Title: Plasma and urine pharmacokinetics of hydroxyzine and cetirizine following repeated oral administrations to exercised horses

Short Running Title: Pharmacokinetics of hydroxyzine and cetirizine in horse

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Abstract

Hydroxyzine and cetirizine are first and second generation oral anti-histamine drugs, respectively, used to treat allergic reactions in horses. Cetirizine is also a metabolite of hydroxyzine which may lead to complexities in regulating their use in equine sporting events. The aim of the research was to be able to provide Detection Times (DT) from pharmacokinetic studies in thoroughbred horses to better inform trainers, and their veterinary surgeons, prescribing these substances for treatment of Thoroughbred racehorses. Six and two horses were given 9 repeated administrations of hydroxyzine HCl (500 mg BID) or cetirizine HCl (190 mg BID), respectively. Plasma and urine hydroxyzine and cetirizine concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). A holistic non-linear mixed effects PK model was developed that described both plasma and urine concentrations of hydroxyzine and cetirizine, either from administration of each individually or

cetirizine as a metabolite of hydroxyzine. Using the parameters obtained from this PK model in conjunction with methodology developed by Toutain afforded possible screening limits (SL) that can regulate for a DT of 4 days in either plasma or urine. Hydroxyzine and cetirizine concentration prediction intervals for the 80^{th}, 95^{th} and 99^{th} percentiles of a virtual horse population were performed in order to assess the statistical protection of the DT. However, it is down to the individual racing authorities to apply their own risk management.

Introduction

Hydroxyzine is a first generation anti-histamine with anti-muscarinic and significant sedative properties as it crosses the blood brain barrier. Cetirizine is an orally active second-generation anti-histamine, and a metabolite of hydroxyzine. Cetirizine shows a low capacity to cross the blood-brain barrier in humans and other mammals, and as a result does not exhibit the same significant sedation properties (Simons & Simons, 2011).

In human medicine, hydroxyzine is mainly used as an anxiolytic, but it is also used to treat allergic skin reactions such as hives or contact dermatitis, and as an adjunct to pre- and post-operative medication. Cetirizine is widely used in human medicine, and preferable to hydroxyzine for treating seasonal allergic rhinitis, dermatitis and hives. On the other hand, hydroxyzine is more commonly used in horses than cetirizine for the treatment of hypersensitivity

reactions, such as atopic dermatitis. The sedative properties of hydroxyzine may however influence the choice of antihistamine used in performance horses.

As a legitimate therapeutic medication, permitted for use in training, but which must not have a pharmacological effect on race day, it is of interest to racing authorities to be able to provide Detection Time (DT) advice to veterinary surgeons. To deal with the race-day scenario where a horse has received medication treatment in its training programme a non-significant pharmacological effect in a population of horses has to be defined. One such definition can be a drug concentration in plasma that is less than the concentration required for a significant therapeutic effect. Toutain & Lassourd (2002) proposed an approach based upon the above definition that also takes into account variation in both pharmacokinetic (PK) and pharmacodynamic (PD) parameters for a population of horses. An estimate of the irrelevant plasma concentration (IPC) is based upon a pharmacologically effective plasma drug concentration divided by an appropriate safety factor. Also, with knowledge of urine PK parameters an irrelevant urine concentration (IUC) can also be estimated. The IPC and IUC can be used for the purpose of deriving possible drug screening limits (SL), which, in turn, can be used in conjunction with drug clearance profiles to obtain appropriate DT for the matrices concerned. The DT is the time post last therapeutic administration when the drug concentration in plasma or urine drops below the IPC/IUC for six observed horses. By using a

DT to form the basis of a Withdrawal Time (WT), veterinary surgeons working with racehorses can help avoid an Adverse Analytical Finding ('positive') on race day following legitimate therapeutic treatment in training.

Recently, Knych et al., (2019) have described the PK of hydroxyzine and cetirizine as metabolite from single dose administration of hydroxyzine to 12 horses in serum and to a limited extent in urine. The plasma/serum PK of cetirizine after repeated oral administration to horse have been previously described by Olsen et al., (2008) and Knych et al., (2016).

