

Evidence-based treatment of the inflammatory component of laminitis

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The evolution of effective therapies is difficult in a disease such as laminitis where the therapeutic targets—the pathologic mechanisms that lead to laminar injury and failure—have been so controversial. Thus, a large number of laminitis treatments have appeared only to be discontinued owing to either the proposed pathologic mechanism being discounted or the drug being proven not to be efficacious for the desired effect. Interestingly, anti-inflammatory drugs are one of the few classes of drugs to stand the test of time and have remained as a cornerstone of laminitis therapy despite the fact that early on there was dogma (actually incorrect) stating that inflammation did not exist in laminitis. During the first AAEP Foundation Equine Laminitis Research Panel and Meeting in 2004 a survey of 60 veterinary practitioners revealed that the most commonly used drugs for the treatment of laminitis is the non-steroidal anti-inflammatory drugs (NSAIDs or AINEs) phenylbutazone (58/60) and flunixin meglumine (40/60). Although there is no direct scientific evidence that laminar injury can be ameliorated by AINEs at this time, there has been a large number of reports the past few years detailing inflammatory events in the laminae and in endotoxic horse that may be addressed by AINEs. These reports include data indicating increased cyclooxygenase-2 expression in the affected laminae, greatly increased concentrations of some pro-inflammatory cytokines in the developmental (prodromal) and acute stages of laminitis. Interestingly although AINEs are used mainly to inhibit cyclooxygenase activity, there is evidence from human-related research that at high doses AINEs can also block other inflammatory pathways, including those involved in cytokine

expression (i.e. NFκB signaling). In support of this concept in equids, in the study introducing the clinical community to “low-dose” flunixin meglumine in 1987, the investigators found that although “low-dose treatment” (0.25 mg/kg) had a similar efficacy as the recommended regular “high dose” (1 mg/kg) of flunixin with regard to decreasing prostanoid concentration, the ponies with low-dose flunixin exhibited more severe clinical signs of endotoxemia than the animals given high dose flunixin. This indicates that the higher dose of flunixin is blocking more than prostanoid production. Thus, at least one of the authors (JKB) uses high dose flunixin (1.1 mg/kg TID for 2-3 days) on animals at risk of laminitis (i.e. exhibiting signs of sepsis/endotoxemia) unless there is ongoing renal compromise or GI ulceration.

Controversy exists about the use of heparin in horse laminitis. Whereas heparin was initially used in medicine only as an anticoagulant, it is now realized that this class of drugs also has anti-inflammatory properties (somewhat due to the fact that platelets and factors involved in coagulation can have pro-inflammatory properties). Recently, heparin was reported to have potential anti-inflammatory effects on equine endothelium exposed to the deleterious activity of neutrophil-derived myeloperoxidase (MPO). However, there is confounding data from retrospective clinical studies on the efficacy of heparin as prophylaxis in horses at risk of laminitis. Furthermore, experimental treatment with heparin 24 hours after CHO administration did not ameliorate signs of laminitis or laminar lesions. One problem with previous heparin studies is that unfractionated heparin was used, which induces autoagglutination of equine red blood cells and become lodged in capillaries (including laminar capillaries); this event may further compromise affected laminar capillaries in laminitis. Low molecular weight heparin (LMWH) may be a valuable alternative as it does not cause equine RBC autoagglutination and has recently been reported to reduce the incidence and severity of laminitis in postoperative colic cases (these data also obtained from a retrospective study).

A constant rate infusion (CRI) of intravenous lidocaine is frequently used in horses with colic to improve peristalsis and is thought to have anti-inflammatory properties. Due to these purported properties, clinicians have also used lidocaine CRI in other inflammatory diseases including laminitis. However, recent findings using the BWE model of laminitis indicate that not only is a lidocaine CRI not effective in inhibiting inflammatory events in affected laminae, endothelial activation appears to be exacerbated by lidocaine.