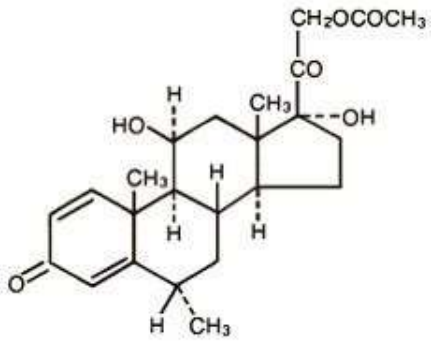
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Methylprednisolone

Background

Methylprednisolone 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. Methylprednisolone is prescribed to reduce inflammation associated with osteoarthritis[ii] and other musculoskeletal conditions.



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Methylprednisolone is a prescription medication and can only be prescribed, dispensed, or used upon the direction of a veterinarian. Methylprednisolone is commercially available in a variety of formulations and concentrations. Depo-Medrol™[iii] is the most common brand name. Methylprednisolone can be used intra-articularly, intrathecally, intramuscularly, by inhalation, and topically.[iv] When administered intra-articularly, it is commonly combined with other substances such as hyaluronan.[v] Intra-articular, intrathecal , and intramuscular dosages range widely based on factors including articular space, medication combination protocol, and practitioner preference.

Methylprednisolone is a glucocorticoid receptor agonist that 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.[vi]

Corticosteroids can exert both disease-modifying and palliative effects and as such 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 methylprednisolone may produce adverse regional and systemic effects including delayed wound healing, disruption of metabolic processes, and decreased immune response.

Administration Study

Intra-articular (IA) Administration

Research into the pharmacokinetics of methylprednisolone acetate was conducted at the Maddy Equine Analytical Pharmacology Laboratory at the University of California – Davis under the direction of Dr. H. Knych. Methylprednisolone, as its acetate ester in suspension, was administered as a 100 mg dose into a single articular space to 16 exercise-conditioned Thoroughbreds. Blood samples were obtained immediately before dose administration and at the following times after dosing: 24, 36, 48, 60 hours and 3, 4, 6, 7, 10, 13, 14, 16, 17, 21, 24, 28, 30, 35, 38, 42, and 44 days.

Extraction and Analysis Procedures

Quantification of methylprednisolone in plasma and urine samples was performed at the Maddy Equine Analytical Pharmacology Laboratory (Davis, California) using validated methods similar to those previously described.[vii] The method was characterized by a Limit of Quantification (LOQ) of 0.1 ng/mL in plasma and 1 ng/mL in urine.

Pharmacokinetic Modelling

Plasma concentrations of methylprednisolone are expressed as the median and range at specified collection points (Table 1.1). Pharmacokinetic analysis was performed 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 data from all sixteen horses to determine a withdrawal interval based on a 100 pg/mL concentration.

Results and Discussion

Peak plasma concentrations were achieved at approximately 6 hours after IA administration. Through a confidentiality agreement with the European Horseracing Scientific Liaison Committee the RMTC's Scientific Advisory Committee was able to review data from an intramuscular (IM) administration study. Methylprednisolone was eliminated much more slowly after IM administration than after intra-articular administration and was detectable in plasma at 99 days post IM injection.

A similar study in Australia found methylprednisolone after a 200 mg IM dose was still detectable after 9 weeks with an estimated terminal half-life over 300 hours.[viii] This slower rate of elimination is consistent with the observations made after similar comparison of intramuscular and intra-articular administration of isoflupredone acetate, and triamcinolone acetonide.[ix]

Mean, median, and range of the methylprednisolone plasma concentrations after intra-articular administration at specific time points for all sixteen horses are shown in Table 1.1.

Table 1.1 Plasma methylprednisolone concentration mean, median, and range at select times following intra-articular administration of 100 mg of methylprednisolone to 16 horses

Time (hours)	Mean (ng/mL)	Median (ng/mL)	Range (ng/ml)
96	0.17 ± 0.13	0.12	< 0.05-0.49
144	0.11 ± 0.09	0.07	< 0.05-0.35
168	0.06 ± 0.03	0.05	<0.05-0.13
240	0.05 ± 0.01	0.05	<0.05-0.08

The methylprednisolone concentrations were above the plasma LOQ in all samples collected at 48 hours after IA administration. At 168 hours after IA administration, the plasma concentration of methylprednisolone from 12.5% (2/16) of the horses remained above the LOQ. At 240 hours post IA administration, the plasma concentrations in all (20/20) samples were below the LOQ. At 21 days, urine concentrations were all below LOQ.

