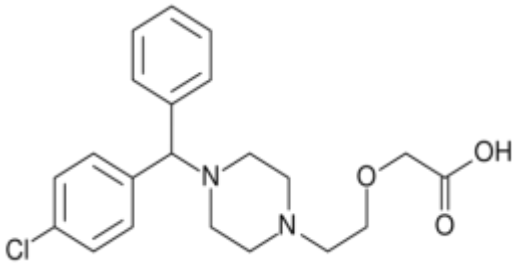
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Cetirizine

Background

Cetirizine is a second-generation histamine antagonist and a hydroxyzine metabolite.[i] Unlike first generation antihistamines such as hydroxyzine, cetirizine lacks sedative properties.[ii,iii] Cetirizine is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. It is FDA approved for use in humans as cetirizine hydrochloride and, consequently, is available for use in horses pursuant to Animal Medicinal Drug Use Clarification Act (AMDUCA). It can be administered orally for the treatment of hypersensitivity conditions in horses.[iv]



"Cetirizine structure" by User:Mysid - Self-made in bkchem; edited in perl.. Licensed under Public Domain via Commons - https://commons.wikimedia.org/wiki/File:Cetirizine_structure.svg#/media/File:Cetirizine_structure.svg.png

Cetirizine is most commonly available as an over the counter medication. It is commercially available in a variety of formulations including Zyrtec™.[v] It is available in syrup and tablet form. Tablet concentrations range from 5 mg to 120 mg strength.[vi]

Cetirizine is a histamine antagonist. Unlike first generation histamine antagonists, it lacks cholinergic activity – and therefore cetirizine does not have some of the undesirable side-effects of a first-generation histamine agonist, (*e.g.,* sedation). This lack of sedation is likely, in part, because cetirizine does not cross the blood-brain barrier.

Hydroxyzine has been a more commonly prescribed antihistamine in equine practice than cetirizine, but because of its sedative and anxiolytic properties hydroxyzine is an ARCI Class 2 drug. Cetirizine is the major metabolite of hydroxyzine which can be considered a pro-drug for cetirizine. [vii] Thus, the administration of hydroxyzine will yield hydroxyzine and cetirizine in blood and urine samples[viii]. Cetirizine, however, does not reconvert to hydroxyzine. Accordingly, veterinarians are encouraged to prescribe ARCI Class 4 cetirizine rather than ARCI Class 2 hydroxyzine for horses subject to testing.

Administration Study

Cetirizine hydrochloride sourced from commercially available 10 mg cetirizine tablets was administered to nine exercise-conditioned Thoroughbred horses (geldings and mares). The number of tablets administered was based upon a dose of 0.4 mg/kg of cetirizine rounded to the closest 10 mg tablet. The horses were administered cetirizine tablets dissolved in water via oral dosing syringe. Horses were dosed twice daily for 5 total doses. The administration was performed at Kentucky Equine Research (KER) and funded by the Kentucky Equine Drug Research Council.

Blood samples were obtained immediately before the first dose administration and immediately prior to each subsequent drug administration. Blood samples were also collected at 1, 2, 4, 6, 12, and 24 hours after the first and last dose administration. Finally, blood samples were collected at 36, 48, 60, 72, 84, and 96 hours after the final dose administration.

Extraction and Analysis Procedures

Quantification of cetirizine in plasma was performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California-Davis using validated methods as described in the published paper by Knych. Cetirizine was determined in plasma by liquid chromatography-mass spectrometry (LC-MS/MS) using an internal standard of cetirizine-d_8. The lower Limit of Quantification (LOQ) for determination of cetirizine in plasma was 0.05 ng/mL.

Pharmacokinetic Modelling

Plasma concentrations of cetirizine are expressed as the mean with standard deviation and median at select collection points (Table 1.1). Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® Version 6.2 pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.,* ln) transformed plasma concentration data at 24 and 48 hours after the last administration.

Results and Discussion

The peak average plasma cetirizine concentration observed in this study was 64.1 ng/mL at 4 hours after oral administration. Plasma cetirizine concentrations remained above the LOQ of 0.05 ng/mL through the 48 hours of the study.

Mean plus standard deviation, median and range of the plasma concentrations at select times are shown in Table 1.1.

