Are Drugs Effective Treatment for Horses With Acute Laminitis?

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Currently, the only therapy for horses with acute laminitis for which there is consensus among practitioners is aggressive treatment for the disease process that has initiated laminitis. Although other treatments may have merit and seem logical based on studies of the pathogenesis of laminitis, the efficacy of these treatments has not been proven. Some of the confusion regarding treatment of horses for laminitis is the result of differing theories regarding the pathogenesis of laminitis and failure of clinicians to distinguish between recommendations made for treatment during the developmental (prodromal) stages (i.e., before signs of foot pain are observed) and recommendations for treatment during the acute phase (i.e., when signs of foot pain are apparent). Controlled studies have not shown the efficacy of any drug for treating horses in the acute phase of laminitis. Authors' addresses: Department of Large Animal Medicine and Surgery, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843 (Moyer, Carter); Department of Large Animal Surgery and Medicine, College of Veterinary Medicine, Auburn University, Auburn, AL 36849-5522 (John Schumacher); Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 77901-1071 (Jim Schumacher); e-mail: wmoyer@cvm.tamu.edu.

1. Introduction

For many years, many different drugs and management practices have been used to treat horses with acute laminitis. Recent studies have shown that lamellar attachments to the basement membrane are destroyed before signs of foot pain are apparent[1] and that, after the laminae have separated, damage is irreparable.[2] Therefore, the question of which specific treatment of horses for laminitis is most efficacious must be preceded by the question: is any specific medical treatment for horses with acute laminitis efficacious after the horse has developed signs of foot pain?

2. Recommended Medical Treatment

Resolution of the Initiating Disease

The most obvious therapy for horses with acute laminitis is treatment to resolve the disease process that likely initiated laminitis. This might involve treatment for grain overload, colitis or enteritis, retained placenta, septic myositis, excessive weight-bearing on a limb, and endocrinopathic/metabolic disorders. Often, however, the initiating cause of laminitis is not apparent.

Alteration of Lamellar Blood Flow

Some studies have investigated the efficacy of treatment designed to either increase or decrease lamellar blood flow during the developmental stage of laminitis to prevent clinical signs of laminitis.[3,4] There are no clinical studies, however, that have investigated efficacy of treatments claimed to increase lamellar blood flow after clinical signs of laminitis are apparent. Although a decrease in lamellar blood flow may prevent the acute phase of laminitis from developing,[3,5] increasing lamellar

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blood flow may speed healing of damaged lamellar tissue during the acute phase of laminitis.[6] The ability of any drug to improve lamellar blood flow in horses with laminitis has not been proven,[7] but proposed methods of increasing lamellar blood flow include the following:

- Digital nerve blocks increase digital blood flow by inhibiting vasomotor control of the digital vasculature. The use of this technique to treat horses for acute laminitis should be discouraged because increased weight bearing and movement likely exacerbate lamellar tearing and separation.
- α-Adrenoceptor antagonists, such as acepromazine maleate,[a] increase digital blood flow by α_1-adrenergic blockade and direct action on vascular smooth muscle. Acepromazine (0.04–0.08 mg/kg, IV/SQ/IM) is commonly administered to prevent laminitis or to treat horses with acute laminitis. Studies using laser flowmetry to measure lamellar blood flow in normal horses failed to show increased lamellar blood flow after administration of vasoactive drugs, including acepromazine.[8,9]
- Isoxsuprine and pentoxifylline are reported to increase blood flow; isoxsuprine HCl[b] (0.6 mg/kg, q 12 h) by directly relaxing smooth muscle, causing vasodilatation through both α antagonistic and β agonistic activity, and pentoxifylline[c] (8.5 mg/kg, orally, q 8 h) by decreasing blood viscosity, perhaps through its effects on platelets or by increasing the flexibility of red blood cells. Neither of these drugs, however, was shown after oral administration to increase lamellar blood flow in normal horses.[8,9] Apparently, neither of these drugs is well absorbed after oral administration.[10,11] If the mechanism of action of pentoxifylline is to increase deformability of red blood cell as the red blood cells are formed, long-term administration would likely be necessary to produce a benefit.
- Nitroglycerin was shown not to increase lamellar blood flow after onset of clinical signs of laminitis induced by administration of black walnut extract.[12] Topical administration of nitroglycerin[d] (60 mg as a 2% ointment on the skin over the digital vasculature) by the authors and others[13] for treatment of horses with acute laminitis has been disappointing.