Although the PK of hydroxyzine has been studied for single dose administration it has not been investigated for its recommend multi-dose regimen. Moreover, as urine is the race day matrix of choice for many equine sports regulators a detailed urine PK analysis of hydroxyzine and cetirizine is required for regulation of these medications.

Given that hydroxyzine is metabolised to cetirizine but cetirizine itself can also be used as a medication in its own right it may be difficult to obtain one single SL for cetirizine. Therefore, the aim of the herein paper is to develop a holistic PK model that describes both plasma and urine concentrations of hydroxyzine and cetirizine in thoroughbred horses, either from administration of each individually or cetirizine as a metabolite of hydroxyzine. Furthermore, the PK model needs to quantify inter-individual variability amongst the horses so as to assess the statistical protection of the proposed DT

Materials and Methods

Horses

Six healthy Thoroughbred horses (3 geldings and 3 mares) aged 4-6 years (mean bodyweight 495±32 kg) were used for the hydroxyzine administration study and two healthy Thoroughbred horses (1 gelding and 1 mare) aged 3 and 4 years (bodyweight 475 and 487 kg) were used for the cetirizine administration study. Horses received ridden exercise six days out of seven. Exercise was a mixture of trotting and cantering, with a minimum of two 4 furlong canters per day and continued for approximately 45 – 60 minutes. In addition, horses were exercised twice daily for 45 minutes on a horse walker. Both studies were carried out at the British Horseracing Authority's Centre for Racehorse Studies, Newmarket, UK.

Drug administration and sampling

All administration and sampling studies were carried out with ethical approval under the UK Animal and Scientific procedures Act. A 14-gauge catheter was placed in the left external jugular vein for blood sampling and the drugs administered orally. 500 mg Atarax® (hydroxyzine hydrochloride) and 190 mg Allacan® (cetirizine hydrochloride) were crushed in water (30 mL) and dosed orally via syringe (3.5 hours after feeding) twice daily (9 am and 4 pm) for four and a half days (9 doses) to six horses and two horses, respectively. Only two

horses were used for oral cetirizine administrations as PK data already existed within the literature.

Pre-dose blood (10 mL) and urine (20 mL) were collected as control samples. Post dose blood (10 mL) and urine (20 mL) were collected at decreasing frequencies as indicated in Figure 2. Catheters were removed following collection of the 24 h post dose blood sample and the remaining samples collected by direct venepuncture. All blood samples were collected in lithium heparin tubes, and all urine samples were obtained using the free catch method. Blood was centrifuged for 10 minutes and plasma stored at -20ºC until analysis. Urine was frozen immediately and stored at -20ºC and centrifuged post thaw prior to analysis.

Chemicals and Reagents

Ultrapure water was purified by a Triple Red ultrapure water system (Triple Red Ltd., Buckinghamshire, UK). Acetonitrile, chloroform, ethyl acetate, hexane, hydrochloric acid, methanol, sodium hydroxide and Methyl tert-butyl ether (TBME) were purchased from Fisher Scientific UK Ltd. (Loughborough, UK). Optima grade formic acid was purchased from LGC Ltd (Middlesex, UK). Hydroxyzine was purchased from Sigma Aldrich (Dorset, UK), Hydroxyzine-d8 was from Lipomed (Switzerland; Kinesis/UK), Cetirizine was from Pfizer Ltd (Tadworth, UK) and Cetirizine-d8 was purchased from Toronto Research Chemicals (Canada).

Sample Preparation:

Sodium hydroxide solution was added to hydrolysed plasma and a liquid-liquid extraction method using 15 % chloroform in TBME was employed to extract hydroxyzine (and hydroxyzine-d8). Samples were rotary mixed for 30 minutes followed by centrifugation at 1000 RCF for 10 minutes and the organic layer was retained. The organic layer was evaporated to dryness without heat and the sample residues were reconstituted in acetonitrile and transferred to a clean plastic vial before evaporating to dryness a second time.

Plasma was acidified and after 5 minutes, acetonitrile and phosphate buffer (pH 6.3) were added and the sample centrifuged at 1000 RCF for 15 minutes before cetirizine (and cetirizine –d8) were extracted using a Focus 20 mg 3 ml cartridge (Agilent Varian, West Sussex, UK) conditioned with methanol and water before the sample was applied. The cartridge was washed with water and eluted with ethyl acetate.

