Pharmacokinetics and Anti-inflammatory Effects of Intramuscular Corticosteroids

Juliana Sullivan, Heather K. Knych

K. L. Maddy Equine Analytical Pharmacology Lab, School of Veterinary Medicine, University of California, Davis

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.
- Limited reports combined with widespread IM administration in horses have resulted in misuse.

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
- 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 inflammatory biomarkers.
- 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)

Results

- Betamethasone Concentrations over 24 Hours
- Betamethasone Concentrations All Time Points
- Cortisol Concentrations All Time Points

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean &amp; Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/mL)</td>
<td>5.92 (4.57-7.00)</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>0.75 (0.5-2.0)</td>
</tr>
<tr>
<td>AUC (ng/h/mL)</td>
<td>6.17 (4.95-7.40)</td>
</tr>
<tr>
<td>Lambda_z (1/h)</td>
<td>0.02 (0.007-0.043)</td>
</tr>
<tr>
<td>HL_Lambda_z (h)</td>
<td>44.3 (16.1-97.8)</td>
</tr>
</tbody>
</table>

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 (t1/2z) effects.
- The prolonged detection time warrants an extended withdrawal time prior to competition in performance horses.

References


Acknowledgements

- I’d like to thank Dr. Heather Knych for mentoring this project, Stacy Skawinetsz, Kirstan Karian, Mohgian Triyamah, and Gabby Nelson for technical help, and Dan McKemie, Sandy Wai-Mun Yim, & Jayanti Bhardani for assistance in the lab
- STAR funding provided by Center for Equine Health Endowment Funds
- Funding for this study provided by the AQHA and the California Horse Racing Board

Figure 1: Method for Concentration Determination

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.

Figure 4: Plasma cortisol concentrations over time following intramuscular administration of 12 mg of betamethasone acetate/phosphate to 12 horses. This curve shows concentrations over the first 12 hours post administration.