CONTROLLED THERAPEUTIC MEDICATIONS

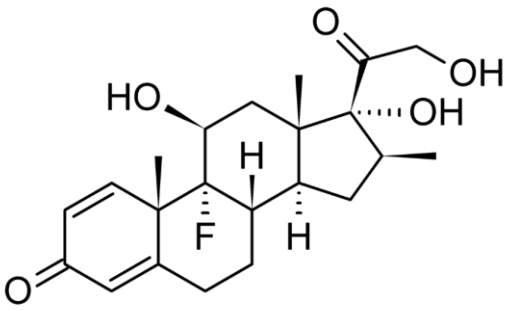
MONOGRAPH SERIES

Betamethasone

Background

Betamethasone is a potent, long-acting, synthetic glucocorticoid widely used in equine veterinary medicine as a steroidal anti-inflammatory.[i] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances

Betamethasone is often administered intra-articularly for control of inflammation associated with osteoarthritis[ii] and other musculoskeletal conditions.



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

Betamethasone is a prescription medication and can only be prescribed, dispensed, or used at the direction of a veterinarian. It is commercially available in a variety of formulations including BetaVet™, BetaVet Soluspan Suspension® and Betasone Aqueous Suspension™.[iii] Betamethasone can be used intra-articularly, intramuscularly, by inhalation, and topically.[iv] When administered intra-articularly, it is often combined with other medications such as hyaluronan.[v] Intra-articular dosages range widely based upon articular space, medication combination protocol, and practitioner preference.

Betamethasone is a glucocorticoid receptor agonist that binds to various glucocorticoid receptors triggering 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.[vi]

Corticosteroids can exert both disease-modifying and palliative effects. Corticosteroids require judicious use to avoid risk of injury when symptoms improve but the underlying orthopedic disorder has not resolved.

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.[vii]

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 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 administered was the same used for the IA study. This product does not have label approval for IM administration and there is no recognized IM dose. This study was performed at the University of Florida by personnel in the 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 was performed at the LGC Science, Inc. Laboratory (Lexington, Kentucky) using validated methods similar to those previously described.[viii] Betamethasone was determined in plasma by liquid chromatography-mass spectrometry (LC-MS) using a stable-isotope labelled analogue of betamethasone as an internal standard to verify quantitative accuracy and precision. The validated method for determination of betamethasone in plasma had a Limit of Quantification (LOQ) of 10 pg/mL and a Limit of Detection (LOD) of 1 pg/mL.

Pharmacokinetic Modelling

Plasma concentrations of betamethasone are expressed as the mean, median, and range at 168 hours (7 days) post-administration in 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).

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. 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. 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.[ix]

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 168 hours following intra-articular administration of 9 mg of betamethasone to 19* horses

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

*** Analysis of one sample collected at 168 hours post IA admin did not meet the analyte's identification criteria; unequivocal identification of betamethasone could not be made. This sample was excluded from statistical analysis.**

Table 1.2 Plasma betamethasone mean, median, minimum and maximum at 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

The betamethasone concentrations were above the plasma LOQ 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 LOQ and at 72 hours post IA administration, the plasma concentrations in all (20/20) samples were below the LOQ.

A subsequent IA study in 12 horses using similar drug administration protocol but with the intra-articular injections into the antebrachiocarpal (radiocarpal) joint had similar results. That study included analysis of synovial fluid. Betamethasone concentrations in the synovial fluid persisted well above 10 pg/ml within the treated antebrachicarpal joint through 14 days post administration and were also detectable in the contralateral, untreated joint.[x]

In contrast to these findings, the betamethasone concentrations in the RMTC study were still above the LOQ 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 LOQ. At 20 days post IM administration, one horse (1/20) had a concentration above the LOQ at 0.01 ng/mL the remaining (19/20) horses were below the LOQ 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 LOQ and LOD. The result of the 168 hour sample 95/95 Tolerance Interval calculation for 19 horses of 7.94 pg/mL of

plasma/blood was rounded up by the SAC to a threshold recommendation of 10 pg/mL of betamethasone in plasma/blood corresponding to withdrawal guidance of 7 days for a single IA injection of 9 mg.

Important Note

On December 13, 2019 the withdrawal guidance and corresponding threshold for betamethasone in the ARCI Controlled Therapeutic Medication Schedule (CTS) were withdrawn for flat and jumps racing, and a 14-day stand down period was enacted for all intra-articular injections. In Model Rule 011-020 (G) the ARCI also established a prohibition on stacking of corticosteroids—the detection of 2 or more corticosteroids in a post-race (blood and/or urine) sample. Upon Commissions' adoption of the Model Rule and updated CTS, betamethasone will be regulated by limit of detection in serum. The prohibition on stacking of corticosteroids will be enforced through a combination of blood and urine testing, with betamethasone in urine regulated consistent with the International Federation of Horseracing Authorities' Screening Limit (https://www.ifhaonline.org/Default.asp?section=IABRW&area=1) In one study, all urine samples did not clear after an intra-articular injection of 9 mg betamethasone in a single antebrachial joint as BetaVet™ until 7 days.[xi] Veterinarians are advised to consult the RMTC's Intra-articular Injection and Corticosteroid Administration Advisory at https://rmtcnet.com/wp-content/uploads/04-2020-IA-Inj-and-CCS-Advisory.pdf for withdrawal guidance.

For harness racing, the 7-day withdrawal guidance and 10 pg/mL serum/plasma threshold remain unchanged in the CTS and ARCI Model Rules. The withdrawal 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 in one metacarpophalangeal joint.

Some regulatory authorities have adopted a 14-day stand down and prohibition on stacking of corticosteroids for all racing breeds and disciplines. Veterinarians are advised to know and follow the rules in the jurisdictions in which they practice.

Practice Tips

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.

Clearance testing is recommended when injecting either of these joints. Peri-articular or extracapsular injections may significantly extend detection times. 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.[xii]

References

[i] 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. (2016) Feb;39 (1): 22-6; 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).

[ii] 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.

[iii] FDA Green Book, available online at: https://animaldrugsatfda.fda.gov/adafda/views/#/search (Enter betamethasone in search box.)

[iv] FDA Green Book

[v] 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.

[vi] *Veterinary Pharmacology and Therapeutics, Ninth Edition*, 2009, p. 783.

[vii] Bailey, S.R., *Corticosteroid-associated Laminitis*, Vet Clin North Am Equine Pract. (2010) 26(2): 277-85.

[viii] 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.

[ix] See, infra, Isoflupredone, Methylprednisolone, and Triamcinolone Acetonide Monographs.

[x] 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.

[xi] Knych, H.K., *et al.*, Drug Testing and Analysis (2017).

[xii] https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/034-010 , https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/049-185