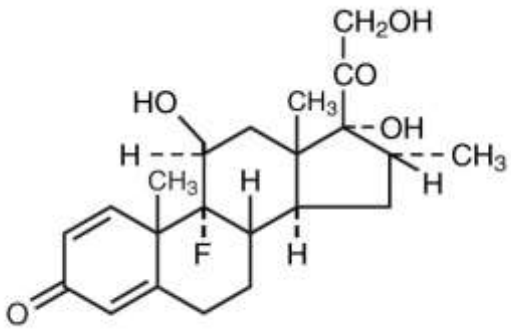
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Dexamethasone

Background

Dexamethasone is a potent glucocorticoid and analogue of prednisolone that is 25 times more potent and longer acting than hydrocortisone[i]. It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Dexamethasone is commonly used in equine veterinary medicine as a steroidal anti-inflammatory. It is often administered for treating musculoskeletal inflammation and for use in treating allergies and immune mediated diseases.[ii]



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Dexamethasone is a prescription medication and can only be dispensed from or used at the direction of a veterinarian. It is commercially available in a variety of formulations and is often referred to as Azium®, an early brand name for dexamethasone.[iii] It is also available as an ester or alcohol, in solution or suspension.[iii] Because of its poor aqueous solubility, dexamethasone is commonly formulated as a phosphate ester, which is rapidly hydrolyzed in blood to form free alcohols.[iv] Dexamethasone is most commonly administered intramuscularly, but it can also be given intravenously, intra-articularly, orally, and topically.[v] Intra-articular and intramuscular dosages range widely based upon administration method, medication combination protocol, and practitioner preference.

Dexamethasone is a glucocorticoid that exerts effects on nearly all cell types and organ systems, particularly in modulating immunologic and anti-inflammatory activity.[vi] Glucocorticoids inhibit inflammation by binding to glucocorticoid receptors within the cytoplasm of specific cells and altering gene expression or repression through genomic control of mRNA production.[vii] They have profound effects on the concentration, distribution, and function of peripheral leukocytes and other mediators of inflammation.[viii] Glucocorticoids can affect glucose metabolism, function of the immune system, behavior and mentation, and alteration of the secretion of the endogenous corticosteroids.[ix]

When used judiciously, corticosteroids can be beneficial in a horse's treatment and recovery from illness or injury. However, repeated administration or excessive doses of corticosteroids, including dexamethasone, may produce adverse effects including delayed wound healing, disruption of metabolic processes, and suppressed immune response. In some case reports, high dose/repeated dose corticosteroid administration is linked to laminitis in susceptible horses.

Administration Studies

Intravenous (IV) Administration

Dexamethasone as a sterile aqueous solution of Dexamethasone Sodium Phosphate was administered intravenously to 20 Thoroughbred horses at a dosage of 0.05 mg/kg. Blood (plasma) samples were collected prior to administration, and at 2, 5, 15, 30, and 45 minutes and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120 hours post administration in 6 out of the 20 horses. For all 20 horses, blood (plasma) samples were obtained prior to administration and at 4, 8, 24, 36, 48, 72, 96, and 120 hours post administration.

Intra-muscular (IM) Administration

Dexamethasone as a sterile aqueous solution of Dexamethasone Sodium Phosphate was administered intramuscularly to 20 Thoroughbred horses at a dosage of 0.05 mg/kg. Blood (plasma) samples were collected prior to administration, and at 2, 5, 15, 30, and 45 minutes and at 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120 hours post administration in 6 out of the 20 horses. For all 20 horses, blood (plasma) samples were obtained prior to administration and at 4, 8, 24, 36, 48, 72, 96, and 120 hours post administration.

Oral Administration

Dexamethasone as oral dexamethasone was administered orally to 20 Thoroughbred horses at a dosage of 0.05 mg/kg. Blood (plasma) and urine samples were collected. Blood (plasma) samples were collected prior to administration, and at 2, 5, 15, 30, and 45 minutes and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120 hours post administration in 6 out of the 20 horses. For all 20 horses, blood (plasma) samples were obtained prior to administration and at 4, 8, 24, 36, 48, 72, 96, and 120 hours post administration.

All the administrations described above were performed at the University of Florida by personnel in the Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan.

Extraction and Analysis Procedures

Quantification of dexamethasone in plasma samples was performed at the LGC-Science (Lexington, KY) using an internally validated method. A deuterium-labelled internal standard, dexamethasone-d4 (CDN Isotopes; Quebec, Canada) was used to verify precision and accuracy. The method was characterized by a Limit of Quantification (LOQ) for determination of dexamethasone of 0.005 ng/mL in plasma and a Limit of Detection (LOD) of 0.001 ng/mL.

Pharmacokinetic Modelling

Plasma concentrations of dexamethasone are expressed as the mean, median, and range at various collection points following each method of administration (Tables 1.1, 1.2, 1.3).

Results and Discussion

Plasma concentrations of dexamethasone peaked around 300 – 400 ng/mL two minutes after intravenous administration. However, these concentrations declined rapidly, and 7/20 horses were below LOQ at 48 hours. All 20 horses were below the LOQ by 72 hours following intravenous administration.

