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Clinical insights: Treatment of laminitis

The treatment of equine laminitis continues to present one of the greatest challenges for veterinarians, allied professionals and horse owners alike. Recent improvements in our understanding of the pathogenesis and diagnosis of laminitis, as highlighted in separate editorials in this issue, have served to open fruitful avenues of discovery in the continued quest to treat and ultimately prevent this debilitating condition. Equine Veterinary Journal's online collection on 'Understanding and managing endocrinopathic laminitis' includes eight recent papers that have provided important contributions to the treatment of laminitis, either through the immediate applicability of their findings to daily veterinary practice or by highlighting novel approaches that hold promise for future therapeutics.

How should we treat the obese equid with Equine Metabolic Syndrome?

Laminitis that is associated with the clinical clustering of obesity and insulin dysregulation, termed equine metabolic syndrome (EMS), is a common concern among domestic equine populations. In a study included in the online collection, Morgan and colleagues [1] describe the practical measures they implemented in treating a series of horses and ponies with EMS. Dietary recommendations included the feeding of hay at 1.5% bwt (as fed, soaked if possible), restriction or elimination of pasture access and provision of a ration balancer. Regular exercise, tailored to the individual animal, was an important part of the treatment plan when possible, although example protocols were not described. Body condition score decreased in all animals alongside overall improvements in insulin sensitivity. The overwhelming success of the treatment plans described in this report can largely be attributed to their proactive approach to maximise owner compliance (i.e. education and support). Detailed hard copies of all information, training in how to monitor progress, regular follow-up

consultations and revisits were provided. The investigation of practical diet and exercise programmes for animals with severe insulin dysregulation, or those that are not obese, warrant similar evaluation.

Clinical conclusions: Dietary modification and exercise can be successful for the treatment of obese animals with EMS when strategies to maximise owner compliance are employed.

Mentioned in the previous study, but not specifically described, was the use of remedial farriery or corrective shoeing in the treatment of EMS cases. In another report included in the online collection, Lynden and colleagues [2] sought to understand the role of farriers in the prevention of laminitis by undertaking a qualitative analysis of interviews with farriers and horse owners. Interviews revealed that farriers tended to operate in either a *holistic-focussed* or *technically-focussed* manner, while the expectations of owners regarding their farrier could be characterised as *welfare-focussed* or *task-focussed*. Owners who valued holistic care from their farrier viewed this relationship as central to informing preventative healthcare practices. These owners highlighted a need for long-term continuity of care from their farrier in achieving optimal welfare for their horse. This article argues for the importance of developing veterinarian–farrier relationships to enable optimal prevention and treatment strategies for laminitis cases through informed decision making.

Clinical conclusions: Farriers with a holistic approach to case management are well placed to support owners in the early identification of animals at risk of EMS-associated laminitis. Strategies to optimise the relationships between veterinarians, farriers and horse owners require further study.

There is a lack of peer-reviewed data to support the efficacy of many farriery interventions for the treatment of laminitis. The reasons for this gap in evidence include technical challenges and lack of funding, which are expanded upon by Weller and colleagues in a recent editorial published in the EVJ [3]. The type of therapeutic shoes applied to animals with chronic laminitis is one such area of controversy and the addition of new data to support their use is certainly welcome. In this issue, Sleutjens and colleagues [4] examined the effect of thermoplastic, mouldable, glue-on frog-supportive shoes in normal and obese, hyperinsulinaemic Shetland ponies. Hoof kinetics were assessed by walking and trotting the ponies over a pressure plate, before and after application of the therapeutic shoes. The first major finding was a difference in hoof loading between unshod normal and obese ponies, which was hypothesised to indicate subclinical laminitis in the obese group. The second major finding was a change in hoof kinetics after application of the therapeutic shoes consistent with increased comfort, especially for the obese group.

Clinical conclusions: The application of thermoplastic, mouldable, glue-on frog-supportive shoes to obese, hyperinsulinaemic Shetland ponies altered hoof kinetics in a manner consistent with improved comfort.

Can we improve pain management for the chronic laminitis case?

The failure to adequately control pain is a common reason for which horses afflicted by laminitis are ultimately subjected to euthanasia. Protocols for multimodal analgesia of acutely painful horses are well described in the hospital setting and are typically delivered using constant rate i.v. infusions. However, treatment options for the management of pain associated with chronic laminitis in an outpatient setting are often limited to oral formulations. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, although failure to achieve adequate analgesia is frequently encountered and the potential for adverse effects with long-term administration is a valid concern. There exists a pressing need to identify medications that can provide more effective analgesia to horses with chronic laminitis.

Tramadol is a centrally acting analgesic that acts as an agonist of μ opioid receptors and inhibitor of synaptic monoamine (serotonin and noradrenaline) reuptake. The pharmacokinetics and pharmacodynamics of tramadol have received attention in the horse, with only weak evidence for providing analgesia when used as a monotherapy. Guedes and colleagues [5] investigated the analgesic potential of tramadol in horses with chronic laminitis. Four horses with chronic laminitis received tramadol orally twice-daily for 7 days at either 5 mg/kg bwt (lower dose) or 10 mg/kg bwt (higher dose) on separate occasions. The higher dose resulted in a modest improvement in the frequency of weight shifting, while no improvement was demonstrated at the lower dose. These data support the continued investigation of tramadol as part of a multimodal therapeutic strategy for chronic laminitis. The potential for tramadol to slow intestinal motility requires thorough evaluation, with observations of reduced borborygmi and transient colic signs when administered to horses at higher doses. Further investigations should therefore aim to determine the optimal dosing regimen to promote analgesia and to assess the safety of longer-term use in the horse.