Thus, it seems that there is no good evidence that vasodilative agents commonly administered to horses with acute laminitis are effective in increasing lamellar circulation. Using these drugs to treat horses with laminitis is questionable.[6]

Non-Steroidal Anti-Inflammatory Drugs

Phenylbutazone[e] (2.2–4.4 mg/kg, orally, q 12 h) is commonly administered to horses with acute laminitis because of its superior ability to relieve pain, but flunixin meglumine[f] (0.25 mg/kg, IV, q 8 h, or 1.1 mg/kg, IV, q 12 h) is often administered for its ability to reduce the effects of endotoxin because many horses suffering from laminitis are also endotoxemic. Administering a non-steroidal anti-inflammatory drug during the developmental stages of laminitis does not prevent acute laminitis, and administration of these drugs has not been shown to alter the course of acute laminitis.[6] On the contrary, an in vitro study indicated that non-steroidal anti-inflammatory drugs slightly potentiated activation of the matrix metalloproteinases that cause breakdown of lamellar attachments indicating that, at least theoretically, administering these drugs might increase lamellar separation.[6] Concurrent administration of phenylbutazone and flunixin meglumine to horses may not be justified because concurrent administration significantly decreases serum protein concentration and increases the incidence of severe gastric ulceration.[14]

From a purely scientific view, administration of a non-steroidal anti-inflammatory drug to treat a horse with laminitis is difficult to justify because the ability of non-steroidal anti-inflammatory drugs to decrease foot pain may be associated with an increase in mobility that may increase lamellar tearing and because there is no evidence that they prevent or influence positively the outcome of horses with acute laminitis. Humane considerations, however, mandate their use.

Anti-Endotoxin Drugs

Many horses suffering from acute laminitis also have clinical signs of endotoxemia, and a recent study investigating the risk factors for developing acute laminitis during hospitalization found an association (not evidence of a direct, causal relationship) between endotoxemia and the development of laminitis.[15] Drugs administered to horses for treatment for endotoxemia include flunixin meglumine[f] (0.25 mg/kg, IV, q 8 h or 1.1 mg/kg, IV, q 12 h) or ketoprofen[g] (2.2 mg/kg, q 24 h), anti-endotoxin hyperimmune plasma,[h] and polymyxin B sulfate[i] (1 mg/kg, IV, q 8 h). Administration of these drugs may ameliorate clinical signs of endotoxemia,[16] but their ability to prevent the development of clinical signs of laminitis or to influence the outcome of horses with acute laminitis has not been shown.[17] Endotoxin has been shown to cause insulin resistance in horses and thus may be involved in the pathogenesis of laminitis by causing decreased use of glucose by lamellar tissue.[18] Even though administration of drugs to ameliorate endotoxemia has not been shown to be effective treatment for horses with acute laminitis, use of these drugs seems reasonable and warranted.

Dimethyl Sulfoxide

Although some clinicians have the clinical impression that dimethyl sulfoxide (DMSO) is useful in the

treatment of horses with acute laminitis,[19] there is no credible evidence that it is of benefit in the treatment of horses with laminitis.[20] DMSO[j] (1 g/kg) is commonly administered parenterally (IV, q 12 h, in a polyionic solution at 20% concentration or less over 30 min once daily) or enterally to horses with acute laminitis for its anti-inflammatory effects and for its ability to scavenge oxygen-derived free radicals, like superoxide, that are formed during hypoxia and reperfusion.[16] There is no clear evidence, however, that hypoxemia or reperfusion injury is involved in the pathogenesis of acute laminitis. The primary source of superoxide in reperfused, re-oxygenated tissues seems to be the enzyme, xanthine oxidase, released during ischemia. Horses administered black walnut extract to experimentally induce laminitis have no increase in activity of xanthine oxidase in tissues, including digital laminae, indicating that hypoxemia and the formation oxygen-derived free radicals during reperfusion are not involved in the pathogenesis of laminitis caused by black walnut extract.[21]

Heparin

High doses of heparin[k] (100 U/kg, IV, q 6 h) have been shown in laboratory conditions to prevent or ameliorate signs of laminitis caused by carbohydrate overload,[22] and a clinical trial evaluating the efficacy of heparin in preventing laminitis in horses with duodenitis/proximal jejunitis found that the proportion of horses that developed laminitis among horses that received heparin was significantly less than that among horses that did not receive heparin.[23] Another clinical study involving more horses, however, showed that administration of heparin to horses (40–100 U/kg, IV or SQ, q 8–12 h) with an intestinal crisis had no significant effect in preventing acute laminitis.[24]

Heparin administered to horses intravenously in high doses rapidly results in a marked decrease in the hematocrit caused by agglutination of erythrocytes because the reticuloendothelial system removes the agglutinated erythrocytes from circulation,[25] possibly in the spleen.[26] Removal of erythrocytes from circulation enhances the flow of blood through the microcirculation because blood viscosity is inversely related to the hematocrit. Because heparin may increase microcirculation through the foot, its use may be indicated after the horse has developed acute laminitis, but to our knowledge, its use in ameliorating signs of laminitis in acutely affected horses has not be studied.

