Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2013, **40,** 440–448 doi:10.1111/vaa.12030

CASE REPORT

# Use of a soluble epoxide hydrolase inhibitor as an adjunctive analgesic in a horse with laminitis

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## Abstract

**History** A 4-year old, 500 kg Thoroughbred female horse diagnosed with bilateral forelimb laminitis and cellulitis on the left forelimb became severely painful and refractory to non-steroidal anti-inflammatory therapy (flunixin meglumine on days 1, 2, 3 and 4; and phenylbutazone on days 5, 6 and 7) alone or in combination with gabapentin (days 6 and 7).

**Physical examination** Pain scores assessed independently by three individuals with a visual analog scale (VAS; 0 = no pain and 10 = worst possible pain) were 8.5 on day 6, and it increased to 9.5 on day 7. Non-invasive blood pressure monitoring revealed severe hypertension.

**Management** As euthanasia was being considered for humane reasons, a decision was made to add an experimental new drug, *trans*-4-{4-[3-(4-Trifluoromethoxy-phenyl)-ureido]-cyclohexyloxy}-benzoic acid (*t*-TUCB), which is a soluble epoxide hydrolase (sEH) inhibitor, to the treatment protocol. Dose and frequency of administration were selected based on the drug potency against equine sEH to produce plasma concentrations within the range of 30 nmol $L^{-1}$ and 2.5 μmol $L^{-1}$. Pain scores decreased sharply and remarkably following *t*-TUCB administration and blood pressure progressively decreased to physiologic normal values. Plasma concentrations of *t*-TUCB, measured daily, were within the expected range, whereas phenylbutazone and gabapentin plasma levels were below the suggested efficacious concentrations.

**Follow up** No adverse effects were detected on clinical and laboratory examinations during and after *t*-TUCB administration. No new episodes of laminitis have been noted up to the time of writing (120 days following treatment).

**Conclusions** Inhibition of sEH with *t*-TUCB was associated with a significant improvement in pain scores in one horse with laminitis whose pain was refractory to the standard of care therapy. No adverse effects were noticed. Future studies evaluating the analgesic and protective effects of these compounds in painful inflammatory diseases in animals are warranted.

*Keywords* analgesia, antinociception, arterial blood pressure, equine, nociception, pain management.

## Introduction

Laminitis is an extremely painful condition of the foot in horses. Its pathophysiology remains poorly understood, but involves both vascular and inflammatory events within the hoof leading to disruption of the lamellar dermo-epidermal junction, impaired biomechanical function, pain and substantial suffering (Hood et al. 1993; Hood 1999; Sumano Lopez

et al. 1999; Parks & O'Grady 2003; Driessen et al. 2010). Ischemia and inflammation in the early stages of laminitis likely cause neuronal injury that eventually shifts the acute inflammatory pain into a chronic syndrome with a prominent neuropathic component (Moalem & Tracey 2006; Peroni et al. 2006; Belknap et al. 2007; Jones et al. 2007). The precise timing and nature of these events remain elusive. The response to treatment can be quite unpredictable. Such complexity makes pain management in horses with laminitis one of the biggest challenges in equine practice. Non-steroidal anti-inflammatory drugs (NSAID) are the most commonly used analgesics for this condition. However, limited efficacy against neuropathic pain and risks of dose-dependent gastrointestinal and renal adverse effects are significant limitations of these compounds (Sumano Lopez et al. 1999; Taylor et al. 2002; Driessen et al. 2010). These constraints often leave euthanasia as the only humane alternative to alleviate pain and suffering in affected horses (Driessen et al. 2010). More efficacious and safer analgesics are needed for this condition.

The oxidative metabolism of polyunsaturated fatty acids (PUFAs) such as arachidonic acid (ARA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and linoleic acid (LNA) produces potent inflammatory mediators. Most of the analgesic research and drug development has focused on inhibiting ARA derivatives formed by cyclooxygenases (COX) (Tokuyama & Nakamoto 2011). Cytochrome P450 enzymes mediate another critical yet relatively unexplored pathway of PUFA metabolism. This pathway transforms PUFAs into various biologically active compounds, including epoxy-fatty acids (EFAs or epoxides), such as epoxy-eicosatrienoic acids (EETs), or hydroxyl derivatives, such as hydroxy-eicosatetraenoic acids (HETEs) (Wagner et al. 2011b). These epoxides have multiple biological activities including the modulation of inflammation and nociceptive signaling (Murakami 2011). The biological activity of these epoxides is restricted as they are metabolized to the corresponding diols by the enzyme soluble epoxide hydrolase (sEH) (Wagner et al. 2011a). This has been confirmed with the development and use of sEH inhibitors (sEHIs) (Morisseau & Hammock 2005; Hwang et al. 2007) in conditions involving several body systems and functions (Revermann 2010). The major function of sEH is the degradation of endogenous lipid metabolites, with a minor role in xenobiotic metabolism (Morisseau & Hammock 2008; Decker et al. 2009).

In the horse, sEH has been characterized in the liver and lungs (Lakritz et al. 2000), but its biological roles have yet to be examined *in vivo*. Several lines of evidence from studies in classic rodent models of inflammatory and neuropathic pain (Inceoglu et al. 2006, 2007, 2008; Schmelzer et al. 2006; Morisseau et al. 2010; Wagner et al. 2011a, b) suggest that analgesia is likely to be produced via sEH inhibition in horses with pain due to laminitis (Sumano Lopez et al. 1999; Jones et al. 2007; Driessen et al. 2010). In a rat model of inflammatory pain, transdermal administration of two distinct sEHIs effectively attenuated LPS-induced thermal hyperalgesia and mechanical allodynia (Inceoglu et al. 2006). Similarly positive results were obtained in other models of inflammatory and neuropathic pain (Inceoglu et al. 2007, 2008). In fact, these compounds are stronger anti-inflammatory and analgesic drugs in rodent models than coxibs or NSAIDs (Inceoglu et al. 2007; Wagner et al. 2011b). These findings along with observations that sEHIs reduce pain induced by direct intra-plantar injection of $PGE_2$, whereas NSAIDs and steroids do not, indicate that these drugs have distinct mechanisms of action that can be useful in multimodal therapies (Inceoglu et al. 2011).

It has been proposed that sEHI-mediated anti-hyperalgesia in inflammatory and neuropathic pain occurs via two distinct mechanisms. One mechanism involves direct anti-inflammatory action of epoxides including down-regulation of induced cyclooxygenase (COX)-2 expression, possibly through a nuclear factor-kappa B (NF-κB)-dependent pathway (Node et al. 1999). The second mechanism involves epoxide-mediated up-regulation in steroid/neurosteroid synthesis in the presence of elevated cAMP levels, which then results in analgesia via GABA channels (Inceoglu et al. 2008). Collectively, the multimodal mechanism of action and the favorable interactions with NSAIDs in the ARA cascade suggest that sEH and COX inhibitor combinations may produce significant pain relief while minimizing the risks of NSAID-associated side effects.

In this case report, we describe the use of an experimental sEH inhibitor as analgesic adjunct in a horse with laminitis.

## Case history, diagnosis and management

On November 2, 2011, a 4-year-old, 500 kg, female Thoroughbred horse was examined by the Veterinary Field Service of the University of California at