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

Alonso GP Guedes*, Christophe Morisseau†, Albert Sole‡, Joao HN Soares‡, Arzu Ulu†, Hua Dong† & Bruce D Hammock†

*Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, CA, USA
†Department of Entomology and U.C.D. Cancer Center, University of California, Davis, CA, USA
‡Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California, Davis, CA, USA

Correspondence: Alonso Guedes, Department of Surgical & Radiological Sciences, 2112 Tupper Hall, University of California, One Shields Avenue, Davis, 95616 CA, USA. E-mail: aguedes@ucdavis.edu

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

Davis (UCDavis) Veterinary Medical Teaching Hospital with the presenting complaint of swelling on the left forelimb and reluctance to walk. The mare was reportedly found that morning unwilling to move, painful in both front feet and a rectal temperature of 38.6 °C. The mare had been donated to UCDavis, Center for Equine Health due to a moderate to severe lesion (44% tear) of the left forelimb superficial digital flexor tendon while on the racetrack in April 2011 and was subsequently enrolled in a stem cell study. In July 2011, the mare underwent angiography using computed tomography followed by intra-arterial regional limb perfusion of ^{99m}Tc-HMPAO labelled mesenchymal stem cells of the left forelimb. The cells were delivered via a catheter placed in the median artery at the level of the distal radius and the perfusion was performed without the use of a tourniquet. Swelling of the region of the left carpus and proximal region of the third metacarpal bone was noted in the immediate post-operative period. It resolved without obvious complications following treatment that included leg bandage, stall rest, and oral administration of phenylbutazone (1 g twice a day) for 3 days.

On Nov. 2nd, physical examination findings included tachycardia (60 beats minute^{-1}), tachypnea (40 breaths minute^{-1}), increased digital pulses in both forelimbs, bilateral forelimb swelling in the region of the third metacarpal bones, focal swelling on the medial and lateral aspect of the left radius that appeared painful on palpation. The mare had symmetrical adequate muscling but had adopted the classic laminitis stance (weight shifted to the hind legs to minimize the load on the front limbs) and was unwilling to walk without much encouragement. All other physical examination parameters appeared normal. Orthogonal radiographic projections of the left and right front distal extremities revealed medial to lateral hoof imbalance bilaterally, mild dorsal hoof wall thickening bilaterally, with fracture of the dorso-distal aspect of the third phalanx bilaterally, but no evidence of rotation or sinking. Orthogonal and craniolateral-caudomedial oblique radiographic projections of the left radius revealed radial soft tissue swelling without evidence of osseous involvement. Irregularity of the caudodistal left radius likely represented remodeling secondary to previous trauma and seemed unlikely to be clinically significant. The changes in the distal extremities were suggestive of laminitis.

A clinical diagnosis of left forelimb cellulitis and bilateral forelimb laminitis was made. Initial therapy included cold hydrotherapy (once daily), flunixin meglumine (1 mg kg^{-1}, twice daily, IV) (Banamine, Intervet Inc., Germany), penicillin G procaine (PPG; 24,000 U kg^{-1}, twice daily, IM) (PenOne Pro, Norbrook Laboratories Ltd, Newry, Northern Ireland), gentamicin (3.5 mg kg^{-1}, once daily, IV). Soft Ride (Soft-Ride, Inc., TX, USA) boots were applied bilaterally. Sweat wraps were used on both forelimbs, containing furazone (0.2% Nitrofurazone; Neogen Corporation, KY, USA), dimethyl sulfoxide (DMSO) (DOMOSO Gel; Fort Dodge Animal Health, IA, USA) and magnesium sulfate ($MgSO_4$; Epson Salt, Aaron Industries, CA, USA). This therapy was continued for the next 4 days (days 2, 3, 4 and 5), although the dose and route of administration of flunixin meglumine were changed (0.5 mg kg^{-1}, twice daily, PO) on days 4 and 5. Over this period, the cellulitis was improving and the mare appeared more comfortable until day 5, when she became increasingly more painful. Phenylbutazone [4 mg kg^{-1} (Oral; Bute Boluses, VEDCO Inc, MO, USA), IV (Phenylbutazone 20%, MWI, ID, USA)] was administered for pain relief and the therapy was changed such that flunixin meglumine and PPG were discontinued and phenylbutazone (4 mg kg^{-1} twice daily, PO), trimethoprim sulfamethoxazole (Amneal Pharmaceuticals, NY, USA) (30 mg kg^{-1} twice daily, PO) and pentoxifylline (Pentoxifylline Extended-release tablets USP, Apotex Inc., Ontario, Canada) (11 mg kg^{-1} twice daily, PO) were instituted. On day 6, the mare became very painful (pain score 8.5/10 on visual analog scale, VAS; '0' = no pain and '10' = worst possible pain) (Vinuela-Fernandez et al. 2011) and was standing but unwilling to walk. Although the cellulitis had improved significantly (almost not noticeable), laminitis appeared to be worse. The hind feet also appeared to be slightly painful, as suggested by the presence of weight shifting. Gabapentin (20 mg kg^{-1} twice daily, PO) (Gabapentin Capsules USP, Actavis Pharma Manufacturing Pvt. Ltd, Tamilnadu, India) was added to the treatment protocol.