3. Client Education

We suggest that as soon as possible after diagnosing laminitis and assessing the horse, the clinician discuss the following points with the client so that misunderstandings can be prevented:

- When applicable, indicate that the exact causes or causes of laminitis can be difficult to determine. Speculation of the cause or causes can be construed as fact and thus could implicate an innocent individual or product.
- Explain that the mechanism/pathogenesis is not well understood.
- Explain that by the time an individual horse has been identified as having laminitis (i.e., lameness and pain) structural and vascular damage has already occurred.
- Explain that although the horse's initial clinical appearance (i.e., when first examined) can often be correlated with outcome, it is not always an accurate predictor of the horse's ultimate outcome; that is, experience indicates that some cases that one would grade at the initial examination as being mildly affected regardless of therapy may progress to being chronically and severely affected. Avoid being overly optimistic.
- Explain that if the disease becomes complicated (i.e., structural damage continues, causing sinking, solar penetration) and thus chronic, the horse is very likely to require special care (e.g., veterinary care, farriery work, and environmental considerations) throughout its life. Explain that a horse with complications is likely to require intensive, personalized, and often expensive care (e.g., medication, farriery, repetitive examinations).
- Explain that even with a good to excellent initial outcome, the horse is likely to have recurring foot-related problems (e.g., recurrence of acute laminitis, wall separation, subsolar infection).
- Explain that controlled studies identifying an ideal regimen to manage a horse with acute laminitis do not exist.
- Explain that any therapeutic regimen may have some risk beyond simple failure to improve the situation.
- Explain to the owner that, if the affected horse is insured, it is the owner or the owner's agent who is responsible for immediately reporting the condition to the insurance carrier.

An additional and at times difficult consideration is handling clients who have acquired information from any number of resources, such as horse magazines, web sites, or phone consultation with farriers and veterinarians. It may be useful to simply inform those involved with the case that information gathered from sources that are not in direct contact with the horse can be misleading. It is very important to indicate that laminitis continues to be under study but is a long way from being adequately understood. Explain that pain and lameness follow the structural damage and that no two horses are affected exactly alike. Explain that no single or combined treatment and management regimen has distinguished itself as being the most ideal.

4. Summary

Multiple medical therapies have evolved that are based primarily on what is known about the developmental stages (before the presence of clinical signs) of laminitis. Unfortunately, the molecular, vascular, and structural changes have taken place before clinical signs appear, and therefore, medical therapy is unlikely to reverse such changes. There are no controlled studies that have shown efficacy of treatment of horses in the acute, clinical stage of laminitis. Aggressive therapy should be directed at the disease process that initiated laminitis. The use of pain-relieving medications to control pain and suffering is generally indicated, but the effect of these drugs on outcome has not been established. Medical therapies, at this time, have not proven to be efficacious. We did not discuss in this manuscript the wide variety of mechanical treatments such as shoeing changes, that have been used to treat horses with laminitis but we point out that these mechanical therapies also lack controlled studies and rely on anecdotal, although useful, information.

References and Footnotes

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[a]Promace, Fort Dodge Animal Health, Fort Dodge, IA 50501.
[b]Isoxsuprine hydrochloride tablets, USP, Columbia Laboratories, Lexington, KY 40511.
[c]Trental, Sanofi-aventis, Bridgewater, NJ 08807.
[d]Nitro-Bid, Hoechst Marion Roussel, Kansas City, MO 64137.
[e]Phenylbutazone paste, Schering-Plough Animal Health, Union, NJ 07083.
[f]Flunixamine, Fort Dodge Animal Health, Fort Dodge, IA 50501.
[g]Ketofen, Fort Dodge Animal Health, Fort Dodge, IA 50501.
[h]Endoserum, IMMVAC, Columbia, MO 65201.
[i]Polymixin B, Bedford Laboratories, Bedford, OH 44146.
[j]DMSO, Fort Dodge Animal Health, Fort Dodge, IA 50501.
[k]Heparin sodium, Abraxis Pharmaceutical Products, Schaumburg, IL 60173.