Hydroxyzine and hydroxyzine-d8 were extracted from hydrolysed urine using a Strata XC 60 mg 3 ml cartridge (Phenomenex, California, USA) conditioned with methanol and water before the sample was applied. The cartridge was washed with acetate buffer (0.1 M, pH 9.0) followed by water, HCl (0.1M) and methanol and eluted with 2 aliquots of ethyl acetate:propan-2-ol:ammonia (80:17:3) and the combined eluates were retained.

Urine was treated with pancreatin and phosphate buffer (pH 6.3) and centrifuged for 10 minutes at 1000 RCF. Cetirizine (and cetirizine –d8) were extracted using a Nexus 60 mg 3 ml cartridge (Agilent Varian, West Sussex, UK) conditioned with methanol and water before the sample was applied. The cartridge was washed with hexane and eluted with methanol in ethyl acetate (10% v/v). A further liquid-liquid extraction with water was carried out and the organic layer was retained.

All extracted eluates were evaporated to dryness at ambient temperature and the sample residues were reconstituted in a small volume of methanol before diluting to a 10% (v/v) solution with water, mixing and centrifuging.

Analytical Methodology:

Ultra-performance liquid chromatography tandem-MS (UPLC-MS/MS) analysis was performed with a Waters Acquity UPLC system coupled to an Applied Biosystems Sciex QTrap 5500 mass spectrometer using electrospray ionisation (ESI) in positive ion mode. Analysis was in selected transition monitoring (SRM) mode, using several transitions for each compound, with a precursor ion of m/z 376.2 for hydroxyzine, m/z 384.1 for hydroxyzine-d8, m/z 389.8 for cetirizine and m/z 398.1 for cetirizine-d8. The lower limit of quantification was 50 pg/ml for hydroxyzine and cetirizine in plasma and 200 pg/ml for hydroxyzine and cetirizine in urine.

A Waters BEH C18 column (2.1 x 100 mm, 1.8 μm) was installed and the injection volume was 3 μl. The mobile phases were methanol [A] and formic acid in water (0.1 % v/v) [B]. The UPLC gradient starting conditions were 5 % A, increasing to 60 % between 0.25 and 1.2 minutes and to 98% between 1.2 and 3 minutes. This was held for 0.15 minutes before returning to 5 % A for 0.25 minutes. The flow rate was 400 μl/minute.

Calibration Method:

Following validation, the analytical methods were deemed suitable for application to the study samples. Specifically, inter- and intra-batch precision (% coefficient of variation) and accuracy (% relative error) were within 20% (25% at the LLOQ), linearity of dilution (% relative error and % coefficient of variation) was within 20% and no significant matrix suppression or interferences were observed.

Pharmacokinetic Analysis

Compartmental NMLE Model

The compartmental model used to describe hydroxyzine and cetirizine concentrations in plasma and urine from oral administrations of each drug is shown in Figure 1 where: Ka_H and Ka_C are the oral absorption rate constants for cetirizine and hydroxyzine, respectively. $V1/F_H$ and $V2/F_H$ are the volumes of the central and peripheral compartments for hydroxyzine unadjusted for

bioavailability, respectively. CLM/F_H, CLR/F_H and CLD/F_H are the clearances for hydroxyzine metabolism, renal excretion and distribution unadjusted for bioavailability, respectively. $V1^*_C$ and $V2^*_C$ are the volumes of the central and peripheral compartments for cetirizine, CLR^*_C and CLD^*_C are the clearances for cetirizine renal excretion and distribution unadjusted for cetirizine bioavailability or in the case of hydroxyzine administration unadjusted for hydroxyzine bioavailability and fraction metabolised to cetirizine, respectively. VU and UF are the average volume of urine in the bladder and urine flow, respectively. Cp_H, Cp_C, Cu_H and Cu_C are the plasma and urine concentrations of hydroxyzine and cetirizine, respectively. As the molecular weights of hydroxyzine and cetirizine are within 5% no correction was made for the difference.

