Pharmacokinetics and Anti-inflammatory Effects of Intramuscular Corticosteroids

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Introduction

- Betamethasone is a potent anti-inflammatory medication used both intra-articularly (IA) and intramuscularly (IM) for treatment of musculoskeletal inflammation in horses.
- Betamethasone prevents conversion of phospholipids to arachidonic acid and subsequent production of eicosanoids responsible for perpetuating the inflammatory process
- Administration of betamethasone can also suppress endogenous cortisol production.
- FDA approved equine product is formulated as a slow-release product, prolonging the pharmacologic effect.
- IA use in horses has been well-described but there are limited reports describing IM administration.
- Limited reports combined with widespread IM administration in performance horses necessitates further study to establish scientifically based withdrawal times prior to competition.

Objectives

1. Describe plasma and urine concentrations, pharmacokinetics, and clearance of betamethasone following intramuscular administration.
2. Describe the duration of the pharmacodynamic effects of betamethasone by assessing concentrations of hydrocortisone and inflammatory biomarkers in an ex vivo model of inflammation.

Methods

Animals

- 12 healthy, university-owned, treadmill-exercised horses aged 4-7 years old

Drug Administration

- 12 mg betamethasone administered intramuscularly in the neck

Sample Collection

- Blood collected at time 0 (prior to drug administration) and up to 17 days post drug administration for determination of betamethasone, cortisol and eicosanoid concentrations (using ex vivo assay; Figure 1)
- Urine collected up to 408 hours post drug administration
- Concentrations determined using LC-MS/MS
- Pharmacokinetic Analysis using non-compartmental (Phoenix Winnonlin v8.2, Certara, Princeton, NJ)

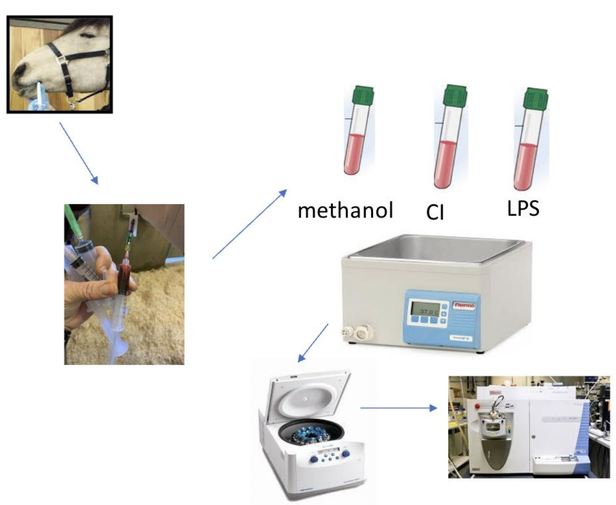

Figure 1. Method for Concentration Determination

Results

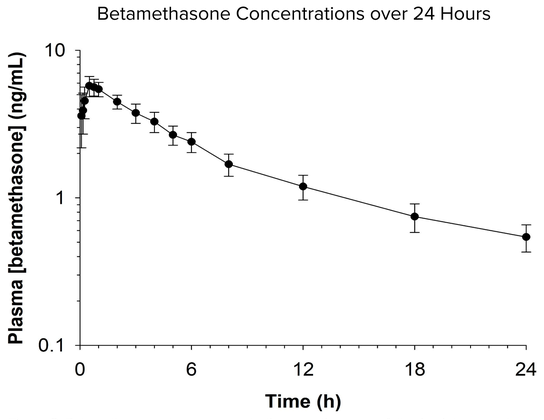

Figure 2: Betamethasone plasma concentration over time curve following intramuscular administration of 12 mg of betamethasone acetate/phosphate to 12 horses. This curve shows concentrations over the first 12 hours post administration.

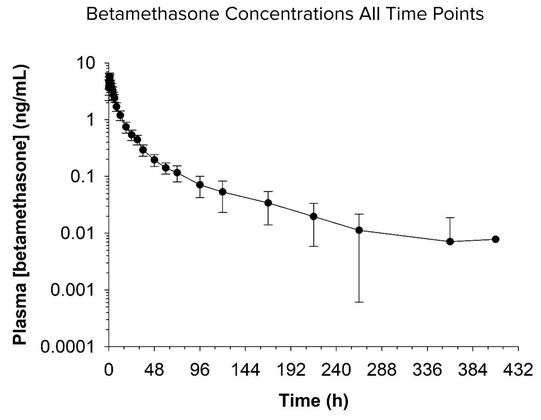

Figure 3: Betamethasone plasma concentration over time curve following intramuscular administration of 12 mg of betamethasone acetate/phosphate to 12 horses. This curve shows concentrations up to 408 hours post administration.

Table 1: Pharmacokinetic parameters (mean and range) for betamethasone following intramuscular administration of 12 mg of betamethasone acetate/phosphate to 12 horses. All parameters were generated with non-compartmental analysis.

Pharmacokinetic Parameters	
Variable	**Mean & Range**
C_{max} (ng/mL)	5.92 (4.57-7.00)
T_{max} (h)	0.75 (0.5-2.0)
$AUC_{0-\infty}$ (h*ng/mL)	61.7 (49.5-74.0)
Lambda_z (1/h)	0.02 (0.007-0.043)
HL_Lambda_z (h)	44.3 (16.1-97.8)

Cmax: maximum plasma concentration; Tmax: time of maximum concentration; AUCinf: area under the curve extrapolated to infinity; lambda z: slope of the terminal portion of the curve; HL lambda z: terminal half-life.

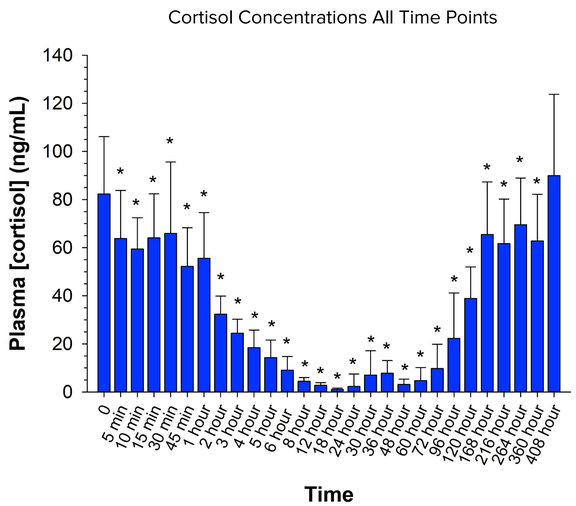

Figure 4. Plasma cortisol concentrations over time following intramuscular administration of 12 mg of betamethasone acetate/phosphate to 12 horses. Asterisks indicate a statistically significant ($p < 0.05$) difference, relative to baseline.

Conclusions

- Intramuscular (IM) administration of betamethasone results in sustained plasma concentrations and prolonged suppression of endogenous cortisol production.
- Prolonged residence time of betamethasone in the body is likely due to slow release resulting in a slower rate of absorption, relative to elimination (flip-flop effect).
- The prolonged detection time warrants an extended withdrawal time prior to competition in performance horses.

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