The condition further deteriorated on day 7, with the mare spending most of the day in lateral recumbency. It required much encouragement to get her to stand up and, once standing, she was unwilling to walk. At this time, systematic assessments of pain with the continued use of a VAS, and the addition of measurement of blood pressure, heart and respiratory rates, and gastrointestinal sounds (Teixeira Neto et al. 2004) were instituted. Blood pressure was measured in triplicate, non-invasively

with an oscillometric technique (Cardell Model 9401 BP Monitor, Sharn Veterinary Inc., FL, USA), with a tail cuff (width equal to 40% of the circumference of the base of the tail) and the horse standing. The measured pressure was normalized for the difference in hydrostatic pressure between the base of the tail and the scapulohumeral joint (base of the heart) such that 7.5 mm Hg was added for each 10 cm in vertical distance. Blood pressure was measured before *t*-TUCB (baseline), during *t*-TUCB administration (daily at 2, 4, 6, 12 and 24 hours following each dosing) and after its discontinuation (daily approximately at 08:00, 14:00 and 20:00 hours). Three individuals (two-third-year residents - equine surgery and anesthesia - and one board certified anesthesiologist) independently assessed the patient throughout the day taking into account changes in expression, demeanor, posture, stance and mobility. Two individuals (residents) were unaware of the identity and mechanism of action of the compound. An overall daily VAS score was then assigned by averaging the values recorded by each evaluator. All assessments were done with the patient in the stall and the results are shown in Fig. 1. On day 7, the average VAS score was 9 out of 10 and blood pressure measurements revealed significant hypertension.

Euthanasia was being considered at this stage for humane reasons. A decision was made to add an experimental drug, *trans*-4-{4-[3-(4-trifluoromethoxy-phenyl)-ureido]-cyclohexyloxy}-benzoic acid (*t*-TUCB; synthesized by one of the authors - BH), to the treatment protocol and this was added early on day 8. This drug is an sEHI with the properties listed above, and is currently being investigated under approval of the Institutional Animal Care and Use Committee of the UC Davis as a potential new analgesic in horses. Dose (0.1 mg kg^{-1}) and frequency of administration (once daily) were selected to produce plasma concentrations within the range of approximately 2500 nmol L^{-1} (peak) and 30 nmol L^{-1} (trough). Concentrations in this range are expected to be sufficient to inhibit the equine sEH *in vivo* on the basis of previous studies in other species (Inceoglu et al. 2006, 2008; Morisseau et al. 2006; Tsai et al. 2010; Ulu et al. 2011) and the *in vitro* potency against the equine sEH (unpublished data). The drug was dissolved in dimethyl sulfoxide (DMSO) to a final concentration of 10 mg mL^{-1}, filter-sterilized with 0.2 μm pore size sterilizing-grade membranes, and administered intravenously as a bolus by hand over a period of approximately