Pharmacokinetic analyses were conducted using non-linear mixed effects methods (NLME) with Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA). Compartmental NLME PK models were applied simultaneously to the plasma and urine concentration data for both hydroxyzine and cetirizine either from administration of each individually or cetirizine as a metabolite of hydroxyzine. Residual error was modelled on a proportional error model. An exponential random effect model was chosen to describe inter-individual variability e.g. parameter = typical parameter * $\exp^{(eta)}$. A continuous covariate for body weight (centred to mean) and a categorical covariate for drug administered

(hydroxyzine or cetirizine) were implemented on the model parameters in a multiplicative exponential way. The model analysis started from the basic compartmental models without the covariate. Next, the contribution of the covariates to the fixed parameters and correlation on the random effects were assessed by a reduction in the objective function using stepwise forward inclusion. Selection of the best model was based on the lowest value of the Akaike and Bayesian Information Criteria (AIC and BIC), chi-square p-value based on the likelihood ratio test, visual inspection of the population predicted concentration versus the observed concentrations and the resulting conditional weighted residual errors. Finally, the best model was checked for robustness using a bootstrap resampling method. The effective plasma concentration (EPC) and irrelevant plasma and urine concentrations (IPC and IUC) were estimated using the Toutain and Lassourd, 2002 methodology which were used for the basis of possible SLs. Briefly, the EPC was estimated from the total daily dose divided by the oral plasma clearance over a 24 hour period. For hydroxyzine the oral plasma clearance was the sum of CLR/F_H and CLM/F_H. The IPC was determined by dividing the EPC by a factor of 500 and the IUC determined by multiplying the IPC by the steady-state ratio of urine to plasma concentration (Rss). The Rss values for hydroxyzine and cetirizine were determined by dividing CLR/F_H or CLR^*_C by UF, respectively. The DTs were determined by the time post dose where all horses had concentrations below the possible plasma and urine SLs. Montecarlo simulations (10,000) were used to determine

hydroxyzine and cetirizine concentration prediction intervals for the 80th, 95th and 99th percentiles of a virtual horse population.

Results

Pharmacokinetics for hydroxyzine following twice daily oral dosing of hydroxyzine

The plasma and urine PK profiles for hydroxyzine are displayed in Figure 2 (C and D) and appear to reach steady-state after 6 doses (3 days). After the final hydroxyzine dose, decay curves appear to have two phases of decline entering into the second phase at approximately 3 days post last administration. Greater variability is observed in the urine PK compared to plasma.

Pharmacokinetics for cetirizine following twice daily oral dosing of hydroxyzine (6 horses) or cetirizine (2 horses)

The plasma and urine PK profiles for cetirizine are also displayed in Figure 2 (A and B). Cetirizine concentrations appear to reach steady-state after 2 doses (1 day) following either hydroxyzine or cetirizine administration. After the final hydroxyzine or cetirizine dose, cetirizine curves appear to decline in a similar manner to hydroxyzine.

The most parsimonious compartmental NLME model obtained had random effects included on all parameters with partial correlation (See supplementary

Table S1). The continuous covariate for body weight did not reduce the objective function for any of the parameters, however, a categorical covariate for cetirizine administration of -0.50 was implemented in a proportional manner for the urine flow (UF) parameter. The residual error standard deviation for Cp_H, Cp_C, Cu_H and Cu_C were 0.68, 0.57, 1.10 and 0.58, respectively. Table 1 shows the outputted typical values (TV) for the parameters resulting from the final model which were encompassed by the 2.5 and 97.5% confidence intervals of the bootstrap resampling analysis. Also included in Table 1 are the mean and CV% of the post hoc empirical Bayes estimates (EBE) for the parameters. Figure 2 also shows the individual horse concentration predictions using the EBE parameters as lines superimposed onto the measured concentrations (circles) versus time graph.

Hydroxyzine EPC, IPC, Rss and IUC

The estimated TV for hydroxyzine oral plasma clearance is 10.05 ml/min/kg ($CLR/F_H + CLM/F_H$) and indicates that 97.5% of this clearance is via conversion to cetirizine. The estimated EPC, IPC, Rss and IUC values for hydroxyzine are 116 ng/ml, 0.23 ng/ml, 2.75 and 0.63 ng/ml, respectively, based on TVs.

