Comparison of the Clinical Efficacy of COX-2 Selective and sEH Inhibitors Using an Equine Model of Naturally Occurring Osteoarthritis

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INTRODUCTION: Current long-term therapy for osteoarthritis, a debilitating and degenerative joint disease, relies heavily on non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Although NSAIDs provide symptomatic relief, they are associated with adverse side effects and impair bone remodeling and repair [2]. Soluble epoxide hydrolase (sEH) is a novel target to control inflammation and pain. Recent studies have demonstrated that sEH-generated dihydroxyeicosatrienoic acids (DHETs) induce chondrocyte apoptosis and are associated with osteoarthritis progression [3,4]. In vitro models of osteoarthritis indicate disease-modifying effects through the reduction in sEH induced DHETs formation and increased collagen synthesis [3,5]. Additionally, evidence suggests that cyclooxygenase (COX) inhibitors and sEH inhibitors may act synergistically and reduce the effective dose of the COX-inhibitor. Our objectives were to compare the clinical efficacy of an sEH inhibitor (t-TUCB; EisOsis) to a COX-2 selective inhibitor (Equioxx (firocoxib); Boehringer Ingelheim) when administered individually and in combination using an equine model of naturally occurring osteoarthritis. We hypothesized that treatment with t-TUCB and firocoxib would reduce lameness without adverse effects on gastric mucosa.

METHODS: The study was conducted following a protocol approved and overseen by the University of Tennessee Knoxville Institutional Animal Care and Use Committee. Six horses with radiographic evidence of tarsal osteoarthritis were utilized. A 3-way crossover study with a two-week washout period was performed with ten days of oral administration of 1) t-TUCB (500mg), 2) firocoxib (57mg), 3) t-TUCB/firocoxib (500 mg/28.5 mg). Pre- and post- treatment gastroscopy was conducted. Gastric ulcers were graded using the Equine Gastric Ulcer Council grading system [6]. Pre-treatment, post-treatment, and two-week post-treatment lameness evaluations utilizing a body-mounted inertial sensor system (Equinosis Q^{TM}) were performed. Raw vector values were calculated in the forelimbs as the vector sum of the HD_{max} and HD_{min} with an 8.5 mm asymmetric threshold and in the hindlimbs as PD_{min} or PD_{max} with a 3 mm asymmetric threshold. Vector values below thresholds were classified as sound (grade 0). Lameness grades (1-5) were determined by intervals of the asymmetric threshold. A mixed model analysis using a randomized block design for repeated effects was performed using SAS 9.4. Significance was set at $p<0.05$.

RESULTS SECTION: Gastric grades did not differ between or within treatment. Combined fore and hindlimb lameness grades significantly improved from baseline across all treatments (Figure 1; $p<0.05$). Forelimb grades improved following ten days of treatment with firocoxib alone and in combination with t-TUCB ($n=4$; $p<0.05$). Treatment with t-TUCB alone ($n=3$) did not significantly improve forelimb grades after ten days of treatment or two weeks post-treatment, compared to baseline ($p=0.0604$). Hindlimb lameness grades improved from baseline with ten days of firocoxib and t-TUCB alone ($n=6$) and in combination ($n=5$) ($p<0.05$). Combined lameness grades remained improved from baseline two weeks following discontinuation of t-TUCB alone and in combination with firocoxib ($p<0.05$). Lameness grades returned to baseline two weeks after discontinuation of firocoxib alone.

DISCUSSION: Treatment with the sEH inhibitor resulted in improved objective lameness grades on par with a COX-2 selective inhibitor and may provide disease-modulating effects with long-lasting benefits. Current pharmacologic recommendations for osteoarthritis therapy across guidelines relies heavily on NSAIDs [7]. Significant improvement in lameness following seven days of firocoxib (0.1 mg/kg) treatment in horses with naturally occurring osteoarthritis has been reported based on force plate analysis [8]. Therefore, firocoxib was selected as an active control treatment. Consistent with previous reports, utilizing a body-mounted inertial sensor system, we found improvement in lameness following treatment with firocoxib for ten days. Treatment with t-TUCB did not differ from our active control treatment, with significant improvement in objective lameness when administered alone and in combination with lower-dose firocoxib (Figure 1). Previous studies demonstrated the therapeutic benefit of t-TUCB in horses when used in a multi-modal approach to laminitis treatment and with significant improvement of inflammatory and mechanically induced lameness models [9,10,11]. Our results provide further evidence to support the use of sEH inhibitors to treat inflammatory and neuropathic conditions.

Studies evaluating treatment with firocoxib indicated that a two-week washout period was sufficient for the compound to be eliminated and previous single-dose evaluation of t-TUCB with induced lameness utilized a two-week washout period [1,9]. The treatment order was randomized to reduce the potential for carryover effect. Although lameness grades two weeks following treatment discontinuation of firocoxib alone did not differ from baseline as expected, lameness grades following discontinuation of t-TUCB alone and in combination with firocoxib remained improved from baseline. Previous studies found sEH inhibition reduced type II cartilage degradation and combined treatment with COX inhibition decreased the ratio of C2C-CPII in vitro and sEH inhibition ameliorated bone resorption via reduced expression of the RANK and RANKL in mice models of periodontal disease [3,12,13,14]. Our results indicate that the addition of the sEH inhibitor to the COX-2 selective inhibitor provided a sustained therapeutic effect, supporting the hypothesis that sEH inhibitors may represent a disease-modifying treatment of osteoarthritis.

No changes in gastric ulcer grades were noted within each treatment. No adverse reactions were observed following oral administration of either firocoxib or t-TUCB. Although further investigation into the safety of long-term sEH inhibitor treatment should be performed, our results support safe and effective usage in our equine model of naturally occurring osteoarthritis.

SIGNIFICANCE/CLINICAL RELEVANCE: Soluble epoxide hydrolase inhibitors are a novel class of drugs that may be a beneficial treatment for osteoarthritis without inducing side effects associated with NSAID usage. Additionally, sEH inhibitors may be able to be used synergistically with lower NSAID doses to relieve pain and inflammation.

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IMAGES AND TABLES:

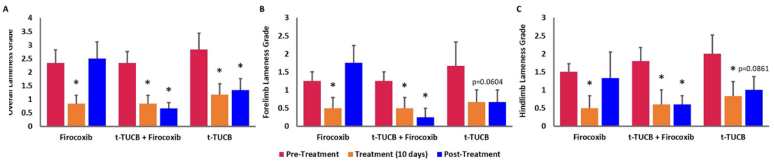

Figure 1. Lameness grades (A) overall (forelimb + hindlimb), (B) forelimb only, and (C) hindlimb only prior to treatment (red), with ten days of treatment (orange), and two weeks following discontinuation of treatment (blue) with firocoxib (57 mg/horse), t-TUCB with firocoxib (500 mg/horse + 28.5 mg/horse), or t-TUCB (500 mg/horse). Lameness grades significantly decreased/improved (*) from baseline following each treatment ($p<0.05$). Data are mean ± SEM.