

# Betamethasone

## Background

Betamethasone is a potent, long-acting, synthetic glucocorticoid widely used in equine veterinary medicine as a steroidal anti-inflammatory.<sup>1</sup>

It is often administered intra-articularly for control of pain associated with inflammation and osteoarthritis.<sup>2</sup>

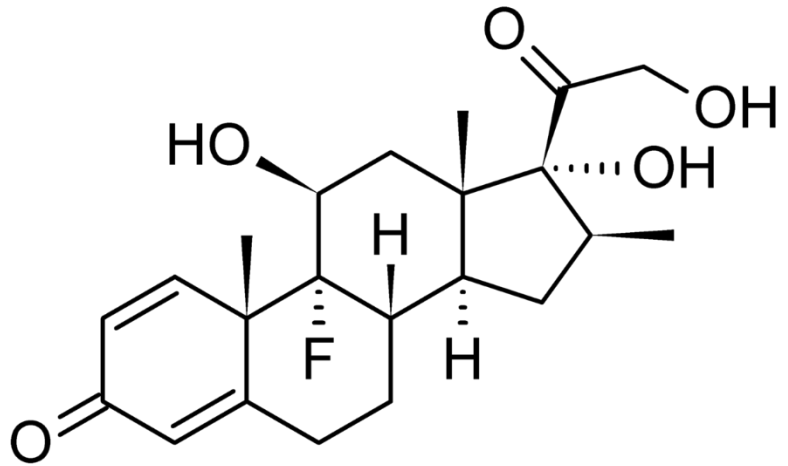
Betamethasone is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is commercially available

in a variety of formulations including BetaVet™, BetaVet Soluspan Suspension® and Betasone Aqueous Suspension™.<sup>3</sup> Betamethasone can be used intra-articularly, intramuscularly, by inhalation, and topically.<sup>4</sup> When administered intra-articularly, it is often combined with other substances such as hyaluronan.<sup>5</sup> Intra-articular and intramuscular dosages range widely based upon articular space, medication combination protocol, and practitioner preference.

Betamethasone is a glucocorticoid receptor agonist which binds to various glucocorticoid receptors setting off a sequence of events affecting gene transcription and the synthesis of proteins. These mechanisms of action include:

- Potential alteration of the G protein-coupled receptors to interfere with intracellular signal transduction pathways
- Enhanced transcription in many genes, especially those involving suppression of inflammation.
- Inhibition of gene transcription – including those that encode pro-inflammatory substances.

The last two of these are considered genomic effects. This type of corticosteroid effect usually occurs within hours to days after administration. The genomic effects persist after the concentrations of the synthetic corticosteroid in plasma are no longer detectable, as evidenced by persistent suppression of the normal production of hydrocortisone following synthetic corticosteroid administration.<sup>6</sup>



<http://en.wikipedia.org/wiki/Betamethasone#/media/File:Betamethasone>

When used judiciously, corticosteroids can be beneficial to the horse. However, repeated administration or excessive doses of corticosteroids, including betamethasone, may produce adverse effects including delayed wound healing, disruption of metabolic processes, and decreased immune response. In some case reports, high dose/repeated dose corticosteroid administration is linked to laminitis in susceptible horses.<sup>7</sup>

## **Betamethasone Administration Study**

### Intra-articular (IA) Administration

Betamethasone as BetaVet™ – a sterile aqueous suspension containing 3 mg of betamethasone acetate and 3 mg of betamethasone as betamethasone sodium phosphate per mL (Luitpold) was administered to twenty exercise-conditioned Thoroughbred horses (geldings and mares). The skin was aseptically prepared for intra-articular injection. Each horse then received a single 9 mg dose (1.5 mL) in the prepared metacarpophalangeal articular space. The dose reflected the manufacturer's label dose recommendation. This study was performed at the University of Florida by personnel in the UF Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan.

Blood samples were obtained immediately before dose administration and at the following times after dosing in six of the twenty horses: 0.033, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 360, and 480 hours. The remaining horses were sampled before and at 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 360, and 480 hours after administration.

### Intra-muscular (IM) Administration

Betamethasone as a sterile aqueous suspension containing 3 mg of betamethasone acetate and 3 mg of betamethasone as betamethasone sodium phosphate per mL (Luitpold) was administered to twenty exercise-conditioned Thoroughbred horses (geldings and mares). Each horse received a single 9 mg dose (1.5 mL) in the *serratus cervicalis* muscle after aseptic site preparation. The dose was set equal to the IA dose because this product is not recommended for intramuscular administration. This study was performed at the University of Florida by personnel in the UF Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan.

Blood samples were obtained immediately before dose administration and at the following times after dosing in six of the twenty horses: 0.033, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 360, and 480 hours. The remaining horses were sampled before and at 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 360, and 480 hours after administration.