Clinical conclusions: The evidence for tramadol to provide sufficient analgesia for horses with chronic laminitis when used as a monotherapy remains weak at present.

Epoxy fatty acids (EpFAs), produced by the metabolism of arachidonic acid by epoxygenases, have been the subject of increasing attention after the recognition that they can reduce pain and inflammation. EpFAs are metabolised to less bioactive molecules by soluble epoxide hydrolase (sEH), and therefore, pharmacologic inhibition of sEH has been investigated in experimental models

for the treatment of inflammatory and neuropathic pain. Guedes and colleagues [6] investigated sEH as a potential therapeutic target to provide analgesia to horses with chronic laminitis. They first demonstrated increased sEH activity within the lamellae of horses with chronic laminitis when compared with normal horses. A compound with efficacy for the inhibition of equine sEH activity *in vitro* was then selected for *in vivo* testing. Ten horses with laminitis received a daily i.v. dose of the sEH inhibitor while continuing to receive medications prescribed by their veterinarian. Pain, as assessed by a visual analogue pain scale and the frequency of weight shifting, was modestly improved in some of the horses following the addition of the sEH inhibitor to the treatment regimen. The absence of a control group, concurrent administration of other medications and lack of investigator blinding are acknowledged as limitations by the authors. These data, however, provide the basis to encourage further investigations of sEH inhibitors for the treatment of pain in horses with laminitis.

Clinical conclusions: Modest short-term improvements in pain were demonstrated in some horses with chronic laminitis after the addition of a sEH inhibitor to their treatment regimen. The potential for this class of drug to act synergistically with NSAIDs (and other analgesic drugs) warrants further investigation.

What method should be used to apply digital cryotherapy?

Digital hypothermia is the only therapeutic intervention proven to dramatically reduce the severity of sepsis-related laminitis in experimental studies and lower the incidence of laminitis in clinical cases of colitis. Current evidence supports recommendations that effective digital hypothermia should result in hoof temperatures that are maintained below 10°C for the duration of therapy. Therefore, the choice of method by which to achieve digital hypothermia is a fundamental consideration for equine veterinarians, especially given the multitude of commercial products marketed for this purpose.

In a study included in the online collection, van Eps and Orsini [7] compared seven methods for cooling the equine digit. Hoof wall surface temperatures (HWST) were measured as four horses were subjected to each method of cryotherapy in a randomised crossover experimental design. Dry applications that applied ice packs to the hoof only or hoof plus a portion of the distal limb performed poorly, achieving HWST barely below 20°C. An ice boot that incorporated the distal limb but not the hoof was also found to be ineffective at lowering HWST below 20°C. Wet applications that immersed the hoof plus a portion of the distal limb in ice and water (wader-style ice boots or empty fluid bags held in place with adhesive tape) achieved excellent results, maintaining HWST below 5°C. A prototype dry sleeve that encompassed the hoof and distal limb, in which a cooling medium is continuously recirculated, performed similarly well to these wet application methods in achieving HWST around 5°C.

Burke and colleagues [8] evaluated the same ice boot that incorporates the distal limb but not the hoof using a different methodology, reasoning that the popularity of this boot in various equine hospitals warranted further evaluation of its ability to provide digital hypothermia. They measured lamellar temperatures by inserting thermocouples into the dorsal lamellae of the forelimbs. In contrast to van Eps and Orsini, who found that this style of ice boot was ineffective at lowering HWST below 20°C, lamellar temperatures were found to reach approximately 10°C in both healthy horses and horses receiving i.v. endotoxin. It was hypothesised that this effect was due to cooling of arterial blood before entering the hoof and perfusing the lamellae. Future studies that compare HWST with lamellar temperatures will make a useful contribution to this important area of research.

Clinical conclusions: Methods that immerse the entire hoof and a portion of the distal limb in ice and water, and a prototype dry sleeve application, can maintain hoof wall temperatures well below 10°C. A sleeve-style ice boot that does not include the hoof also appears capable of cooling lamellar tissues to recommended levels.

What novel therapies for laminitis are on the horizon?

Gene therapy is a rapidly expanding field of research for the treatment of a range of human diseases including inherited disorders and cancers. Gene therapy aims to transduce exogenous nucleic acids into target cells to replace or disrupt the expression of deleterious genes, or to induce *de novo* production of beneficial proteins. In the online collection, Mason and colleagues [9] report their proof of concept study that sought to deliver marker genes into tissues of the equine hoof. Using recombinant adeno-associated viral vectors administered by regional perfusion of the distal forelimbs, transgenes were successfully demonstrated in multiple regions of the hoof, including the lamellae. Several vector serotypes, doses and diluents were evaluated to determine optimal protocols for future studies. The long-term goal of this research group is to develop gene therapies for the prevention of supporting limb laminitis, although such therapies may equally be applicable to other forms of laminitis.

Clinical conclusions: Gene therapy may hold promise for the treatment of laminitis. Future work to identify and test candidate transgenes for efficacy in the treatment and prevention of laminitis will be truly fascinating.

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