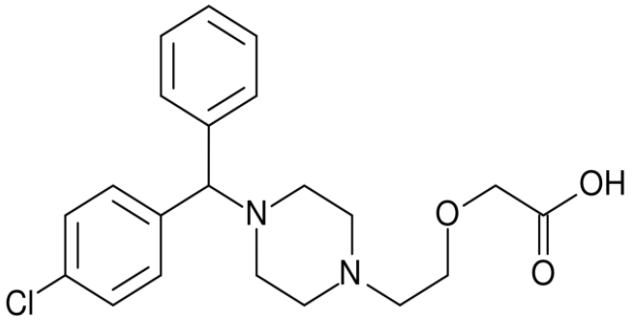
Cetirizine

Background



"Cetirizine structure" by User:Mysid - Self-made in bkchem;
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Cetirizine is a second-generation histamine antagonist and a hydroxyzine metabolite.[1] It Upon the recommendation of the RMTC Scientific Advisory Committee cetirizine was assigned a 4/C classification by the ARCI. Unlike first generation antihistamines such as hydroxyzine, cetirizine lacks sedative properties.[2,3] It is FDA approved for use in humans as cetirizine hydrochloride and, consequently, is available for use in horses pursuant to AMDUCA (Animal Medicinal Drug Use Clarification Act). It can be administered orally for the treatment of hypersensitivity conditions in horses.[4]

Cetirizine is available as an over the counter medication in a variety of formulations including Zyrtec™.[5] It is available in syrup and tablet form. Tablet concentrations range from 5 mg to 120 mg strength.[6] Cetirizine can be compounded from FDA approved products for veterinary use.

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 anti-histamine in equine practice than cetirizine, but because of its sedative and anxiolytic properties hydroxyzine is an ARCI Class 2/B drug. Cetirizine is the major metabolite of the hydroxyzine which can be considered a pro-drug for cetirizine. [7] Thus, the administration of hydroxyzine will yield hydroxyzine and cetirizine in blood and urine samples. Cetirizine, however, does not reconvert to hydroxyzine.

Cetirizine Administration Study

Cetirizine hydrochloride sourced from commercial 10 mg cetirizine tablets was administered to nine exercised 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 orally via 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 University of California – Davis Maddy Laboratory using validated methods as described in the published paper by Knych [iii]. Cetirizine was determined in plasma by liquid chromatography-mass spectrometry (LC-MS) using an internal standard of cetirizine-d_8. The Lower Limit of Quantification (LLQ) for cetirizine in plasma was 0.05 ng/mL.

Pharmacokinetic Modelling

Plasma concentrations of cetirizine are expressed as the mean with standard deviation and median prior to the first administration and 48 hours after the last administration (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 48 hours after the last administration.

Results and Discussion

The LC-MS method for determination of cetirizine in plasma was characterized by an LLQ of 0.05 ng/mL.