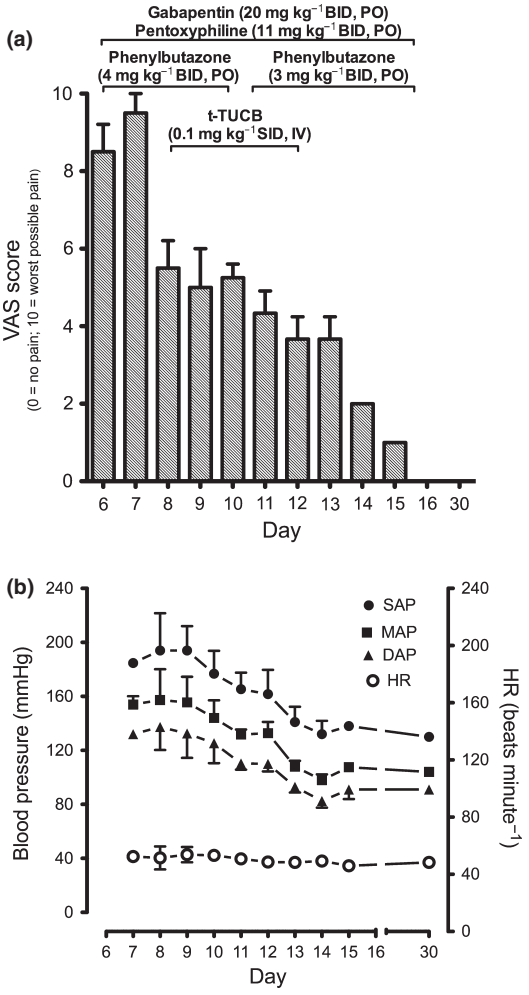

Figure 1 Daily visual analog pain scores (**a**), systemic arterial blood pressure and heart rate (**b**) in one horse with pain due to laminitis, which was treated with multimodal analgesic therapy that included an investigational new drug inhibitor of soluble epoxide hydrolases (*t*-TUCB). The time frame of drug administration, along with doses, frequency and route of administration is presented above panel **A**. VAS = visual analog scale (0 = no pain, 10 = worst pain possible); SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure; HR = heart rate. BID = twice daily; SID = once daily; PO = orally; IV = intravenously.

1 minute. To determine the plasma concentrations of *t*-TUCB, blood samples were collected from the opposite jugular vein just prior to *t*-TUCB administration (baseline), at 5, 15 and 30 minutes, and at 1, 2, 4, 8, 12 and 24 hours following each of the first three doses (days 8, 9 and 10), at 6, 12, 18 and 24 hours following each of the next two doses (days 11 and 12), and at 36, 48, 72 and 96 hours

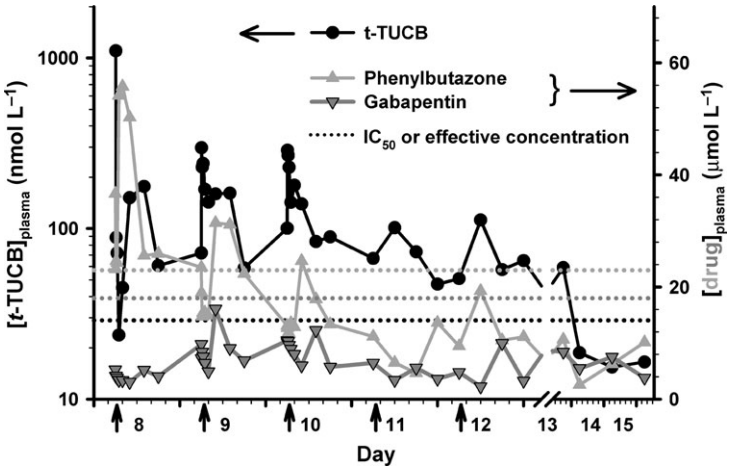

Figure 2 Plasma concentrations of the experimental drug inhibitor of soluble epoxide hydrolases *t*-TUCB (0.1 mg kg^{-1} SID, IV), phenylbutazone (3–4 mg kg^{-1} BID, PO) and gabapentin (20 mg kg^{-1} BID, PO) in one horse with pain due to laminitis. The arrows along the *X*-axis indicate when drug was administered.

following the last dose (day 12). Plasma concentrations of phenylbutazone and gabapentin were determined by LC-MS/MS analyses (You et al. 2009; Liu et al. 2011) in these same blood samples, but corresponded to slightly different time points since they were being administered 1 hour after (phenylbutazone) or 5 hours before (gabapentin) *t*-TUCB. The results are shown in Fig. 2. In addition, blood was collected before dosing on day 8 and 24 hours after each dosing on days 9, 10 and 13 for laboratory analyzes of complete blood cell count (CBC) and serum biochemistry (CHEM).

The first dose of *t*-TUCB was administered early on day 8. The mare spent the majority of that day standing in the stall, was interested in surroundings, began to walk spontaneously and was frequently looking out the front stall door. The average VAS pain score was 5.5. Hypertension was still present. Initial laboratory analyzes of CBC and CHEM revealed no significant changes after the first dose of *t*-TUCB. With these encouraging results, *t*-TUCB continued to be administered for 4 more days (days 9, 10, 11 and 12) during which time the mare continued to improve in expression, demeanor, posture, stance and mobility, which was reflected by lower VAS pain scores (Fig. 1a). As treatment progressed, the hypertension improved gradually towards normal physiologic values (Fig. 1b).

