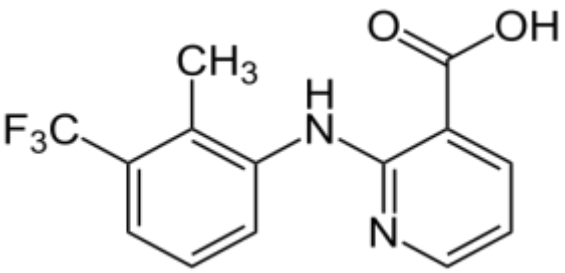
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Flunixin

Background

Flunixin is a non-steroidal anti-inflammatory (NSAID).[i] It is often used in the treatment of pain and inflammation associated with musculoskeletal disorders in racehorses.[ii] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Flunixin also has FDA label approval for treatment of pain associated with colic.[iii]



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Flunixin is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is commercially available as flunixin meglumine and is often referred to by the brand name Banamine™.[iv] It is available in injectable, oral paste and topical formulations.[v] Because of the increased variability of the pharmacokinetics of other routes of administration, only intravenous (IV) administration is discussed in this monograph. The FDA approved protocol for IV administration of flunixin meglumine is 1.1 mg/kg once per day for up to five days.[vi] A common practice, however, is the administration of a single flunixin injection 48 hours before a race.

Flunixin is a potent cyclooxygenase inhibitor.[vii] It inhibits the production of COX-1 and COX-2, which provides both analgesia and anti-inflammatory activity and can compromise the gastrointestinal tract resulting in ulcer formation.[viii]

The effect of NSAID administration on lameness 24 hours following a single dose was studied in 2004.[ix] Using both traditional subjective lameness examinations and force-plate technology, which determines the maximum force a horse exerts with each limb, researchers determined that significant analgesia could be observed in horses treated with either flunixin or phenylbutazone 24 hours after administration as compared to saline control (*i.e,* placebo).[x] Analgesia was observed 24 hours after administration of either 1.1 mg/kg of flunixin or 4.4 mg/kg of phenylbutazone. In the same study, researchers determined that no significant effect was detectable 30 hours after administration of either substance. However, work published by Knych *et al.* in 2020 demonstrated significant suppression of COX-1 activity (i.e. decreased thromboxane

B2) at rest for96 hours following administration of a 1.1 mg/kg dose of flunixin, with evidence for suppression of COX-1 activity in response to LPS-stimulation for up to 168 hours[xi].

Administration Study

Flunixin meglumine as Banamine™ was administered to sixteen exercise-conditioned Thoroughbreds ranging in age from 4-7 years.[xii] Horses were administered a single intravenous injection of 1.1 mg/kg of flunixin meglumine.[xiii] Blood samples were obtained immediately before dose administration and at the following times: 5, 10, 15, 30, and 45 minutes post administration as well as 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, 72, and 96 hours after administration.[xiv] This study was conducted at the Maddy Equine Analytical Pharmacology Laboratory, University of California-Davis under the direction of Dr. H. Knych.

Extraction and Analysis Procedures

Extraction and analysis were performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California - Davis, using methods described in the associated publication[xv]. The LC-MS method for determination of flunixin meglumine in serum was characterized by a Limit of Quantification (LOQ) of 0.5 ng/mL and a Limit of Detection (LOD) of 0.25 ng/mL.

Pharmacokinetic Modeling

Pharmacokinetic modeling was performed on the flunixin plasma concentration versus time data using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO).

The 95/95 tolerance interval was calculated using the data from samples collected at 48 hours.

Results and Discussion

Serum flunixin concentration peaked quickly with the highest concentrations observed in this study at approximately 2 hours post administration. Mean plus standard deviation and median of the serum concentrations after intravenous administration in all 16 horses are shown in Table 1 (adapted from Knych *et al.,* 2015).

Table 1 Serum flunixin mean and median values ±SD at select times following IV administration of 1.1 mg/kg flunixin meglumine to 16 horses.

Time (hours)	Mean±SD (ng/mL)	Median (ng/mL)
24	17.2 ±8.76	13.5
36	2.61 ±1.39	2.14
48	1.11 ±0.51	0.51

Scientific Advisory Committee Recommendation

Historically, flunixin was regulated by a 24-hour Restricted Administration Time (RAT) and a plasma threshold of 20 ng/mL. The corresponding 24-hour withdrawal guidance was for a 1.1 mg/kg single intravenous dose. This regulatory approach predated the introduction of the schedule of Controlled Therapeutic Substances in 2013.