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

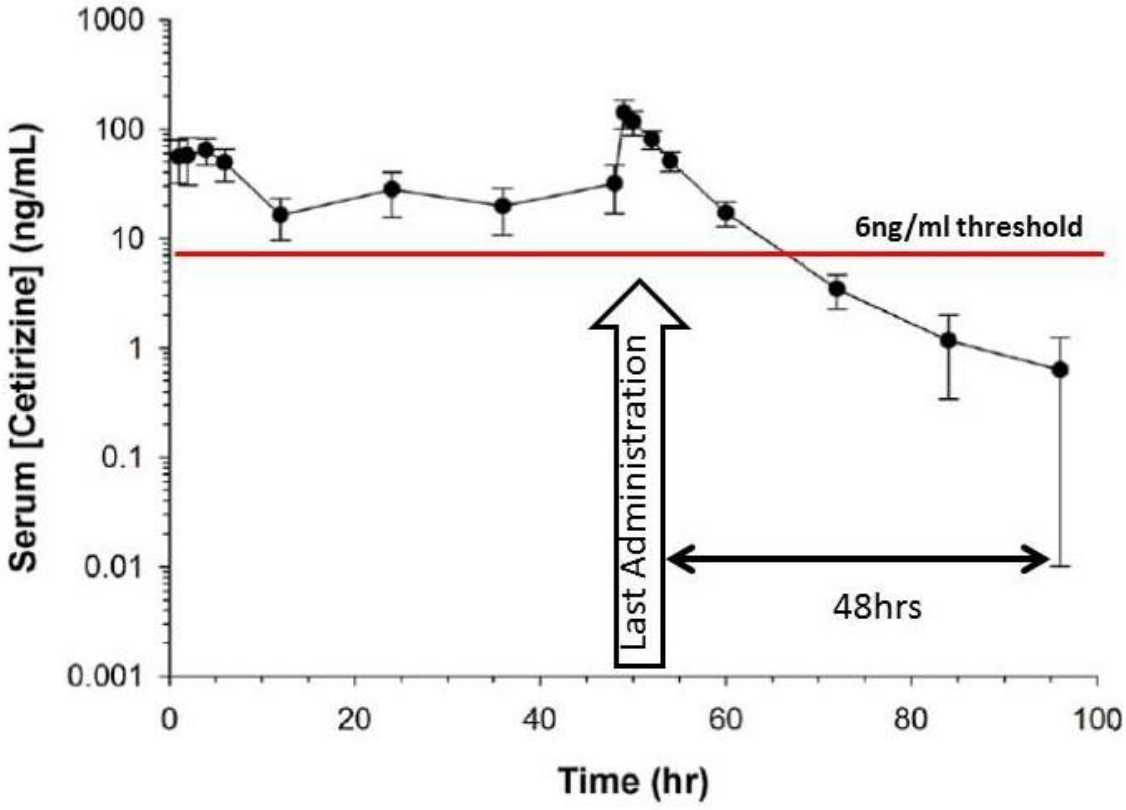
Mean plus standard deviation, median, and range of the plasma concentrations prior to the first administration and at 48 hours after the final administration are shown in table 1.1.

Table 1.1 **Plasma cetirizine mean with standard deviation, median values, and range at 48 hours after the last administration of approximately 0.4 mg/kg of cetirizine to 9 horses**

Time (hours)	Mean ± SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
48	0.628 ± 0.618	0.379	0.15 – 2.12

The cetirizine concentrations were above the plasma LLQ in all samples collected at 48 hours after the final administration.

Figure 1.1 **Plasma concentrations cetirizine (mean±SD) following an approximate 0.4 mg/kg cetirizine administration (Note – last administration at 48 hours), adapted from Knych, *et al.*)**



Scientific Advisory Committee 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 data was log transformed (ln) and the mean (-0.78) and standard deviation (0.79) of the log transformed data were used to calculate a threshold based upon a 95/95 tolerance interval. The calculation for a tolerance interval using the K factor for 9 horses yielded a threshold of 5.72 ng/mL of plasma/blood. This number was then rounded to 6 ng/mL of plasma/blood by the SAC.

Practice Tips

The withdrawal guide recommendation of 48 hours is based upon a 0.4 mg/kg dose of cetirizine hydrochloride commercial tablets. Different formulations of cetirizine, administration of higher doses, or combinations of cetirizine with other substances, particularly hydroxyzine, may result in concentrations above the threshold unless an extended withdrawal time is observed.

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.

Warning: Specifically, the withdrawal time recommendation does not apply to cetirizine administered concurrently with avermectin products – including ivermectin containing dewormers. Co-administration of ivermectin and cetirizine changes the pharmacokinetics of cetirizine increasing the half-life.[8] Trainers should avoid using these products concurrently in racing horses prior to race day.

Veterinarians are advised to assess the impact of all potential risk factors on the withdrawal time and to advise their clients accordingly.

References

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

[2] *Id.*

[3] 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.

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

[5] Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021150&TABLE1=OB_OTC.

[6] See, e.g., http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021150&TABLE1=OB_OTC.

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

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