Laminitis treatment by regional drug delivery to the horse’s foot

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This project explored how anti-laminitis therapeutic agents could be delivered where they are most needed; directly to the horse’s foot. The lamellae arrayed around the inside of the hoof attach the outer surface of the distal phalanx (coffin bone) to the inner hoof wall and thus suspend the bone inside the hoof capsule. The lamellar hoof (epidermal) and connective tissue (dermal) components interdigitate and together support the vertical load of the horse and resist the forces of locomotion. Laminitis results when the lamellar suspensory apparatus of the distal phalanx fails and the bone sinks into the hoof capsule painfully crushing and shearing the soft tissues surrounding it. Thus, for laminitis treatment to be effective, the drug delivery target should be the lamellar interface. Techniques were developed that not only infused a drug into the lamellar region of the horse’s foot but also measured the concentration of the drug in that region. The potential anti-laminitis drug Marimastat was tested against experimentally induced laminitis. When laminitis pathogenesis can be effectively arrested by the efficacious delivery of a safe, potent anti-laminitis drug, genuine progress will have been made.

Background

Laminitis is a crippling disease of horse’s feet in which the bone inside the foot detaches from its lamellar connections inside the hoof and descends downwards crushing the sensitive corium of the sole. No validated laminitis drug therapy exists, yet pharmaceutical agents with potential for laminitis prevention have been identified. Demonstrating that therapeutic drug concentrations have been achieved in lamellar tissue is key to experimentally evaluating the efficacy of these agents. Some drugs, including the enzyme inhibitor Marimastat, are impractical for systemic administration but may be effective if administered locally. Enzyme activation has been implicated in the development of laminitis pathology. The enzyme inhibitor Marimastat prevents in vitro laminitis (laminitis duplicated in a test tube) but has never been tested against clinical laminitis in the live horse.
Aims/objectives

The principal aim of this project was to compare different methods of lamellar drug delivery and establish an optimal method for delivery of candidate anti-laminitis drugs (ALDs) to equine digital lamellar tissue. The central hypothesis was that a local or targeted delivery method would be necessary to achieve therapeutic lamellar drug concentrations and prevent laminitis.

Methods used

Marimastat was used as an example candidate ALD. To know if correct drug concentrations in the lamellae were achieved, a detection method was needed. This was achieved using lamellar ultrafiltration, a minimally invasive method of collecting lamellar interstitial fluid for drug concentration studies. Two different methods of drug delivery were tested; intraosseous infusion of the distal phalanx (IOIDP) and regional limb perfusion (RLP). The method that resulted in the highest lamellar Marimastat concentrations was selected to test against laminitis induction to evaluate the efficacy of Marimastat in preventing laminitis.

After testing on cadaver limbs ultrafiltration probes were placed in the lamellar tissue of 6 living horses and the resultant ultrafiltrate was collected continuously for up to 14 days and analysed (Fig 1). Sections surrounding the probe and control tissue from the contralateral limb were harvested at the end of the study and studied with the microscope. The ability of IOIDP and RIVI to deliver Marimastat was tested by measuring the concentration of Marimastat in lamellar ultrafiltrate. The best delivery technique was used to deliver Marimastat locally to test if it could prevent or at least ameliorate laminitis severity.

Figure 1 A, B and C

A: Under local anaesthesia, using sterile technique, a sharpened introducer is inserted up into the lamellar region through a window cut into the toe of the hoof.

B: The ultrafiltration probe is threaded up the introducer until it exits above the coronet (arrowed). The filtration membrane of the probe (arrowhead) is placed in the lamellar region by drawing the tubing up the introducer to a pre-measured position. When the introducer is withdrawn the probe remains correctly located in the lamellar region.

C: The probe collection tubing is connected to an evacuated test tube and ultrafiltrate of lamellar interstitial fluid is collected for analysis.
Results/key findings

Ultrafiltration probes, placed in the lamellar tissue of 6 horses were well tolerated with minimal signs of discomfort. The concentration of lamellar ultrafiltrate constituents was stable for 3 days after which it gradually declined. Lamellar drug delivery using IOIDP was inconsistent and did not achieve satisfactory lamellar Marimastat concentrations. RLP was superior for lamellar Marimastat delivery but frequent (6 hourly) dosing was necessary to achieve therapeutic lamellar concentrations.

All horses that underwent experimental laminitis induction using the oligofructose model developed laminitis despite the presence of Marimastat in their lamellar tissues. RLP with concurrent ultrafiltration successfully delivered Marimastat and confirmed target Marimastat concentrations. Marimastat did not prevent laminitis pathology in the oligofructose model, but may have reduced its severity.

Implications for relevant stakeholders

The results suggest that proteases within the inhibitory spectrum of Marimastat are not the key factor initiating laminitis pathology. The investigative model developed by this project will be suitable for evaluating other locally acting pharmaceuticals for laminitis. The successful application of the model during laminitis induction demonstrated its usefulness for investigating alternative pharmaceuticals, with the caveat that quantification of in vitro recovery and lamellar pharmacokinetics in normal horses would be necessary for each pharmaceutical investigated.

Recommendations (for veterinary and animal scientist laminitis researchers)

The novel research described in this report advances laminitis science by presenting a new investigative model for lamellar drug delivery and lamellar tissue analysis. Further work should utilise this model to investigate alternative pharmaceuticals with potential to prevent laminitis, then delivery techniques can be optimised for clinical application. When laminitis pathogenesis can be effectively arrested, by the efficacious delivery of a safe, potent anti-laminitis drug, genuine progress will have been made.
Publications arising from this project

The following scientific publications describe in detail the methods and results of the research undertaken for this project. These papers may be obtained through a university library or the publisher web site for specific journals.


C. Underwood, S.N. Collins, A.W. van Eps, P.C. Mills, R.E. Allavena, C.E. Medina Torres, A. Meizler, C.C Pollitt. Intraosseous infusion of the distal phalanx compared to systemic intravenous infusion for marimastat delivery to equine lamellar tissue. Submitted to The Equine Veterinary Journal

C. Underwood, S.N. Collins, P.C. Mills, A.W. van Eps, R.E. Allavena, C.E. Medina Torres, C.C Pollitt. Regional intravenous limb perfusion compared to systemic intravenous administration for marimastat delivery to equine lamellar tissue. Submitted to The Equine Veterinary Journal

C. Underwood, A.W. van Eps, P.C. Mills, C.E. Medina-Torres, E.M. Castro-Olivera, C.C Pollitt. Regional delivery of marimastat during oligofructose-induced laminitis development has minimal effect on lesion severity Submitted to The Equine Veterinary Journal

Publications arising from this project

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