# Cimetidine

## Background

Cimetidine is an anti-ulcer treatment commonly used in performance horses to treat gastric and duodenal ulcers and equine gastric ulcer syndrome (EGUS).[i] It is assigned a 5/D classification by the ARCI. Cimetidine is an $H_2$-receptor antagonist.[ii] Cimetidine was the first $H_2$ blocker available in both oral and parenteral forms and is relatively inexpensive when compared to other ulcer treatments. There is no evidence that newer $H_2$-receptor antagonists are more efficacious than cimetidine; however, increased potency and fewer interactions with other medications has increased their popularity.[iii]

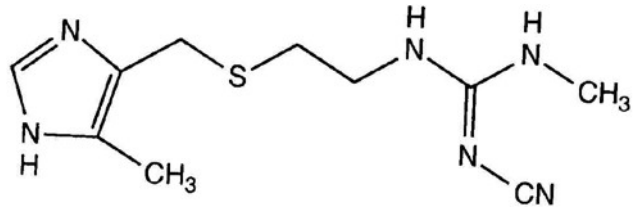


*Figure 1.1: http://www.stabilis.org/images/Molecules/Molecule.157.jpg*

Cimetidine is available in both over the counter and prescription strength formulations (that can only be dispensed from, or upon the request of, a veterinarian). There are no veterinary-labeled cimetidine products, so all equine use is considered extra-label use of a human-labeled product. Cimetidine is given both intravenously and orally.

Cimetidine has been used as a prophylactic treatment of gastric and duodenal ulcers; uremic gastritis; stress-related or drug-induced erosive gastritis; esophagitis; and the treatment of melanomas.[iv] When administered orally, the recommended dose of cimetidine to treat ulcers in adult horses ranges from 8.8 mg/kg to 48 mg/kg per day.[v]

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.[vi] Gastric ulcers in performance horses have been correlated with poor coat, selective eating, signs of abdominal discomfort, and decreased performance.[vii]

Although commonly used for the treatment or prevention of ulcers in horses, cimetidine does have interactions with many other medications. Cimetidine can inhibit hepatic enzymes that metabolize certain drugs. Therefore, caution should be used when cimetidine is administered to horses also being treated with theophylline, warfarin, and/or calcium channel blockers. Cimetidine may also decrease the clearance of some drugs, such as lidocaine and propranolol, because of its tendency to decrease hepatic blood flow.[viii] This decreased clearance could result in a longer elimination half-life, requiring a longer withdrawal period for these agents.

## Cimetidine Administration Study

Cimetidine tablets produced by Mylan Pharmaceuticals Inc. (Morgantown, WV) were administered orally via dosing syringe at a dose of 20 mg/kg BID for a total of seven doses to nine healthy exercised adult Thoroughbred horses.[i] This dose selection was determined based on an informal survey of equine practitioners conducted by the Racing Medication and Testing Consortium. The horses were fed one hour after drug administration. The study was performed at the Kentucky Equine Research (KER).

Blood Samples were obtained immediately before administration and at 1, 2, 4, 6, and 12 hours after the first dose. Additional blood samples were collected at 12-hour intervals during administration study. Following the last dose, blood samples were collected at 1, 2, 4, 6, 12, 24, 36, 48 hours post this administration.

## Extraction and Analysis Procedures

Quantification of cimetidine in plasma using a validated method was performed at the K.L. Maddy Analytical Chemistry Laboratory at the School of Veterinary Medicine, University of California, Davis under the direction of Dr. H.K. Knych. Cimetidine concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a reference standard obtained from Sigma-Aldrich (St. Louis, MO). The Lower Limit of Quantification (LLQ) for determination of cimetidine in plasma was 0.05 ng/mL and the Limit of Detection (LOD) was 0.005 ng/mL.

## Pharmacokinetic Modeling

Plasma concentrations of cimetidine are expressed as the median and range at the 24-hour collection point (Table 1.1). Pharmacokinetic analysis was performed using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

## Results and Discussions

Concentrations varied between horses at each time point. Serum cimetidine concentrations were still above the LLQ at 72 hours post administration after the last dose in all horses studied. The terminal serum half-life of 7.05 ± 1.02 hour for cimetidine in this study was

prolonged compared to other studies. Mean, median, and range of the cimetidine plasma concentrations 24 hours after administration are listed in Table 1.1 below.

**Table 1.1** Mean ± SD and range of cimetidine serum concentrations following 20 mg/kg BID (7 doses) at 24 hours post the final administration to nine exercised Thoroughbred horses.

| Time (h) after final administration | Mean ± SD (ng/mL) | Median (ng/mL) | Range (ng/mL) |
|---|---|---|---|
| **24** | 59.7 ± 32.9 | 49.5 | 19.4-116.9 |

## Scientific Advisory Committee Recommendation

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.,* ln) transformed plasma concentration data from the 24-hour collection time point for all nine horses. The 95/95 tolerance interval yielded a concentration of 307.9 ng/ml threshold recommendation. This threshold recommendation was rounded to 400 ng/ml of plasma with a 24-hour withdrawal guideline.

## Practice Tips

Cimetidine withdrawal time is based on an oral administration of 20 mg/kg twice daily for a total of 7 doses. A 24-hour withdrawal guideline may be used for longer treatment periods as there was no evidence for bioaccumulation when comparing the pharmacokinetics following the first and last doses. Different formulations of cimetidine, administration of higher doses, use of other administration methods, or combinations of cimetidine with other substances may result in concentrations above the threshold 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. Veterinarians should be especially cognizant of the possible drug interactions posed by cimetidine discussed in the background section above.

## References:

[i] H.K. Knych, *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., DOI: 10.1111/jvp.12328.

[ii] R.P. Hunter, *et al, Cimetidine Inhibits Nitric Oxide Associated Nitrate Production In A Soft-Tissue Inflammation Model In The Horse,* J. Vet. Pharmacol. Therap., 1999, 22:136-147.

[iii] M.G. Papich, *Antiulcer Therapy,* Gastrology: The 1990s, Veterinary Clinics of North America: Small

Animal Practice, 1993, 23(3): 497-512.

[iv] Plumb, Donald, *Plumb's Veterinary Drug Handbook,* Eight Edition, p. 300.

[v] R.A. Sams, *et al, Pharmacokinetics of Intravenous and Intragastric Cimetidine in Horses: Effects of Intravenous Cimetidine on Pharmacokinetics of Intravenous Phenylbutazone,* J. Vat. Pharmacol. Tharap., 1997, 20: 355-361.

[vi] RJW Bell, *et al*, *Equine Gastric Ulcer Syndrome in Adult Horses: A Review*, New Zealand Vet. J., 2007, 55(1): 1-12.

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

[viii] M.G. Papich, *Antiulcer Therapy,* Gastrology: The 1990s, Veterinary Clinics of North America: Small Animal Practice, 1993, 23(3): 497-512.