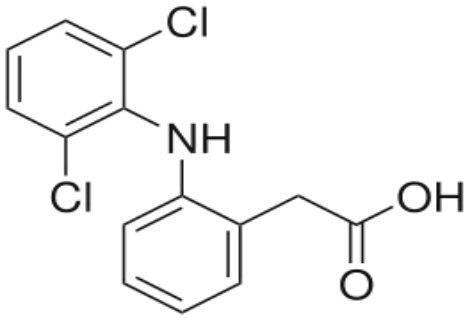
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Diclofenac

Background

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used to treat conditions such as pain and swelling associated with osteoarthritis.[i] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Unlike other NSAIDs on the Controlled Therapeutic Substances List diclofenac is available for equine use only as a topical treatment. Used in this manner the side effects associated with systemic NSAIDS such as gastrointestinal ulcers and kidney damage are decreased.[ii]



"Diclofenac" by Harbin - Own work. Licensed under Public Domain via Commons - https://commons.wikimedia.org/wiki/File:Diclofenac.svg#/media/File:Diclofenac.svg

Diclofenac is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is commercially available for horses in the topical formulation under the trade name Surpass™.[iii] The FDA approved protocol is for a 5" ribbon of Surpass™ (7.3 g) applied at the site of the affected joint.[iv]

It is a liposome based NSAID containing a phenyl group and a carboxylic acid group. The liposomal formulation allows diclofenac to rapidly penetrate the skin and remain effective for longer periods of time than other delivery methods.[v,vi]

Diclofenac is a non-specific cyclooxygenase inhibitor (COX-1 and COX-2) and may have some lipooxygenase inhibition.[vii] COX inhibition results in decreased concentrations of prostaglandins associated with inflammation and pain.

Diclofenac was found to improve lameness in horses with experimentally induced osteoarthritis.[viii] In this same study, researchers observed decreased sclerosis of the carpal bone and improved cartilage retention when compared with phenylbutazone.[ix]

Administration Study

The RMTC referred to a study by D. Anderson et al where diclofenac, as Surpass™, a liposomal cream that contains 10 mg of diclofenac sodium per gram was administered to six exercise-

conditioned Thoroughbred geldings ages 5-11 years old.[x] In that study, horses were administered the label dose of a 5" ribbon on a single joint twice daily for 10 days.[xi]

Blood samples were obtained immediately before dose administration and at the following times: 0.25, 6, 12, 24, 48 and 72 hours after administration.[xii]

Extraction and Analysis Procedures

Quantification of diclofenac in plasma was performed at the University of Florida Racing Laboratory using validated methods.[xiii]

In the referenced study, diclofenac was determined in plasma by liquid chromatography-mass spectrometry (LC-MS) using a prepared sodium diclofenac standard from Sigma-Aldrich as an internal standard to improve quantitative accuracy and precision.[xiv] The Limit of Quantification (LOQ) for determination of diclofenac in plasma was 0.2 ng/mL.[xv]

Results and Discussion

Peak plasma and urine concentrations of diclofenac occurred at 6 hours following the final dose application. Plasma concentrations were below LOQ at 72 hours. Urine concentrations remained above LOQ at the final sampling time point of 72 hours.

Table 1.1 Plasma diclofenac mean values ±SD at select times following topical administration of a 5" ribbon of diclofenac as Surpass™ to 6 horses (copied from Anderson, D. *Urinary and Serum Concentrations of Diclofenac after Topical Application to Horses.*)

Time (hours)	Mean±SD (ng/mL)
24	0.8±0.4
48	0.4±0.0
72	<LOQ

Scientific Advisory Committee (SAC) Recommendation

In December 2019, the previous threshold for diclofenac of 5.0 ng/mL in serum/plasma and corresponding withdrawal guidance of 48-hours was withdrawn from the schedule of

Controlled Therapeutic Substances. Further, the ARCI adopted a prohibition on stacking of NSAIDs. Diclofenac is now regulated by laboratory limit of detection in serum or plasma. For the purposes of enforcing the prohibition on stacking, the regulation of diclofenac in urine is consistent with the International Federation of Horseracing Authorities' screening limit for diclofenac (https://www.ifhaonline.org/Default.asp?section=IABRW&area=1). While plasma concentrations of diclofenac are below LOQ at 72 hours, urine concentrations remain detectable for longer intervals of unknown duration. In consideration of the potential for variability in dosing, the SAC recommends a minimum withdrawal interval of 168 hours following treatment with topical diclofenac, as Surpass, applied at the label dose.

