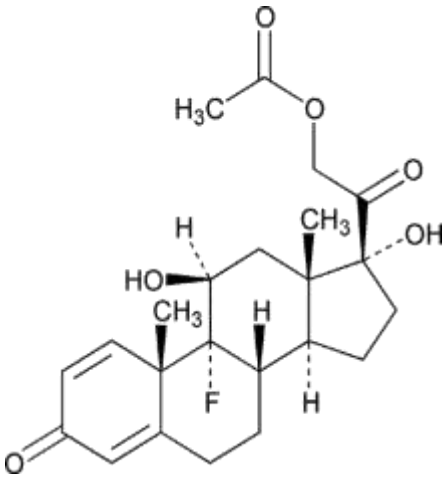
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Isoflupredone

Background

Isoflupredone is a potent corticosteroid often used to treat clinical signs associated with musculoskeletal disorders, allergic reactions, recurrent airway obstruction, and cases of shock.[i,ii] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Isoflupredone has FDA approval for use in the horse as a topical powder, ointment, and injectable formulation.[iii] The injectable formulation is approved for intramuscular and intrasynovial administration.[iv] The approved intramuscular and intrasynovial dose is 5-20 mg.[v]. The route of administration can significantly affect the pharmacokinetic behavior of isoflupredone.[vi]



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Isoflupredone is a prescription medication that can only be dispensed from or upon the request of a licensed veterinarian. It is commercially available as isoflupredone acetate and is sold in several formulations with FDA-approval for use in the horse including the trade name product Predef 2x™, a sterile aqueous solution.[vii]

Isoflupredone, as with other corticosteroids, is a glucocorticoid receptor agonist that triggers a sequence of events affecting gene transcription and protein synthesis in many types of cells[viii].

Corticosteroids exhibit genomic effects that usually occur within hours to days of administration. The genomic effects persist after the plasma concentrations of the corticosteroid are no longer detectable, as evidenced by persistent suppression of the normal production of hydrocortisone following synthetic corticosteroid administration.[ix]

Corticosteroids can exert both disease-modifying and symptom-modifying effects and require judicious use to avoid risk of injury when symptoms improve but the underlying orthopedic disorder has not yet resolved. Repeated administration of corticosteroids, including isoflupredone, may produce adverse effects including delayed wound healing, disruption of metabolic processes, changes in mentation, and suppression of the immune response.

Administration Studies

Three isoflupredone administration studies were performed. The first was an intra-articular administration study of a single dose of 20 mg of isoflupredone acetate as Predef 2x™ into one metacarpophalangeal joint. The second was an intramuscular administration of 20 mg intramuscularly into the *serratus cervicalis* muscle. The first two studies were performed at the University of Florida in a cross-over design with 7 days between doses. For the intra-articular and intramuscular studies, an additional two horses each received intra-articular and intra-muscular isoflupredone as Predef 2x™ at Rood and Riddle Equine Hospital (RREH), in Lexington, Kentucky. The third study was conducted at RREH, where six horses received a 10 mg administration of isoflupredone as Predef 2x™ peri-ligamentously over the front proximal suspensory ligament.

Intra-Articular (IA) Administration Study

The University of Florida performed an administration of isoflupredone to 6 exercise-conditioned Thoroughbred horses. An additional two horses (1 Thoroughbred and 1 Quarter Horse) were administered isoflupredone IA at RREH. Each horse received 20 mg of isoflupredone as Predef 2x™ in a forelimb metacarpophalangeal joint.

Blood samples were obtained immediately before dose administration and for all horses at the following times: 2, 4, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. The University of Florida horses also had additional blood collection times at 5, 10, 15, 20, 30, and 45 minutes post administration as well as at 1, 1.5, 2.5, 3, 3.5, 5, 6, 8, 12, 18, and 36 hours after administration. The RREH horses also had blood samples collected at 336 hours after dosing.

A subsequent IA administration study was performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California - Davis under the direction of Dr. H. Knych.[x] That study used a lower dose and had a higher limit of quantification (LOQ) than the RMTC study on which the threshold and 7-day withdrawal guidance is based. It does, however, provide practitioners additional information for making withdrawal interval decisions.

Intramuscular (IM) Administration Study

An IM administration of isoflupredone in 6 exercise-conditioned Thoroughbred horses was performed at the University of Florida Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan. An additional two horses (1 Thoroughbred and 1 Saddlebred) were similarly administered isoflupredone at RREH. Each horse received 20 mg of isoflupredone as Predef 2x™ in the *serratus cervicalis* muscle.

Blood samples were obtained immediately before dose administration and for all horses at the following times: 2, 4, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. The University of Florida horses also had additional blood collection times at 5, 10, 15, 20, 30, and 45 minutes post administration as well as at 1, 1.5, 2.5, 3, 3.5, 5, 6, 8, 12, 18, and 36 hours after administration. The RREH horses also had blood samples collected at 336 hours after dosing.