In reviewing the results of the administration study, the SAC determined that the 24-hour withdrawal guidance did not provide an adequate margin of safety applied when the 95/95 Tolerance Interval (TI) calculation was applied to the 24-hour flunixin data.

In order to ensure that flunixin administration had minimal impact on regulatory veterinarian inspections, the RMTC SAC recommended that the threshold be no higher than 20 ng/ml of serum. Therefore, the administration study data were reviewed to determine when the serum concentration for each horse dropped below 20 ng/mL. Applying a 95/95 TI calculation to the time data (i.e. the time at which each horse fell below 20 ng/mL) yielded a recommended withdrawal time of 31.8 hours, which was rounded to 32 hours by the SAC to correspond with the 20 ng/mL plasma threshold. The 32-hour withdrawal guidance was based upon a single 1.1 mg/kg IV dose of flunixin meglumine as Banamine™.

Subsequent research demonstrated that NSAIDs have continued anti-inflammatory effects past 24 hours.[xvi] In 2019, the ARCI adopted a Model Rule for a 48-hour restricted administration time for all NSAIDs in conjunction with a prohibition on stacking (the detection of 2 or more NSAIDs in a blood and/or urine sample). A 95/95 tolerance interval calculation was performed using flunixin plasma concentration data from the 48-hour collection time point from the 16-horse UC-Davis administration study. The resultant value of 4.6 was rounded up to a threshold recommendation of 5.0 ng/ml for flunixin in plasma, corresponding with a single 1.1 mg/kg IV dose at 48 hours prior to post time.

Practice Tips

The prohibition on stacking of NSAIDs is enforced through analysis of both blood and urine. When one NSAID is administered at 48-hours, an extended withdrawal interval must be observed for others to avoid a stacking violation. Veterinarians are advised to refer to the RMTC's Advisory on Non-steroidal Anti-inflammatory Drugs (NSAIDs): 48-hour Restricted Administration Time and Prohibition on Stacking for guidance.[MS1]

Differing doses, formulations of flunixin meglumine (e.g. oral paste or top-dress granules), routes of administration, or serial administrations 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.

References

[i] Knych, H.K., *et al.*, *Pharmacokinetics and Effects on Thromboxane B2 Production Following Intravenous Administration of Flunixin Meglumine to Exercised Thoroughbred Horses*, (2015) J. Vet. Pharmacol. Therap. 38(4):313-20.

[ii] Knych, H.K., *et al.*, J. Vet. Pharmacol. Therap., 2015.

[iii] Plumb, D.C., "*Flunixin Meglumine."* Plumb's Veterinary Drug Handbook, 8th ed. Stockholm, WI: PharmaVet, (2015) 620-23.

[iv] FDA Green Book. Available online at: https://animaldrugsatfda.fda.gov/adafda/views/#/search (Enter flunixin in search box.)

[v] FDA Green Book. Note: injectable formulations are labeled for both IV and IM injections. Intramuscular injections are not recommended, however, as there is a risk of clostridial myositis (see: http://www.extension.umn.edu/agriculture/horse/health/intramuscular-banamine-risk/)

[vi] FDA Green Book.

[vii] Plumb, Donald, 2015.

[viii] Plumb, Donald, 2015.

[ix] Erkert, R.S., et al., *Use of force plate analysis to compare the analgesic effects of intravenous administration of phenylbutazone and flunixin meglumine in horses with navicular syndrome*, AJVR (2005); 66(2): 284-88.

[x] Erkert, R.S., et al., AJVR, 2005.

[xi] Knych, H.K., *et al.*, *Pharmacokinetics and anti-inflammatory effects of flunixin meglumine as a sole agent and in combination with phenylbutazone in exercised Thoroughbred horses,* (2020) Equine vet J. doi:10.1111.evj.13260

[xii] Knych, H.K., *et al.,* Equine vet J., 2020.

[xiii] Knych, H.K., *et al.,* Equine vet J., 2020.

[xiv] Knych, H.K., *et al.,* Equine vet J., 2020. (Note: The cited article conflicts regarding whether there was a collection at 6 or 8 hours post administration).

[xv] Knych, H.K., *et al.,* Equine vet J., 2020.

[xvi] Knych, H.K., *et al.,* Equine vet J., 2020.