Table 1.1 Plasma dexamethasone mean, median, and range values at selected times before and following intravenous administration of 0.05 mg/kg of dexamethasone to 20 Thoroughbred horses.

Time (Hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	0.11 ± 0.03	0.11	0.06 – 0.17
48	0.01 ± 0.00	0.01	<LOQ – 0.01

Following intramuscular administration, absorption was again very rapid. Maximum plasma concentrations were found 2 minutes after administration but declined rapidly and 3/20 horses were below LOQ at 48 hours. All 20 horses were below LOQ by 72 hours following intramuscular administration.

Table 1.2 Plasma dexamethasone mean, median, and range values at selected times before and following intramuscular administration of 0.05 mg/kg of dexamethasone to 20 Thoroughbred horses.

Time (Hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	0.14 ± 0.04	0.14	0.06 – 0.17
48	0.01 ± 0.00	0.01	<LOQ – 0.01

Absorption from oral administration was the slowest of the three administration methods. Peak plasma concentrations occurred within 2 hours and declined rapidly, and 6/20 horses were below LOQ at 48 hours. All 20 horses were below LOQ by 72 hours following oral administration.

Table 1.3 Plasma dexamethasone mean, median, and range values at selected times before and following oral administration of 0.05 mg/kg of dexamethasone to 20 Thoroughbred horses.

Time (Hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	0.12 ± 0.03	0.12	0.06 – 0.20
48	0.01 ± 0.01	0.01	<LOQ – 0.03

Scientific Advisory Committee (SAC) Recommendation

The SAC recommended a 5 pg/mL threshold corresponding to withdrawal guidance of 72 hours for a single 0.05 mg/kg dose of dexamethasone administered intravenously, orally, or intramuscularly. This threshold is not based on the 95/95 Tolerance Interval. Plasma concentrations for all 20 horses were below LOQ by 72 hours and the SAC declined to be permissive of dexamethasone administrations at less than 72 hours.

In December 2019, the ARCI adopted a Model Rule that established a 14-day stand down period for all intra-articular injections AND a prohibition on stacking of corticosteroids (the detection of two or more corticosteroids in a horse's blood and/or urine sample). The serum threshold of 5 pg/mL was withdrawn, with dexamethasone regulated by laboratory limit of detection in blood and urine. In 2020 Knych, et al.[x], dexamethasone was detectable in plasma in 3/11 horses at 72 hours and below LOD in all horses by 96 hours following a 30 mg dose IV dose. Dexamethasone was still detectable in plasma in 4/12 horses at 72 hours and 1/12 horses at 96 hours following a 20 mg PO dose. In that study the LOQ for dexamethasone in urine was 0.1 ng/ml; the LOD was 0.05 ng/ml. All urine samples in both administration regimens were below the LOQ by 72 hours.

Practice Tips

Different formulations of dexamethasone, administration of higher doses, use of other or multiple injection sites, or combinations of dexamethasone with other substances may result in concentrations above the threshold unless an extended withdrawal time is observed. 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 dexamethasone administered topically because it is cleared slowly after this route of administration.

When considering the administration of alternative dexamethasone formulations (e.g. dexamethasone isonicotinate or sodium phosphate) in proximity to a race, veterinarians are referred to the International Federation of Horseracing Authorities Detection Times (https://www.ifhaonline.org/resources/DetectionTimes.pdf). Unless noted otherwise, the published Detection Times refer to urine.

References

[i] Merck Veterinary Manual. https://www.merckvetmanual.com/pharmacology/anti-inflammatory-agents/corticosteroids

[ii] Soma, L. R., *et al*, *Pharmacokinetics of Dexamethasone Following Intra-articular, Intravenous, Intramuscular, and Oral Administration in Horses and its Effects on Endogenous Hydrocortisone,* J. Vet. Pharmacol. Therap., 2012, DOI: 10.1111/j.1365-2885.2012.01412.x.

[iii] FDA Green Book. Avaliable at: https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/011-885

[iv] Soma, L. R., *et al*, J. Vet. Pharmacol. Therap., 2012.

[v] Capolongo, F., *et al*, *Endocrine Evaluation After an Intra-Articular Therapeutic Dosage of Dexamethasone in Horses,* J. Vet. Pharmacol. Therap. 2013, 36: 542-549.

[vi] *The Merck Veterinary Manual, Ninth Edition,* 2005, p. 2036-7.

[vii] Grady, J., *et al, Pharmacokinetic and Pharmacodynamics of Dexamethasone After Oral Administration in Apparently Healthy Horses,* AJVR, 2010, 71(7):831-839.

[viii] Katzung, B.G., *Basic and Clinical Pharmacology,* 10th Edition, p. 640.

[ix] Soma, L. R., *et al*, J. Vet. Pharmacol. Therap., 2012.

[x] Knych, H.K. *et al, Serum concentrations, pharmacokinetic/pharmacodynamic modeling, and effects of dexamethasone on inflammatory mediators following intravenous and oral administration to exercised horses,* Drug Test Anal 2020, 12:8 https://doi.org.10.1002/dat.2862