## Extraction and Analysis Procedures

Quantification of betamethasone in plasma and urine samples was performed at the LGC Science, Inc. Laboratory (Lexington, Kentucky) using validated methods similar to those previously described.<sup>8</sup> Betamethasone was determined in plasma and urine by liquid chromatography-mass spectrometry (LC-MS) using a stable-isotope labelled analogue of betamethasone as internal standard to improve quantitative accuracy and precision. The validated method for determination of betamethasone in plasma had a Lower Limit of Quantification (LLQ) 10 pg/mL and a Limit of Detection (LOD) of 1 pg/mL.

Urine quantification was based upon measurement of total betamethasone in the sample after hydrolysis of conjugated metabolites to betamethasone. The LLQ of the validated method was 50 pg/mL of urine. Both the urine and plasma methods and method validation study reports were submitted to the *ad hoc* Chemist Advisory committee of the RMTC for review and were approved.

## Pharmacokinetic Modelling

Plasma concentrations of betamethasone are expressed as the median and range at each collection point (Tables 1.1 and 1.2). Pharmacokinetic analysis was performed on individual plasma concentrations from the six horses with more extensive sampling using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO).

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.*, ln) transformed plasma concentration data at each collection time for all twenty horses.

## Results and Discussion

Plasma betamethasone concentration increased rapidly and peak plasma concentrations were achieved at 4 hours after IA administration and 0.5 hours after IM administration. The rapid absorption was attributed to the high aqueous solubility of the phosphate ester (Fig. 1.1). Plasma betamethasone concentrations decreased more rapidly after IA administration; however, betamethasone remained detectable through the end of the sampling period (twenty days) after intramuscular administration in some horses (Figure 1.1). Betamethasone was eliminated much more slowly after intramuscular administration than after intra-articular administration. This observation is consistent with the observations made after similar comparison of intramuscular and intra-articular administration of methylprednisolone acetate, isoflupredone acetate, and triamcinolone acetonide.<sup>9</sup>

Mean, median, and range of the plasma concentrations after intra-articular and intra-muscular administration in all twenty horses are shown in tables 1.1 and 1.2, respectively.

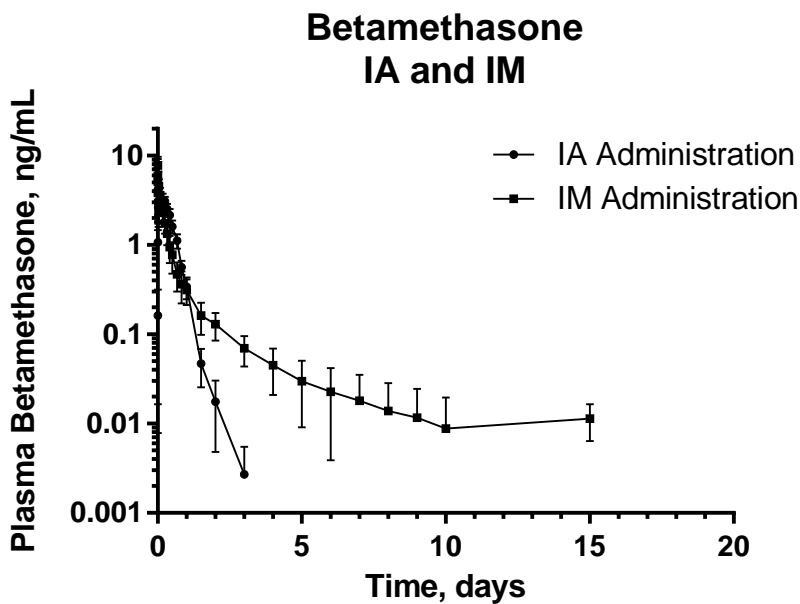
**Table 1.1 Plasma betamethasone mean, median, minimum and maximum values at recommended withdrawal time following intra-articular administration of 9 mg of betamethasone to 20 horses**

Time (hours)	Mean (ng/mL)	Median (ng/mL)	Range (ng/mL)
168	0.001	0	<LLQ-<LOD

**Table 1.2 Plasma betamethasone mean, median, minimum and maximum 168 hours post intramuscular administration of 9 mg of betamethasone to 20 horses**

Time (hours)	Mean (ng/mL)	Median (ng/ml)	Range (ng/mL)
168	0.018	0.014	0.04-ND

**Figure 1.1 Plasma concentrations betamethasone (mean±SD) before and following a 9 mg betamethasone intra-articular and intramuscular administration**



The betamethasone concentrations were above the plasma LLQ in all samples collected at 24 hours after IA administration. At 48 hours after IA administration, the plasma concentration of betamethasone from 80% (16/20) of the horses remained above the LLQ and at 72 hours post IA administration, the plasma concentrations in all (20/20) samples were below the LLQ.

