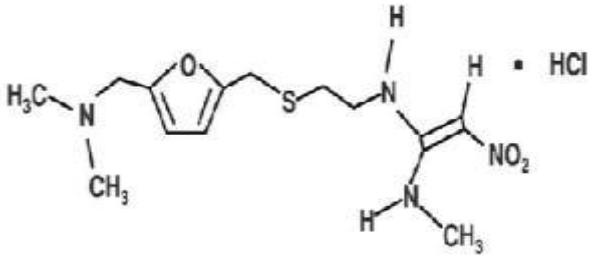
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Ranitidine

Background

Ranitidine is an anti-ulcer treatment commonly used in performance horses to prevent and treat gastric ulcers, duodenal ulcers, and equine gastric ulcer syndrome (EGUS).[i] It is assigned 5/D in the ARCI's Uniform Classification of Foreign Substances. Ranitidine is a histamine type-2 receptor antagonist used to inhibit gastric acid secretion.[ii]



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April 1, 2020 the FDA issued an immediate market withdrawal notice for all ranitidine-containing products due to concerns related to contamination by probable carcinogens. As of publication of this monograph it is not known if, or when, ranitidine will be available in the US. Ranitidine remains available in other countries.

Ranitidine was one of the few anti-ulcer medications that was available in a parenteral formulation which made it particularly useful in treatment and prevention of gastric ulcers in horses with postoperative ileus or duodenitis-proximal jejunitis.[iii] The commercially available product has since been removed from the market.

Ranitidine is four times more potent than the similar medication, cimetidine.[iv] It is administered both orally and parenterally.[v] Typical equine doses are 1.5 mg/kg IV every 6 hours or 6.6 mg/kg orally every 8 hours.[vi] -

Ranitidine works as an H_2 antagonist, inhibiting hydrochloric acid (HCl) secretion by competing with histamine receptor sites on parietal cells. Because histamine is the most potent trigger for HCl secretion, the more H_2 antagonists present on the site, the more HCl secretion is suppressed.[vii]

Ulcers affect between 58-100% of adult horses in training; most racehorses will develop gastric ulceration at some time in their careers, although not all affected horses show clinical signs.[viii] Gastric ulcers in performance horses have been correlated with poor haircoat, selective eating, signs of abdominal discomfort, and decreased performance.[ix]

Administration Study

Ranitidine tablets produced by Amneal Pharmaceuticals (Hauppauge, NY) were administered orally via dosing syringe at a dose of 8 mg/kg two times a day for a total of seven doses to nine healthy exercise-conditioned adult Thoroughbred horses.[x] This dose administered was determined based on an informal survey of equine practitioners conducted by the RMTC. The horses were fed one hour after drug administration. The study was performed at Kentucky Equine Research (Versailles, KY.)

Blood samples were obtained immediately before administration and at the following times after dosing 1, 2, 4, 6, and 12 hours after the first dose. Samples were collected at 1, 2, 4, 6, 12, 24, 36, 48 hours after administration of the final dose. Additional samples were collected at 12-hour intervals prior to treatment during the administration period.

Extraction and Analysis Procedure

Quantification of ranitidine in plasma was performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California – Davis using validated methods. Ranitidine concentrations in plasma were determined by LC-MS/MS using a certified refence standard obtained from Sigma-Aldrich (St. Louis, MO) to demonstrate quantitative accuracy and precision. The Limit of Quantification (LOQ) for determination of ranitidine in plasma was 0.05 ng/mL and the Limit of Detection (LOD) was 0.01 ng/mL.

Pharmacokinetic Modeling

Plasma concentrations of ranitidine are expressed as the median and range at select collection points (Table 1) adapted from Knych et al, 2017. Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

Table 1 Mean ± SD and range serum ranitidine concentrations following 8 mg/kg BID (7 doses) at 24- and 48-hours post-oral administration to nine exercise-conditioned Thoroughbred horses. Times are hours after administration of the final dose.

Time (hours)	Mean ± SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	2.88 ± 2.83	1.83	0.72 – 9.76
48	0.42 ± 0.30	0.30	0.14-0.91

Results and Discussions

Concentrations varied widely between horses at each sampling time point. Serum ranitidine concentrations were above the LOQ at 72 hours post-administration of the last dose in all horses studied. The terminal serum half-life of ranitidine in this study was 7.43 ± 0.851 hours.

Scientific Advisory Committee (SAC) Recommendation

The 95/95 Tolerance Interval (TI) calculation was performed on log-transformed data from samples collected 24 hours post administration and resulted in a value of 31.14 ng/ml.

The RMTC SAC rounded up the 95/95 TI value to recommend a ranitidine threshold of 40 ng/mL in serum/ plasma with corresponding 24-hour withdrawal guidance. This withdrawal guidance is based on an oral administration of 8 mg/kg twice daily for up to 7 doses.

Practice Tips

Different formulations of ranitidine, administration of higher doses, use of other administration methods, or combinations of ranitidine with other substances 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.

Some regulatory authorities have prohibitions on the administration of any medication, other than furosemide, at less than 48 hours, and veterinarians are obligated to know and follow the rules under which they are practicing. The withdrawal guidance of 24 hours does not apply when local regulations prohibit the use of medication at that time.

To the extent that ranitidine formulations may be made available by compounding pharmacies following the FDA-mandated withdrawal of the commercially available formulations, veterinarians are reminded that there is unknown risk in using these products which are not subjected to external quality controls to assess purity, stability, safety or concentration.

References

[i] Knych, H.K., *et al*, *Disposition of the Anti-ulcer Medications Ranitidine, Cimetidine, and Omeprazole Following Administration of Multiple Doses to Exercised Thoroughbred Horses,* J. Vet. Pharmacol. Therap., 2017; 40(1):92-96.

[ii] Maher, O., *Evaluation of the Effect of Ranitidine on Gastroduodenal Contractile Activity and Gastric Emptying in Horses,* Am J Vet Res, 2008; 69(9): 1153-1157.

[iii] Maher, O., Am J Vet Res, 2008.

[iv] Buchanan, B.R., *Treatment and Prevention of Equine Gastric Ulcer Syndrome,* Vet. Clin. Equine, 2003; 19: 575-597.

[v] Lester, G., *et al, Effectd of Treatment with Omeprazole or Ranitidine on Gastric Squamous Ulceration in Racing Thoroughbreds,* JAVMA, 2005; 227(10): 1636-1639.

[vi] Buchanan, B.R., *Treatment and Prevention of Equine Gastric Ulcer Syndrome,* Vet. Clin. Equine, 2003; 19: 575-597.

[vii] Murray, M., *Suppression of Gastric Acidity in Horses,* JAVMA, 1997; 211(1): 37-40.

[viii] Bell, R.J.W., *et al*, *Equine Gastric Ulcer Syndrome in Adult Horses: A Review*, New Zealand Vet. J., 2007 ;(1): 1-12.

[ix] Nieto, J.E., *et al*, Effect of Gastric Ulceration on Physiologic Responses to Exercise in Horses, Am J Vet Res, 2009; 70(6): 787-795.

[x] Knych, H.K., *et al*, J. Vet. Pharmacol. Therap., 2017.