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Do we need to worry about NSAID side effects?

Although side effects are uncommon, they can be life-threatening. This is particularly problematic for a drug class that equine veterinarians frequently administer to horses because the tendency is not to think carefully about side effects.

What are the most important actions of NSAIDs?

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively for treatment of inflammation and pain in horses, particularly those with gastrointestinal or musculoskeletal disease. The mechanism of action of the NSAIDs used in equine practice is inhibition of cyclo-oxygenase (COX) activity, thereby inhibiting prostaglandin production. However, the recent discovery of multiple isoforms of COX has revolutionised the field of NSAID pharmaceutical development, leading to a number of drugs that are preferential for one of the COX isoforms. Of the 2 COX isoforms, COX-1 is constitutively expressed in most tissues, and has therefore been credited with synthesising prostanoids involved in physiological organ function, whereas COX-2 is typically upregulated by inflammatory stimuli such as endotoxin, and has therefore been the target of selective drugs aimed at inhibiting inflammation without disrupting normal organ function. The COX-2 inhibitors are now being extensively studied in the horse, and there is potential for improving anti-inflammatory treatment by lessening the onset of side effects.

Right dorsal colitis is the most concerning of the side effects

Right dorsal colitis, most often associated with phenylbutazone administration for orthopaedic disease, is particularly alarming given the high mortality rate and the possibility of it developing rapidly without warning. There are essentially 2 presentations of right dorsal colitis. In the more slowly developing form (subacute - chronic), horses will gradually develop a protein-losing colonicopathy over a number of days - weeks of therapy. Patients at risk are those treated with phenylbutazone at the upper limit of the dose range (4.4 mg/kg bwt, per os, q. 12 h), particularly those that are dehydrated or undergo surgery during the therapeutic period. In a more rapidly developing form (acute), horses can appear to be completely healthy with minimal risks for side effects, but very rapidly develop fulminant right dorsal colitis that is often fatal. This can appear to be an idiosyncratic reaction to phenylbutazone, and the predispositions to such a rapid onset of colitis are poorly understood. These horses will tend to show signs of colic, presumably related to pain from a degenerating right dorsal colon, including an elevation in heart rate and a lack of interest in food and water. Unfortunately, because of signs of pain, horses are sometimes given an increased dose of phenylbutazone. This is particularly problematic if a trainer or owner has decided to alter treatment as this may occur without the veterinarian's knowledge. If there are any concerns with a particular horse, there are several options: 1) give a lower dose of phenylbutazone; 2) give an alternative NSAID with an improved safety profile, such as a COX-2 selective inhibitor; 3) Monitor the horse's total protein.

Where there are particular concerns based on clinical signs, the horse should be taken off all NSAIDs immediately and have an ultrasound examination of the colon. The latter is an additional highly sensitive technique for monitoring the health of the right dorsal colon. Treatment includes provision of a low residue diet, feeding corn oil, and most importantly treatment with misoprostol (5 μg/kg bwt, per os, q. 12 h).

Other complications of clinical importance

Additional complications to be concerned about are gastrointestinal ulcers and renal injury. Ulceration can be found anywhere in the gastrointestinal tract or mouth, but is most likely to be seen in the stomach. Differentiating these ulcers from typical management-induced ulceration of the squamous portion of the equine stomach is very difficult. However, NSAIDs given via the oral route contribute to the risk of stomach ulceration. Use of antacids, particularly the proton pump inhibitor omeprazole, makes sense in select horses considered to be at risk. The veterinarian should remember that it takes several days to increase the gastric pH using omeprazole. Renal injury is typically detected in horses that have other contributory risk factors, particularly dehydration.

Treatment of post operative colic patients

Horses that already have gastrointestinal compromise, particularly horses deemed to be in need of surgery, are frequently treated with NSAIDs. Flunixin meglumine is the most frequently used NSAID, although dipyrone is a component of Buscopan compositum. The latter is an interesting compound that appears to work centrally to inhibit pain, possibly via a third COX isoform - COX-3. This action also means that dipyrone has a higher safety profile than nonselective NSAIDs inhibiting COX-1 and COX-2. Interestingly, when treating colics, veterinarians do not typically think of side effects of NSAIDs aside from masking of pain. However, a series of recent studies have shown that flunixin meglumine retards mucosal repair of the small intestine as compared with COX-2 preferential (meloxicam, 0.6 mg/kg bwt, i.v., q. 24 h) or COX-2 selective (firocoxib, 0.9 mg/kg bwt, i.v., q. 24 h) NSAIDs. Specifically, flunixin meglumine (1.1 mg/kg bwt, i.v., q. 12 h) increased permeability of ischaemic-injured jejunum to endotoxin. Whether or not this translates into a clinically identifiable problem is not known. However, before conclusive results from clinical trials, it is reasonable to have some concerns about mucosal healing and consider reducing the number of days of treatment with flunixin meglumine or consider alternative analgesics such as butorphanol.

Further reading