A subsequent study of 12 horses using similar drug administration protocol but with the intra-articular injections into the antebrachio-carpal (radiocarpal) joint had similar results. That study included analysis of synovial fluid. Betamethasone concentrations in the joint persisted well above 10 pg/ml within the antebrachio-carpal joint through 14 days post administration.<sup>10</sup>

In contrast to these findings, the betamethasone concentrations in the RMTC study were still above the LLQ in all (20/20) plasma samples collected 72 hours after IM administration. At 120 hours after IM administration, plasma concentrations from 75% (15/20) horses were above the LLQ. At 20 days post IM administration, one horse (1/20) had a concentration above the LLQ at 0.01 ng/mL the remaining (19/20) horses were below the LLQ or LOD.

### **Scientific Advisory Committee (SAC) Recommendation**

In order to ensure that intra-articular injections were performed with sufficient time for the veterinarian to gauge the efficacy of the treatment, the threshold was based upon the IA data obtained at 7 days, including estimated concentrations between the LLQ and LOD. The data was log transformed (ln) and the mean (-6.609) and standard deviation (0.683) of the log transformed data were used to calculate a threshold based upon a 95/95 tolerance interval. The calculation for a tolerance interval using the K factor for 20 horses yielded a threshold of 7.94 pg/mL of plasma/blood. This number was then rounded to 10 pg/mL of plasma/blood by the SAC.

The withdrawal guide recommendation of 7 days is based upon a 9 mg dose of betamethasone as betamethasone acetate 3 mg/mL and betamethasone sodium phosphate 3 mg/mL (Luitpold) in one metacarpophalangeal joint. Different formulations of betamethasone, administration of higher doses, use of other injection sites, or combinations of betamethasone with other substances may result in concentrations above the threshold unless an extended withdrawal time is observed. Injections into stifles, or the distal intertarsal and tarsal-metatarsal joints may require extended withdrawal times particularly if injected into the fat pad of the stifle or subcutaneously in any joint. Clearance testing is recommended when injecting either of these joints if there are any concerns. Veterinarians are advised to assess the impact of these potential risk factors on the withdrawal time and to advise their clients accordingly.

Specifically, the withdrawal time recommendations do not apply to betamethasone administered intramuscularly because it is cleared slowly after this route of administration and they do not apply to products such as Betavet Soluspan Suspension™ or Betasone Aqueous Suspension™ because these products contain the two components in different proportions or they contain a different betamethasone ester from the one that was investigated. Specifically, the former product contains a higher proportion of betamethasone acetate compared to the investigated product and the latter contains betamethasone dipropionate instead of betamethasone acetate.<sup>11</sup>

## References

---

<sup>1</sup> Menendez, M.I., et al., *Pharmacokinetics of Intra-articular Betamethasone Sodium Phosphate and Betamethasone Acetate and Endogenous Hydrocortisone Suppression in Exercising Horses*, J. Vet. Pharmacol. Therap. (2015) [epub ahead of print] doi:10.1111/jvp.12229 (Note: the lower Limit of Quantification for this study is five-fold higher than the RMTC threshold – therefore this paper may not be instructive in jurisdictions regulating to the lower RMTC threshold).

<sup>2</sup> Trotter, G.W., *Intra-articular corticosteroids*. In, *Joint disease in the horse*, (1996) W.B. Saunders, Philadelphia, PA, 237-56; see also, McIlwraith, C.W., *Management of Joint Disease in the Sport Horse*, In, *Proceedings, Kentucky Equine Research Nutrition Conference*, (2010) Kentucky Equine Research, Lexington KY, 64-66.

<sup>3</sup> Available online at:

<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/index.cfm?gb=2>.

<sup>4</sup> *Id.*

<sup>5</sup> Lindholm, A.C., et al., *Clinical Effects of Betamethasone and Hyaluronan, and Defocalized Carbon Dioxide Laser Treatment on Traumatic Arthritis in the Fetlock Joints of Horses*, J. Vet. Med A, (2002) 49: 189-94.

<sup>6</sup> *Veterinary Pharmacology and Therapeutics, Ninth Edition*, p. 783.

<sup>7</sup> Bailey, S.R., *Corticosteroid-associated Laminitis*, Vet Clin North Am Equine Pract. (2010) 26(2): 277-85.

<sup>8</sup> Luo, Y., et al., *Resolution, Quantification, and Confirmation of Betamethasone and Betamethasone in Equine Plasma by Liquid Chromatography/Tandem Mass Spectrometry*, Rapid Communications in Mass Spectrometry (2005) 19:825-32; Luo, Y., et al., *Simultaneous Analysis of Twenty-one Glucocorticoids in Equine Plasma by Liquid Chromatography/Tandem Mass Spectrometry*, (2005) Rapid Communications in Mass Spectrometry (2005) 19:1245-56.

<sup>9</sup> See, *infra*, Isoflupredone, Methylprednisolone, and Triamcinolone Acetonide sections.

<sup>10</sup> Knych, H.K., et al., *Pharmacokinetics of Betamethasone in Plasma, urine, and Synovial Fluid Following Intra-Articular Administration to Exercised Thoroughbred Horses*, Drug Testing and Analysis (2017) 9:1385-91.

<sup>11</sup> <http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=034-010>,  
<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=049-185>.