Peri-Ligamentous (Subcutaneous) Administration Study

RREH veterinarians performed a subcutaneous administration of isoflupredone in 5 Thoroughbred horses and 1 Warmblood horse. Each horse received a total of 10 mg of isoflupredone as Predef 2x™ subcutaneously to the palmar aspect of the left forelimb distal to the carpus and over the proximal suspensory ligament with 5 mg administered to the lateral aspect of the proximal suspensory ligament and 5 mg administered to the medial aspect.

Blood samples were obtained immediately before dose administration and at the following times: 2, 4, 24, 48, 72, 96, 120, 144, 168 and 336 hours after dosing.

Extraction and Analysis Procedures

Sample analysis was performed at LGC Sport Science (Lexington, Kentucky). Extraction of isoflupredone from plasma was performed using solid phase extraction. After extraction, the extracts were analyzed using a validated LC-MS/MS method with a Limit of Quantitation (LOQ) of 10 pg/mL and a Limit of Detection (LOD) of 5 pg/mL.

Pharmacokinetic Modeling

Plasma concentrations of isoflupredone are expressed as the mean (± SD), median, and range at select time points (Tables 1.1, 1.2, 1.3). Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

The 95/95 tolerance interval was calculated based the concentration of isoflupredone at the 168-hour time point after IA injection.

Results and Discussion

Plasma concentrations of isoflupredone peaked after IA (6 hours) and SC (4 hours) administration. Plasma concentrations of IM isoflupredone peaked at about 12 hours. The mean, standard deviation, median, and range for each route of administration at various time points can be found in Tables 1.1-1.3.

Table 1.1 Plasma mean ±SD and median values at select times following IA administration of 20 mg isoflupredone acetate to 8 horses.

Time (hours)	Mean ±SD (pg/mL)	Median (pg/mL)	Range (pg/mL)
120	14.13 ±11.72	13.13	< 5 - 31.5
144	11.30 ±8.20	13.40	< 5 – 22.7
168	9.58 ±7.04	11.1	< 5 – 18.0

Table 1.2 Plasma mean ±SD and median values at select times following IM administration of 20 mg isoflupredone acetate to 8 horses.

Time (hours)	Mean ±SD (pg/mL)	Median (pg/mL)	Range (pg/mL)
120	105.76 ±71.84	100.05	25.7-229.0
144	77.96 ±54.28	78.70	10.0-149
168	54.35 ±43.67	54.10	16.0-110.0

Table 1.3 Plasma mean ±SD and median values at select times following SC administration of 10 mg isoflupredone acetate to 6 horses.

Time (hours)	Mean ±SD (pg/mL)	Median (pg/mL)	Range (pg/mL)
120	36.8 ±11.7	34.5	25.2-58.9
144	20.1 ±10.01	19.4	10.0-36.3
168	16.3 ±7.3	14.2	6.2-27.1

Scientific Advisory Committee Recommendation

The SAC performed a 95/95 Tolerance Interval Calculation on the 7-day IA data for isoflupredone, with a resultant value of 91.20 pg/mL in plasma or serum. The calculation using the peri-ligamentous (SC) data yielded a value of 59.28 pg/mL in plasma or serum. Only 6 of the 8 horses in the IM study had isoflupredone concentrations below 100 pg/mL of plasma at 7 days. The SAC rounded up the IA 95/95 TI value to a threshold recommendation of 100 pg/mL in serum or plasma with corresponding withdrawal guidance of 7 days for a single IA injection of 20 mg or a SC administration of 10 mg.

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 serum/plasma threshold for isoflupredone of 100 pg/ml was withdrawn; with isoflupredone regulated by LOD in plasma or serum. To support the regulation prohibiting stacking of corticosteroids, the use of isoflupredone is also controlled by LOD in urine. In the administration studies for doses of 20 mg IA or 10 mg SC, all concentrations of isoflupredone in urine were < LOD by the end of the mandatory stand down period.

The 7-day withdrawal guidance and corresponding threshold for isoflupredone 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 train and race.

Practice Tips

Increasing the dose, increasing the number of joints treated, using a different route of administration, use of compounded products, co-administration of other medications, or the use of products with different formulations may represent unknown risk for a concentration in excess of the threshold and therefore an extended withdrawal time is recommended. Veterinarians are advised to use caution when deviating from doses and routes that have been studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition. Clearance testing in blood and urine is advisable, particularly when isoflupredone is administered intramuscularly. There can be high variability in the rate of elimination for medications administered IM, with elimination occurring more slowly than when compared to administration by other routes.

References

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[iii] FDA Green Book. Available online at: https://animaldrugsatfda.fda.gov/adafda/views/#/search Enter isoflupredone in search box.

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[v] Plumb, Donald, 2015.

[vi] Lillich, J.D., *et al.*, *Plasma, Urine and Synovial Fluid Disposition of Methylprednisolone Acetate and Isoflupredone Acetate After Intra-Articular Administration in Horses*, Am J Vet Res 1996; 57(2): 187-92.

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[viii] Scheschowitsch, K., *et al., New Insights in glucocorticoid Receptor Signaling—More Than Just a Ligand-Binding Receptor*, Front. Endocrinol., 2017 Feb 6; 8:16; doi:10.3389/fendo.2017.00016

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