A study published by researchers at The Ohio State University investigated the pharmacokinetics of a 100 mg or 200 mg dose of methylprednisolone as the acetate ester in suspension divided among several intra-articular spaces.[x] In that study, five exercised Thoroughbreds were administered a 100 mg intra-articular total dose then, after a washout period, were administered a 200 mg intra-articular dose. The 100 mg intra-articular dose was divided between the tarsometatarsal joint (60 mg) and the metatarsophalangeal joint (40 mg). Based upon this dosing protocol, plasma concentrations were below 50 pg/mL at an average of 7 days. The higher dose of 200 mg was divided between the contralateral tarsometatarsal joint (80 mg), the contralateral metatarsophalangeal joint (60 mg), and one metacarpophalangeal joint (60 mg). The researchers found a statistically significant longer time between administration with the higher dose and the time that plasma concentrations were below 50 pg/mL. With a 200 mg total dose, the plasma concentrations were below 50 pg/mL at an average of 18 days.

Scientific Advisory Committee (SAC) Recommendation

The 95/95 Tolerance Interval was calculated based on the time points at which each study horse's plasma concentration of methylprednisolone was less than 100 pg/mL. The resulting value was 397.5 hours or 16.6 days. The SAC rounded up to withdrawal guidance of 21 days for a single 100 mg dose of methylprednisolone in one metacarpophalangeal joint.

Practice Tips

Different formulations of methylprednisolone, administration of higher doses, use of other injection sites, multiple injection sites, or combinations of methylprednisolone with other substances may result in plasma 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.

Clearance testing is advisable, particularly when the femoropatellar or tarsometatarsal (TMT) joints are treated. Inadvertent deposition of methylprednisolone into the retropatellar fat pad will result in a longer interval to subthreshold concentrations. Likewise, the risk of extracapsular deposition or expulsion of methylprednisolone from the TMT, with its relatively small joint space, into the surrounding subcutaneous tissues will also result in delayed clearance.

Specifically, the withdrawal time recommendations do <u>not</u> apply to methylprednisolone administered intramuscularly because it is cleared slowly after this route of administration and in some cases can be detected above the 100 pg/mL threshold for months following IM administration.

December 2019, the ARCI adopted a prohibition on stacking of corticosteroids (the detection of more than one corticosteroid in a blood and/or urine sample) for flat and jumps racing. In the RMTC administration study, the Detection Time for methylprednisolone in urine, following a single 100 mg IA dose, was 21 days. For methylprednisolone-treated horses, this must be a consideration when other, additional corticosteroid treatments are considered.

References

[i] Menendez, M.I., *et al., Pharmacokinetics of Intra-articular Methylprednisolone Sodium Phosphate and Betamethasone Acetate and Endogenous Hydrocortisone Suppression in Exercising Horses*, J. Vet. Pharmacol. Therap. 2015; 39, 22-26.

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[iii] FDA Orange Book. Available online at: https://animaldrugsatfda.fda.gov/adafda/views/#/search (Enter methylprednisolone in the search box.)

[iv] FDA Orange Book.

[v] Lindholm, A.C., *et al., Clinical Effects of Methylprednisolone 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] Riviere, J.E. and Papich, M.G., eds., *Veterinary Pharmacology and Therapeutics, Ninth Edition*, 2012, p. 783.

[vii] Luo, Y., *et al., Resolution, Quantification, and Confirmation of Methylprednisolone and Methylprednisolone 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,* Rapid Communications in Mass Spectrometry 2005; 19:1245-56.

[viii] *The Pharmacokinetics of Equine Medications*, RIRDC Publication No. 11/117, https://www.agrifutures.com.au/wp-content/uploads/publications/11-117.pdf

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

[x] Menedez, M., *et al.*, J. Vet. Pharmacol. Therap. 2015.