Daily plasma concentrations of *t*-TUCB were within the expected range, although it did not reach the expected peaks of 2500 nmol L^{-1} on any day, and it decreased below the expected trough of 30 nmol L^{-1} on one time point in the first day. The plasma concentrations typically decreased rapidly within the first hour and increased again at 3 hours, most notably on the first day (day 8). The calculated volume of distribution of the central compartment, elimination half-life and clearance of *t*-TUCB for this horse were 1.22 L kg^{-1}, 29.8 hours and 0.04 mL $hour^{-1}$ kg^{-1}, respectively. The highest and lowest measured plasma concentrations of phenylbutazone were 55 μmol L^{-1} and 2 μmol L^{-1}, and those of gabapentin were 18 μmol L^{-1} and 1 μmol L^{-1}. The true peaks of gabapentin were likely missed because of the scheduled times for administration and that the primary goal in this case was to determine the plasma concentrations of *t*-TUCB.

No adverse effects were observed both in the clinical examinations and evaluation of blood work. All hematologic and serum biochemistry values were within the reference range with the exception of AST on day 8 (506 IU L^{-1}; reference range 168–494) and fibrinogen on day 13 (500 mg dL^{-1}; reference range 100–400). At 30 days follow-up the mare was normotensive and had no evidence of lameness. At 120 days, a few irregularities were apparent on the hoof wall but no episodes of lameness have been noticed. At this time, orthogonal projections of the distal extremity of both forelimbs were taken and compared to a similar study from November 2, 2011. Main new findings included increased dorsal hoof

wall thickness bilaterally, rotation of the distal phalanx (mild on the left and moderate on the right forelimb), mildly broken-back hoof pastern axis in both forelimbs. There was also evidence of remodeling/osteoproduction on the dorsal solar margin of the right forelimb seen on the lateral projection. While not causing clinical signs of laminitis post-recovery, these changes might explain the worsening of the condition and refractory pain observed on days 5, 6 and 7.

Discussion

This case report is the first description of the successful use of the sEH inhibitor *t*-TUCB, as an analgesic adjunct in a horse with laminitis. The horse was being treated for laminitis for 7 days and had severe pain that was not responding to NSAIDs and gabapentin therapy. A remarkable reduction in pain scores occurred after the addition of *t*-TUCB and after the first dose the horse was willing to walk in the stall, albeit somewhat reluctantly, and had good appetite. Inhibitors of sEH have been shown to be potent anti-inflammatory and analgesic agents in classic rodent models of both inflammatory and neuropathic pain (Inceoglu et al. 2006, 2007, 2008; Schmelzer et al. 2006; Morisseau et al. 2010; Wagner et al. 2011a,b). The observations in this horse with naturally occurring laminitis suggest that these compounds work not only in experimental models, but may have utility in the treatment of diseases associated with inflammation and pain. This notion is being tested in ongoing experiments. Preliminary data show that the concentration of several epoxides and respective diols derived from relevant long-chain fatty acids is changed in laminitic compared to healthy horses (unpublished data).

Inhibitors of sEH have been shown to be stronger anti-inflammatory and analgesics than coxibs or NSAIDs in rodent models of inflammatory pain (Inceoglu et al. 2007; Wagner et al. 2011b). While it is not possible to ascertain the sole analgesic contribution of *t*-TUCB in the case reported here, it is noteworthy that pain refractory to phenylbutazone and gabapentin promptly improved once the sEHI was administered. Interactions of *t*-TUCB with phenylbutazone, gabapentin and/or pentoxifylline likely occurred. It is known that co-administration of NSAIDs and sEHIs result in enhancement of antinociception (Schmelzer et al. 2006). In a mouse model of inflammatory pain, sEHI administered alone decreased COX-2 protein expression and prostaglandin E_2 (PGE_2) production in LPS-treated mice with no effect on COX-1 expression. When NSAIDs and sEHIs were combined, inhibition of COX-2 protein expression was enhanced with reduction in PGE_2 concentrations without disrupting prostacyclin and thromboxane levels (Schmelzer et al. 2006). Interestingly, measured phenylbutazone plasma concentrations were below its 80% inhibitory concentration (IC_{80}; Approximately 23 μmol L^{-1}) against COX-2 for most of the time. The IC_{80} rather than the IC_{50} value seems more suitable for evaluation of NSAIDs, particularly since valid anti-inflammatory effects are achieved when COX-2 activity is 80% inhibited (Beretta et al. 2005). However, an additive or even a synergistic effect between *t*-TUCB and phenylbutazone could be responsible for the analgesic efficacy in this report.