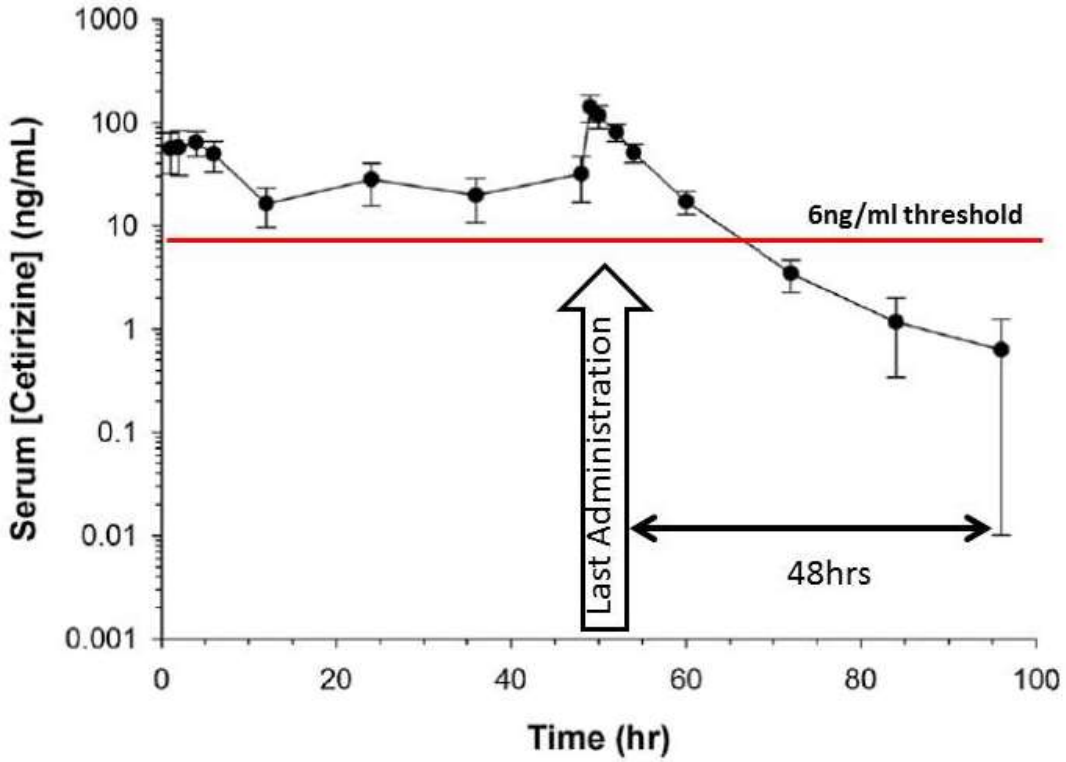
Table 1.1 Plasma cetirizine concentration mean with standard deviation, median and range values at select times following the last administration of approximately 0.4 mg/kg of cetirizine via dose syringe BID for 5 doses to 9 horses.

Time (hours)	Mean ± SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	3.46 ± 1.21	3.28	1.94 -6.20
48	0.628 ± 0.618	0.379	0.15 – 2.12

The cetirizine concentrations were above the plasma LOQ in all samples collected at 48 hours after the final administration as shown in Figure 1.1

Accumulation of cetirizine following multiple administrations was minimal as indicated by the calculated accumulation ratio of 1.30 (median). Nevertheless, continuous- and long-term administration of cetirizine prior to racing may still pose a risk of an inadvertent positive.

Figure 1.1 Plasma concentrations cetirizine (mean±SD) before and following an approximate 0.4 mg/kg cetirizine administration (Note –BID for 5 administrations via dose syringe with last administration at 48 hours), adapted from Knych, *et al.*)



Scientific Advisory Committee (SAC) Recommendation

The RMTC SAC determined that cetirizine administration should be discontinued 48 hours prior to racing. Accordingly, the threshold was based upon the data obtained at 48 hours after the final oral administration. The 48-hour data were used to calculate a 95/95 tolerance interval that resulted in a value of 5.72 ng/mL of plasma/serum. This was then rounded up by the SAC to a threshold recommendation of 6.0 ng/mL of cetirizine in plasma/serum.

Practice Tips

The withdrawal guidance of 48 hours is based upon a 0.4 mg/kg dose of cetirizine hydrochloride commercial tablets. Different formulations of cetirizine, administration in feed, administration of higher doses, or combinations of cetirizine 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.

Warning: Withdrawal guidance does not apply to cetirizine administered concurrently with avermectin products – including ivermectin containing dewormers. Co-administration of ivermectin and cetirizine alters the pharmacokinetics of cetirizine increasing the half-life.[ix] Concurrent use of these products should be avoided in racing horses.

References

[i]Olsen, L., *et al.*, *Pharmacokinetics and Effects of Cetirizine in Horses With Insect Bite Hypersensitivity*, The Veterinary Journal, (2011) 187:347-51.

[ii] Olsen, L., *et al.,* The Veterinary Journal, (2011).

[iii] Knych, H.K., Stanley, S.D., Arthur, R.M. and McKemie, D.S., *Elimination of Cetirizine Following Administration of Multiple Doses to Exercised Thoroughbreds*, J. vet. Pharmacol. Therap. (2016) 39(5):522-24.

[iv] Olsen, L., *Cetirizine in Horses: Pharmacokinetics and Effect of Ivermectin* Pretreatment, J. Vet. Pharmacol. Therap. (2007) 30:194-200.

[v] FDA Orange Book. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (Enter cetirizine in search box)

[vi] FDA Orange Book.

[vii] Plumb, Donald C. "Cetirizine HCL" *Plumb's Veterinary Drug Handbook*. 8th ed. Stockholm, WI: PharmaVet, 2015. 271-73.

[viii] Bizkova, P., *et al.,* Hydroxyzine and cetirizine pharmacokinetics and pharmacodynamics after oral and intravenous administration of hydroxyzine to healthy dogs, Vet Dermatol. (2008) 19(6): 348-357.

[ix] Olsen, L., J. Vet. Pharmacol. Therap. (2007).