Pharmacokinetics of grapiprant and effects on TNF-alpha concentrations following oral administration to horses

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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 centric 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 PGE_2 EP_4 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.

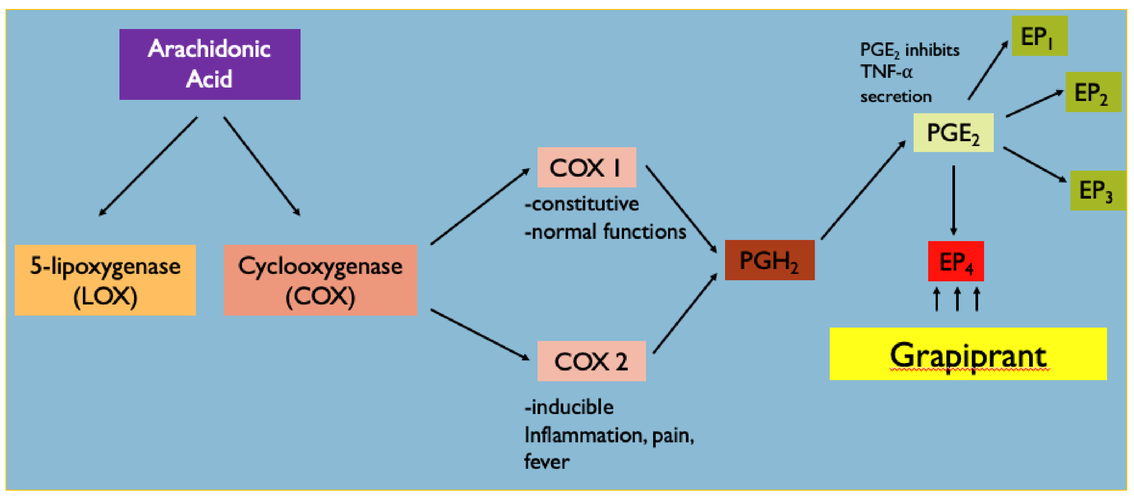

Figure 1: Arachidonic acid pathway showing the site of action of grapiprant.

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.

Fig 2: Oral dosing of grapiprant A) dosing syringes filled with crushed and suspended grapiprant tablets. B) Delivery of drug into the oral cavity via dosing syringe.

- Aliquot of blood spiked with PGE_2 and lipopolysaccharide (LPS) to simulate an inflammatory response. Following incubation, plasma was collected and TNF-α concentrations determined via ELISA.
- ANOVA used to compare post drug administration concentrations of TNF-α to baseline concentrations.