The minimum effective analgesic plasma concentration of gabapentin in horses is unknown (Terry et al. 2010) although it was used successfully in one horse with neuropathic pain (Davis et al. 2007). Measured plasma concentrations in the horse of the present report were well below the concentration that has been associated with analgesia (Approximately 18 μmol L^{-1}) in human volunteers (Eckhardt et al. 2000). Although antinociceptive effects of sEHI and gabapentin co-administration have not been investigated, sEHI produced dose-dependent anti-allodynic effects more potently and efficaciously than gabapentin in a rat model of diabetic neuropathy (Inceoglu et al. 2012). There probably was a positive interaction with the phosphodiesterase inhibitor pentoxifylline since analgesia produced by sEHIs is cyclic AMP (cAMP)-dependent, other phosphodiesterase inhibitors have been shown to increase EET concentrations (Inceoglu et al. 2011), and pentoxifylline itself may have analgesic effects in inflammatory and neuropathic pain states (Vale et al. 2004; Liu et al. 2007). Collectively, the above information corroborates the conclusion that sEH inhibition with *t*-TUCB played a central role in this horse's pain management. The favorable interactions between sEHIs and NSAIDs in the arachidonic acid cascade might allow for the use of lower doses of NSAIDs while maintaining efficacy and minimizing the risks of NSAID-associated side effects.

Drugs or techniques that provide complete control of nociception are not desirable in horses with laminitis because pain also has a protective function. It is important to prevent placement of exces-

sive weight on the affected limb that could lead to disruption of the inflamed lamellar dermo-epidermal tissues. Therefore, a useful analgesic would control maladaptive pain (i.e., hyperalgesia, allodynia) while maintaining some degree of adaptive pain (i.e., pain that is protective to the organism). In the case reported here, the pain scores dropped sharply with the inclusion of *t*-TUCB but, as in rodents, the sEHI did not abolish all nociceptive input from the feet. Modulation of hyperalgesia and allodynia with the use of sEHIs has been demonstrated in rodent models (Inceoglu et al. 2006, 2007, 2008, 2011; Schmelzer et al. 2006; Morisseau et al. 2010; Wagner et al. 2011a,b). An analgesic that provides the above and is also able to arrest the progression of the disease would be highly desirable. In this context, pharmacologic inhibition of sEH fully prevented mortality in LPS-exposed mice by promoting inflammatory resolution as shown by reductions in plasma concentrations of pro-inflammatory cytokines and nitric oxide metabolites and increased synthesis of lipoxins (Schmelzer et al. 2005). As such, it is feasible that the improvement seen in this case of laminits resulted from nociceptive modulation via several mechanisms, and possibly also by arresting inflammatory events in laminar tissue. Future studies are warranted to test this hypothesis.

Because laminitis is a complex disease we cannot distinguish the comparative contributions of the different known biological effects of sEHI. However, laminitis presents as laminar inflammation and inflammatory pain transitioning into chronic and possibly neuropathic pain (Hood 1999; Driessen et al. 2010). The associated hypertension could have a number of causes including a response from pain itself (Bussieres et al. 2008). However, this complex disorder addresses the multiple advantages of sEHI in reducing inflammation, inflammatory pain, neuropathic pain and toxicity associated with NSAIDs (Node et al. 1999; Yu et al. 2000; Schmelzer et al. 2005, 2006; Inceoglu et al. 2006, 2007, 2008; Chiamvimonvat et al. 2007; Imig & Hammock 2009; Revermann 2010; Wagner et al. 2011a).

No undesirable effects were detected in the horse of this report. To date, no overt adverse effects associated with sEH inhibition have been observed in studies in rodents (Inceoglu et al. 2006, 2007, 2008; Schmelzer et al. 2006; Morisseau et al. 2010) dogs (Tsai et al. 2010), and non-human primates (Ulu et al. 2011) even when co-administered with NSAIDs (Schmelzer et al. 2006).

Conclusion

Administration of *t*-TUCB, an sEHI, 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.

Acknowledgements

This work was partially funded by NIEHS grant ES02710, NIEHS Superfund Basic Research Program grant P42 ES04699, and by the UCDavis Center for Equine Health.

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Received 24 May 2012; accepted 28 June 2012.