HYPOTHESIS/STUDY OBJECTIVES

Hypothesis: Administration of grapiprant will result in a significant increase in TNF-α concentrations, compared to baseline, following oral administration to horses.

Study Objectives:
• Describe the pharmacokinetics of grapiprant following oral administration of a single dose of 15 mg/kg to horses.
• Describe the magnitude and duration of the pharmacodynamic effect of grapiprant using an ex vivo inflammatory model and assessment of TNF-α concentrations.

INTRODUCTION

Rationale
When inflammation occurs in the body, cell membranes release phospholipids which are broken down into arachidonic acid. Arachidonic acid is further converted into COX and LOX, which are responsible for the generation of inflammatory mediators (Figure 1). Non-steroidal anti-inflammatory (NSAID) therapy is central to equine-medicine for the treatment of musculoskeletal-related diseases and pathologies. However, traditional NSAIDs have demonstrated adverse effects. Grapiprant is a "non-traditional" NSAID that is an PGE2 EP4 receptor antagonist. It is currently only FDA approved for the use in dogs but appears to be effective and well tolerated, in this species. Previous reports describe the pharmacokinetics of grapiprant following low dose administration to horses but to date there are no reports of its anti-inflammatory effects.

METHODS

• 8 healthy, exercised thoroughbreds ranging from 4-8 years and 487.0-572.0 kgs.
• Single oral administration of 15mg/kg grapiprant (Galliprant®) suspended in water and administered via dosing syringe.
• Blood samples collected for concentration determination prior to and up to 96 hours post administration into heparin blood tubes. Plasma grapiprant concentrations determined by liquid chromatography-tandem mass spectrometry. Non-compartmental analysis used to determine pharmacokinetic parameters.
• Aliquot of blood spiked with PGE2 and lipopolysaccharide (LPS) to simulate an inflammatory response. Following incubation, plasma was collected and TNF-α concentrations determined by ELISA.
• ANOVA used to compare post drug administration concentrations of TNF-α to baseline concentrations.

RESULTS

Figure 3: Plasma grapiprant (average +/- SD) concentrations over time following oral administration of 15mg/kg grapiprant tablets to 8 horses.

Pharmacokinetic Parameters
• Maximum grapiprant concentration (Cmax) : 327.5 ng/mL
  Range: 188.4-663.0 ng/mL
• Time to maximum concentration (Tmax): 1 hour
  Range: 0.75-2.0 hours
• Area under the curve: 831.8 h*ng/mL
  Range: 512.6-1421.6 h*ng/mL
• Terminal half life: 11 hours
  Range: 8.27-21.2 hours

Figure 4: TNF-α concentration (average +/- SD) over time prior to and following an oral administration of 15mg/kg grapiprant to horses. Asterisks (*) represent statistically significant differences in TNF-alpha concentrations compared to baseline.

Pharmacodynamics
• Significant increase in TNF-alpha for 2 hours post-drug administration
• Anti-inflammatory effect for 2-4 hours

FUTURE DIRECTION

• Test higher or multiple doses to try to maintain an effective concentration for a longer time period.

ACKNOWLEDGEMENTS

The authors would like to thank the National Institute of Health and the University of California, Davis STAR program for providing funding for this study. The authors would also like to thank Stacy Steinmetz, Kelsey Sminoff, Kirsten Kanarr, and Sandy Yin-Yim for their technical support.