fewer side effects because the total dose of drug administered is generally less than that required for systemic therapy. In human medicine topical administration of NSAIDs has been shown to be efficacious for the treatment of many conditions including rheumatoid arthritis and to have an improved safety profile compared to orally administered agents.14

The NSAID diclofenac sodium is a dual cyclooxygenase and lipoxygenase inhibitor that is commonly used in human medicine.15 It is available formulated for oral, ophthalmic, and parenteral administration. In addition, several topical formulations, including creams and patches, have been evaluated for the treatment of human osteoarthritis and were found to be both safe and efficacious.14,16 A diclofenac liposomal suspension formulated for topical administration has recently been evaluated for use in horses. In one recent study the anti-inflammatory effects of topically applied diclofenac were evaluated in 7 horses using subcutaneously implanted tissue cages.16 The results of the study indicated that pre-treatment with a diclofenac liposomal suspension significantly decreased PGE2 concentrations in the carrageenan-induced inflammatory exudates collected from the tissue cages. In a different study the effects of diclofenac applied topically as a liposomal suspension were evaluated in horses with naturally occurring pain and inflammation localized to a single joint. The results of this double blind, placebo-controlled study indicated that a 5-day course of diclofenac therapy significantly improved clinical signs of lameness as determined by both clinicians and horse owners.17 Diclofenac formulated in a liposomal suspension is an effective, safe, and convenient way to treat areas of localized inflammation in horses. The effectiveness of therapy is maximized by appropriate application and by allowing sufficient time for absorption.

Carprofen
Carprofen, a propionic acid derivative, is an effective analgesic and weak antiinflammatory agent. Carprofen contains a chiral center at the C2 of the propionic moiety and therefore exists in two stereoisomeric forms, the S(+) and R(-) enantiomers. The products approved in Europe for use in the horse and in the U.S. for use in dogs and cats are racemic mixtures of the two antipodes. In the horse the S(+) form has a more rapid clearance, due to selective glucuronidation and subsequent biliary excretion of that enantiomer. Unlike many NSAIDs in the horse, the half-life of carprofen is long, with estimates ranging from 14 to 31 h.19 Despite the slow clearance, there was no evidence of accumulation of carprofen in plasma when the drug was given orally at a dose of 0.7 mg/kg once a day for 14 days. In this study, the bioavailability of carprofen was estimated to be approximately 70%.

In the horse, carprofen appears to have a favorable therapeutic index. For example, when carprofen was administered, on a single occasion intravenously at five times the recommended dose (3.5 mg/kg) or orally at twice the recommended dose rate (1.4 mg/kg) for 14 days, it was well tolerated with no observable sign of toxicity20 In addition, the intramuscular administration of carprofen (0.7 mg/kg) did not cause obvious signs of swelling or inflammation, but was associated with significant increases in creatine kinase, suggesting muscle cell damage. As with many NSAIDs intramuscular administration should be avoided if possible.

The exact mechanisms of action of carprofen are unclear; as in many species it is a more efficacious analgesic agent than its anti-inflammatory effects would predict. In various laboratory animals, however, carprofen was found to be an effective analgesic only when the pain was associated with inflammation. As mentioned previously the activity and selectivity of carprofen in the horses has yet to be determined. Regardless, typical side effects of NSAID therapy, such as gastrointestinal ulceration, are not commonly observed following carprofen administration to dogs or horses. An idiosyncratic reaction involving mild to fatal, severe hepatocellular damage has been reported in the dog but not, to the author’s knowledge, in the horse.

ELTENAC
Eltenac is an acetic acid derivative that appears to be effective and relatively safe when used in horses (Prugener et al 1991). The pharmacokinetics of eltenac has been examined in several studies. It has a short plasma half-life of between 1.7 and 3 h and a small Vd (approximately 0.2 l/kg).21 There was no indication of accumulation in the plasma after 4 days of repeated intravenous administrations (0.5 mg/kg) unlike phenylbutazone.

The safety of eltenac in horses appears to be similar to other commonly used NSAIDs. In one study carried out in 24 horses, the four horses administered eltenac at the recommended dose rate (0.5 mg/kg) intravenously, once daily for 15 days either had no lesions or extremely mild erosions in the glandular mucosa of the stomach.22 In the horses administered higher doses of eltenac (1.5 and 2.5 mg/kg) intravenously, daily for 15 days there was a dose-related increase in signs of toxicity, such as gastric ulcers, decreases in white blood cell counts and total serum protein concentrations, although these effects were not profound.

Although not extensive, there is evidence that eltenac is an efficacious NSAID in horses when used at recommended doses. In one study eltenac (0.5 mg/kg) was as effective as flunixin meglumine (1.1 mg/kg) in relieving pain and inflammation in an experimentally induced carpalitis model in horses. In addition, the effects of eltenac are long lasting with a dosing interval of once every 24h recommended for most conditions. Together these findings suggest that eltenac may be an effective and useful NSAID in horses was approved for use.
CONCLUSION
It is tempting to view the development of so many agents that are selective COX2 inhibitors in other species as a great
development for equine medicine. Unfortunately, this is not the
case. First, as discussed above the selectivity of these agents
in the horse, has yet to be determined. The may be
equally selective or the may be selective inhibitors of COX1
in the horse. In addition, the roles of COX2 enzymes in
the horse have not yet been elucidated. A particular concern is
the indication from other species that COX2 may play a role
in renal function and specifically in maintaining renal blood
flow. The horse appears exquisitely susceptible to renal
dysfunction induced by NSAIDs. Whether agents that
selectively inhibit COX2 isoenzymes would be an
improvement remains to be determined.

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