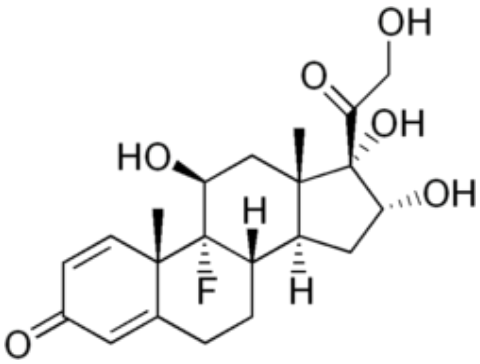
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Triamcinolone

Background

Triamcinolone is a potent, long-acting, synthetic glucocorticoid widely used in equine veterinary medicine as a steroidal anti-inflammatory. It is often administered intra-articularly for control of pain associated with inflammation and osteoarthritis.[i] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances.



https://en.wikipedia.org/wiki/Triamcinolone.png

Triamcinolone 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 Vetalog™.[ii] Triamcinolone can be administered via multiple routes including intra-articularly, intramuscularly, intra-thecally, and topically.[iii] When administered intra-articularly, it is often combined with other substances such as hyaluronan.[iv] Intra-articular and intramuscular dosages range widely based on multiple factors including articular space, medication combination protocol, and practitioner preference.

Triamcinolone 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.[v]

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 triamcinolone may produce adverse effects including delayed wound healing, disruption of metabolic processes, and decreased immune response. In some case reports, triamcinolone administration has been linked to laminitis in susceptible horses.[vi]

Administration Study

Intra-articular (IA) Administration

Triamcinolone acetonide as Vetalog™ (Boehringer Ingelheim Vetmedica), a sterile aqueous suspension containing 6 mg/ml, was administered to twelve exercise-conditioned Thoroughbred horses (geldings and mares) aged 3-6 years. The skin was aseptically prepared, and each horse then received a single 9 mg dose (1.5 mL) in the antebrachiocarpal articular space. This study was performed under the direction of Dr. H. Knych at the Maddy Equine Analytical Pharmacology Laboratory at the University of California - Davis.

Blood samples were obtained immediately before dose administration and at the following times after dosing: 15, 30, and 45 minutes and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96 hours. Additionally, samples were collected every other day to 60 days post-administration.

Intra-muscular (IM) Administration

Triamcinolone acetonide as Vetalog™ (Boehringer Ingelheim Vetmedica), a sterile aqueous suspension containing 6 mg/ml, was administered to twelve exercise-conditioned Thoroughbred horses (geldings and mares) aged 3-6 years. Each horse received a single injection of the label dose of 0.1 mg/kg in the *serratus cervicalis* muscle after aseptic site preparation. This study was performed under the direction of Dr. H. Knych at the Maddy Equine Analytical Pharmacology Laboratory at the University of California - Davis.

Blood samples were obtained immediately before dose administration and at the following times after dosing: 15, 30, and 45 minutes and 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96 hours. Additionally, samples were collected every other day to 60 days post-administration.

Extraction and Analysis Procedures

Quantification of triamcinolone in plasma samples was performed at the Maddy Equine Analytical Pharmacology Laboratory Davis - California using validated methods similar to those previously described.[vii]. The Limit of Quantification (LOQ) for determination of triamcinolone in plasma was 0.1 ng/mL. The Limit of Detection (LOD) was 0.025 ng/mL.

Pharmacokinetic Modelling

Pharmacokinetic analysis was performed using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO).

Results and Discussion

Peak plasma triamcinolone concentrations were achieved at approximately 7 hours following IA administration and 13 hours following IM administration. Triamcinolone was eliminated much more slowly following IM administration when compared to IA administration. The average half-life for triamcinolone following IA administration was approximately 19 hours whereas the half-life following IM administration was an average of 11.5 days.[viii] This observation is consistent with the observations made after similar intramuscular and intra-articular administrations of methylprednisolone acetate and isoflupredone acetate.[ix]

Following IA administration, triamcinolone acetonide plasma concentrations for all 12 horses were below LOQ at 144 hours and LOD at 168 hours (7 days). Urine concentrations were below LOD for all horses at 240 hours (10 days).

Following IM administration, triamcinolone acetonide average plasma concentrations for all 12 horses were below LOQ at 32.5 days post-administration, however concentrations remained above LOD until the last sampling time on day 60.

Scientific Advisory Committee Recommendation

In 2013 the RMTC recommended a 7-day withdrawal interval for triamcinolone to facilitate appropriate assessment of a horse following IA injection and prior to entry to race. The 7-day withdrawal guidance was also intended to eliminate intra-articular injections of corticosteroids after a horse was entered to race. The corresponding threshold of 100 pg/mL corresponded to the laboratories' Limit of Quantification. The 95/95 Tolerance Interval calculation could not be applied as the concentrations of all samples at 168 hours were below LOD.

In 2019 the RMTC recommended a Model Rule, subsequently adopted by the ARCI, for a 14-day stand down period for all intra-articular injections and a prohibition on the stacking of corticosteroids for horses engaged in flat and jumps racing. The threshold for triamcinolone of 100 pg/ml was withdrawn, with triamcinolone regulated by LOD in serum. To support the regulation prohibiting the stacking of corticosteroids urine is analyzed, consistent with IFHA Screening Limits (https://www.ifhaonline.org/Default.asp?section=IABRW&area=1).

The 7-day withdrawal guidance and corresponding threshold for triamcinolone acetonide of 100 pg/ml in serum/plasma remain unchanged in the ARCI's Model Rules for horses engaged in harness racing.

Note: Some regulatory authorities have adopted the 14-day stand down and prohibition on stacking for all racing disciplines. Veterinarians and horsemen are advised to know and follow the rules where their horses race and train.

Different formulations of triamcinolone, administration of higher doses, use of other injection sites, or combinations of triamcinolone with other substances may result in detectable concentrations 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, caution is advised when triamcinolone administered IM because it is cleared slowly after this route of administration; clearance testing is recommended.

References

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

[ii] https://www.bi-vetmedica.com/species/equine/products/joint_health_portfolio/vetalog.html

[iii] Harkins, J.D., *et al., Clinical use and characteristics of the corticosteroids.* Vet. Clin. N. Am.: Equine Pract. 9, 543-562.

[iv] Lindholm, A.C., *et al., Clinical Effects of Triamcinolone 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.

[v] Riviere, J.E. and Papich, M.G., eds., *Veterinary Pharmacology and Therapeutics, Ninth Edition*, 2009; p. 783.

[vi] McCluskey, M.J. and Kavenagh, P.B., *Clinical use of triamcinolone acetonide in the horse (205 cases) and the incidence of glucocorticoid-induced laminitis associated with its use,* Equine vet. Educ., 2004; 16 (2): 86-89.

[vii] Luo, Y., *et al., Resolution, Quantification, and Confirmation of Triamcinolone and Triamcinolone 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.

[viii] Knych, H.K., *et al., Pharmacokinetics of triamcinolone acetonide following intramuscular and intra-articular administration to exercised Thoroughbred Horses*, Equine Vet J, 2013 Nov; 45 (6): 715-20.

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