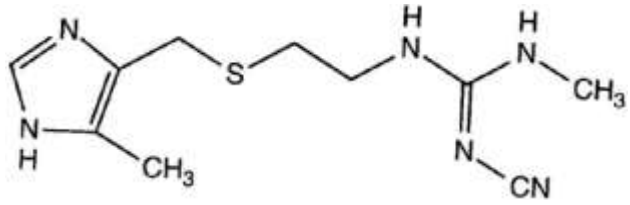
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Cimetidine

Background



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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 compared to other ulcer treatments. Although there is evidence from studies conducted in human patients that proton-pump inhibitors are more effective than H_2-receptor antagonists like cimetidine; no comparison studies have been conducted in horses.[iii] Proton pump inhibitors, such as omeprazole, however have fewer drug-drug interactions and their longer duration of effect allows for once a day dosing, which has contributed to their increased popularity.[iv]

Cimetidine is available in both over the counter and prescription strength formulations. There are no veterinary labeled cimetidine products, so all equine use is an extra-label use of a human-labeled product form. It is given both intravenously and orally.

Cimetidine has multiple indications for use including prophylaxis of gastric, abdominal, and duodenal ulcers; uremic gastritis; stress-related or drug-induced erosive gastritis; esophagitis; and the treatment of melanomas.[v]

Oral cimetidine doses recommended for oral administration to adult horses to treat ulcers range from 8.8 mg/kg to 48 mg/kg per day.[vi]

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

Cimetidine has been one of the most common treatments for ulcers, however it has significant side

effects through its interactions with other medications. Cimetidine can inhibit hepatic enzymes that metabolize other substances. Therefore, caution should be used, especially with theophylline, warfarin, and calcium channel blockers although it is unlikely that these medications would be indicated for use in a horse engaged in training or racing. Cimetidine may also decrease the clearance of lidocaine and propranolol because of its tendency to decrease hepatic blood flow.[ix]

Administration Study

Cimetidine tablets produced by Mylan Pharmaceuticals Inc. (Morgantown, WV) were suspended in water and administered orally via dosing syringe at a dose of 20 mg/kg for a total of seven doses to nine healthy exercise-conditioned adult Thoroughbred horses.[x] This dose was selected 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. Administrations were performed at the Kentucky Equine Research (KER).

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 also collected at 1, 2, 4, 6, 12, 24, 36, 48 hours after the final administration. Additional samples were collected at 12-hour intervals prior to dosing and during the study period.

Extraction and Analysis Procedures

Quantification of cimetidine in plasma was performed at the K.L. Maddy Equine Analytical Chemistry Laboratory at the School of Veterinary Medicine, University of California, Davis using validated methods. The concentration of cimetidine was determined in plasma samples s by liquid chromatography-mass spectrometry (LC-MS) using an internal reference standard obtained from Sigma- Aldrich (St. Louis, MO). The Limit of Quantification (LOQ) 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 24 hours post administration (Table 1.1). Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

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

Time (hours)	Mean ± SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24 h	59.7 ± 32.9	49.5	19.4-116.9

Results and Discussion

Plasma cimetidine concentrations were still above the LOQ in all horses at 72 hours after the last dose was administered. In this study, the terminal elimination half-life for cimetidine in plasma was 7.05±1.02 hours. Mean, median, and range of the cimetidine plasma concentrations after administration are shown in Table 1.1

Scientific Advisory Committee (SAC) Recommendation

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.,* ln) transformed plasma concentration data from the 48-hour collection time point for all nine horses. The 95/95 tolerance interval yielded a concentration of 307.9 ng/mL of cimetidine in serum/plasma. This threshold recommendation was rounded to 400 ng/mL of serum/plasma with 24-hour withdrawal guidance.

Practice Tips

The cimetidine withdrawal time is based in an oral administration of 20 mg/kg twice daily for 7 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. In particular, the half-life reported for cimetidine in this study (7.05 hrs) suggests that bioaccumulation can occur, and extended withdrawal intervals may be warranted for horses receiving treatments for periods longer that used in this study.

Veterinarians are advised to assess the impact of these potential risk factors on the withdrawal time and to advise their clients accordingly. Veterinarians should note the possible drug-drug interactions posed by cimetidine discussed in the Background section above.

Some regulatory authorities have prohibitions on the administration of medications within 48 hours of a race. The 24-hour withdrawal guidance for cimetidine does not apply when regulations prohibit the use of medication at that time. Veterinarians are expected to know and follow the regulations in the jurisdictions where they practice and where their horses race

References

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