RESULTS

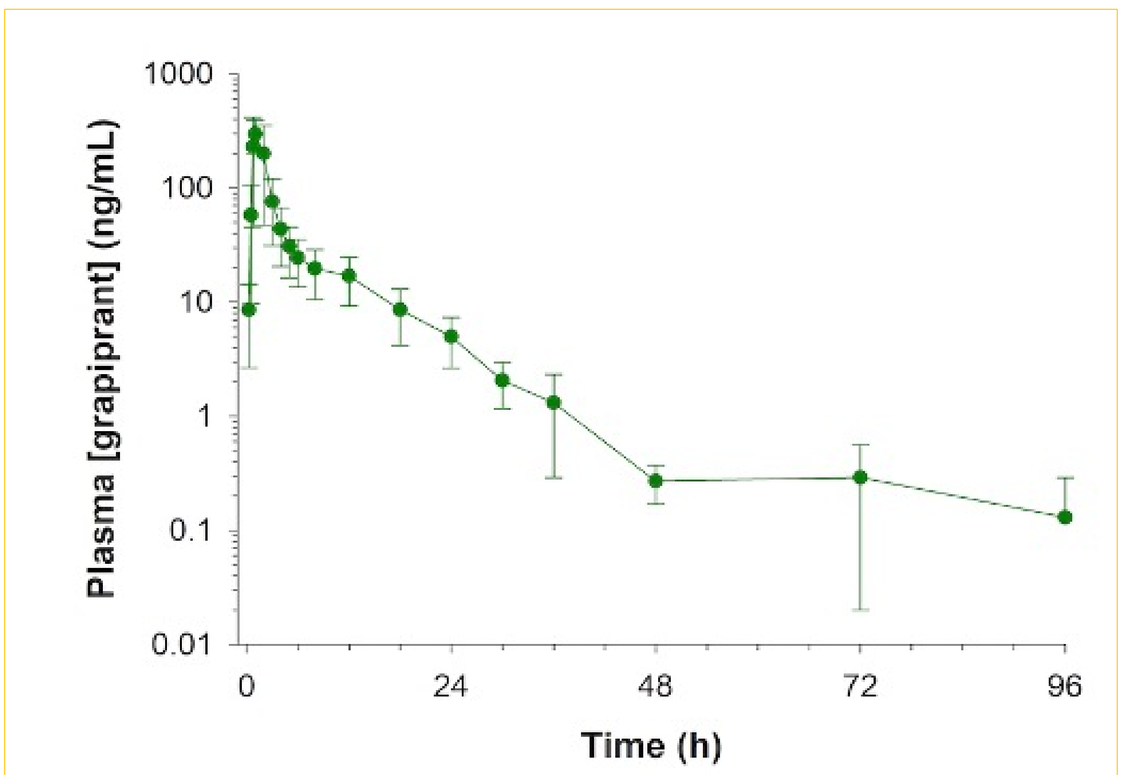

Figure 3: Plasma grapiprant (average +/- SD) concentrations over time following oral administration of 15mg/kg grapiprant tablets to 8 horses.

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

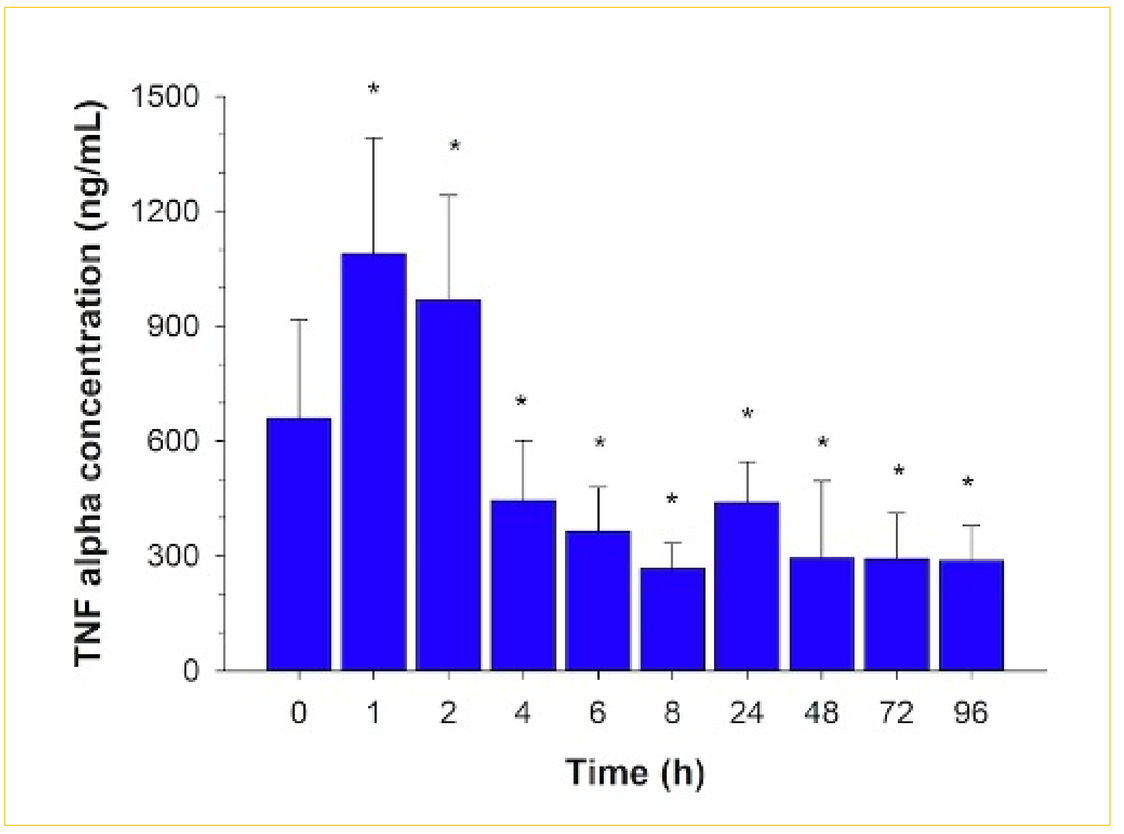

Figure 4: TNF-α concentration (average +/- SD) over time prior to and following an oral administration of 15mg/kg grapiprant to horses. Asterisks (*) represent statistically significant differences in TNF-alpha concentrations compared to baseline.

Pharmacodynamics

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

FUTURE DIRECTION

Future Direction

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

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