Veterinarians and horsemen are advised to refer to the RMTC Advisory NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs): 48-hour Restricted Administration Time and Prohibition on Stacking for additional withdrawal guidance.

Practice Tips

This withdrawal guidance is based on the treatment of a single area with a 5" strip of Surpass cream twice daily for 10 days. The use of alternate doses, multiple treatment sites, or extended duration of treatment 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. As there are no data for determining a Detection Time in urine, clearance testing may be advisable to avoid risk of a stacking violation.

Individuals applying diclofenac to horses should wear gloves to avoid absorption through their skin OR cause inadvertent transfer of medication to other horses not intended for treatment with diclofenac.

The use of diclofenac topical cream in the horse is limited to the FDA approved product Surpass™. Other FDA-approved diclofenac products not labeled for use in the horse are marketed for human use. Oral tablets and delayed-release tablets, topical gels and patches, and ophthalmic solutions are all available in the US and intravenous products are available in other countries. Use of these products in the horse may pose a significant risk for both adverse reactions and medication violations.

There is also risk for equine exposure through human use of topical formulations of diclofenac (available by prescription and over-the-counter). There is potential for residual gel on human hands to be transferred to a horse and absorbed through its skin. Stable employees using any kind of topical medication should exercise caution (by wearing gloves during application or washing hands after application) to avoid transfer of their medication to horses in their care.

One small study compared the administration of topical vs. oral diclofenac in healthy ponies.[xvi] Ponies receiving phenylbutazone served as a positive control. Each diclofenac group received 2.5 mg/kg BID for 3 days. The time to maximum plasma concentration (Tmax) in both groups was similar but the maximum plasma concentration (Cmax) differed widely (30.56 +/-13.04 ng/mL in the topical group vs. 1854.76 +/- 555.51 ng/mL in the oral group). While not addressed in the study, it is possible that this large oral Cmax may affect elimination time. The authors recommended against oral diclofenac administration in ponies due to mild hematological, biochemical, and coagulation profile changes that occurred in this group.

In a separate study, diclofenac could be detected by GCMS in racing camels for four days after administration of a single intravenous dose of 2.5 mg/kg BW.[xvii] Elevations in BUN and creatinine occurred on day two in 3/6 treated camels. One camel was euthanized on day 7 for persistently elevated BUN and creatinine concentrations; BUN and creatinine in the two other camels returned to baseline by day 4. The authors postulated that this was inappropriate dose for camels, however veterinarians may wish to monitor renal function in horses undergoing extended treatments with diclofenac.

References

[i] Surpass package insert. Available at: http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/DrugLabels/UCM305340.pdf.

[ii] Caldwell FJ, Mueller E, Lynn RC, et al. 2004. *Effect of topical application of diclofenac liposomal suspension on experimentally induced subcutaneous inflammation in horses*. Am J Vet Res 65(3): 271-276.

[iii] Boehringer Ingelheim. https://www.bi-vetmedica.com/species/equine/products/joint_health_portfolio/surpass.html

[iv] Available at: https://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=141-186

[v] Frisbie DD, McIlwraith CW, Kawcak CE, et al. *Evaluation of topically administered diclofenac liposomal cream for treatment of horses with experimentally induced osteoarthritis*. 2009. Am J Vet Res 70(2): 210-215.

[vi] Caldwell, FJ, *et al.,* Am J Vet Res, 2004.

[vii] Caldwell, FJ, *et al.,* Am J Vet Res, 2004.

[viii] Frisbie, DD, *et al,* Am J Vet Res, 2009.

[ix] Frisbie, DD, *et al,* Am J Vet Res, 2009.

[x] Anderson D, Kollias-Baker C, Colahan P, et al. *Urinary and serum concentrations of diclofenac after topical application to horses*. 2005. Vet Therap 6(1): 57-66.

[xi] Anderson, D *et al.,* Vet Therap, 2005. (Note this study also included 2x and 3x labeled dose administrations.)

[xii] Anderson, D *et al.,* Vet Therap, 2005. (Note, the cited article conflicts whether there was a collection at 6 or 8 hours post-administration.

[xiii] Anderson, D *et al.,* Vet Therap, 2005.

[xiv] Anderson, D *et al.,* Vet Therap, 2005.

[xv] Anderson, D *et al.,* Vet Therap, 2005.

[xvi] Azevedo MS, *et al., Bioavailability and Tolerability of Topical and Oral Diclofenac Sodium Administration in Healthy Ponies,* J Eq Vet Sci 2013 33:22-26.

[xvii] Wasfi IA, *et al*., *The disposition of diclofenac in camels after intravenous administration,* Vet J 2013, 166(3):277-283.