Screening Limits and Detection Times for hydroxyzine or cetirizine administration

The estimated nominal IPC and IUC values of 0.23 and 0.63 ng/ml for hydroxyzine administration clip their respective terminal phases which contribute little to overall hydroxyzine elimination. IPC and IUC values form the basis of possible SLs and it is down to the individual racing authorities to apply their own risk management. If the nominal IPC of 0.23 ng/ml is adjusted to an ordinal value of 0.5 ng/ml then the terminal plasma phase is avoided and affords a DT of 96 hours after final administration. However, the estimated nominal IUC value of 0.63 ng/ml would have to be increased to 5 ng/ml in order to maintain a DT of 96 hours in urine. Cetirizine, as a metabolite of hydroxyzine, can be used as a marker of hydroxyzine administration. Plasma and urine cetirizine concentrations of 0.3 and 100 ng/ml, respectively, would support a DT of 96 hours post hydroxyzine or cetirizine administration.

DTs are an experimental observation from a small number of horses, however, the risk of exceeding a SL in a population of horses is very useful in assessing the statistical protection afforded by the DT. Figure 3 shows the plasma and urine pharmacokinetics of hydroxyzine and cetirizine after the last administration of hydroxyzine or cetirizine. The red dashed horizontal lines represent possible SLs corresponding to a DT of 96 hours. The upper black dotted, solid and dashed lines in Figure 3 represent hydroxyzine and cetirizine concentration prediction intervals for the 80^{th}, 95^{th} and 99^{th} percentiles, respectively, of a virtual horse population (10,000 simulations). A DT of 96

hours would cover the 80th percentile for a possible hydroxyzine plasma SL of 0.5 ng/ml but slightly less than this for a possible cetirizine plasma SL of 0.3 ng/ml. Furthermore, a DT of 96 hours would cover between the 95-99th percentile for a possible hydroxyzine urine SL of 5 ng/ml and the 80th percentile for a possible cetirizine urine SL of 100 ng/ml.

Discussion

The analytical methods applied in the current study are more sensitive than those previously applied for determining the disposition of hydroxyzine and cetirizine in the horse. The LLOQs for hydroxyzine and cetirizine in plasma from the current study are 50 pg/ml, which are lower than previously reported (LLOQ = 100 pg/ml for hydroxyzine and cetirizine in serum, Knych et al., 2016). The LLOQs in urine from the current study are 200 pg/ml. Compared to plasma, there are fewer existing reports that measure the concentrations of these analytes in urine. Knych et al., 2016 reported an LLOQ for hydroxyzine and cetirizine in urine of 100 pg/ml (ie 2 fold lower for urine) however, they only looked at 4 urine time points post administration. The significantly enhanced analytical sensitivity provided by the methods applied herein permits a lengthened window of detection for all of the analytes. In turn, it is anticipated that this should permit a more accurate assessment of the PK disposition of the drugs at the later time points. Furthermore, the concurrent measurement of plasma and urine concentrations allows for the calculation of urine to plasma

drug ratios, which enables urinary drug concentrations to be used as surrogates for plasma concentrations when regulating the use of these medications.

The resulting NMLE model affords a quantitative description of both plasma and urine concentrations of hydroxyzine and cetirizine, either from administration of each individually, or cetirizine as a metabolite of hydroxyzine. The clearance values for hydroxyzine metabolism versus renal excretion suggest that hydroxyzine is almost exclusively converted to cetirizine. The CV% from the post hoc EBE for the average volume of urine in the bladder (VU) is high (100%), however, this would be expected as VU will be dependent on the hydration status of the horse and frequency of bladder emptying. Furthermore, parameters associated with cetirizine have a high CV% from the post hoc EBE. This may be due to a single set of model parameters for cetirizine that encompass both the bioavailability and fraction metabolised of hydroxyzine to cetirizine on one hand and the bioavailability of cetirizine on the other. The CV% for residual error on Cp_H, Cp_C, and Cu_C varied between 57 to 68%, however, CV% for residual error on Cu_H was 110% which is a reflection of the large variability of Cu_H in the terminal urine PK phase. The continuous covariate for body weight was not significant for any of the parameters which was probably due to the narrow body weight range for the study. The estimated hydroxyzine oral plasma clearance from the herein repeated dose study is 10.1 ml/min/kg which is slightly less than the serum value obtained from the Knych et al., 2019 single dose study (13.4 ml/min/kg). On the other hand, the estimated

cetirizine oral plasma clearance from the herein study (20 ml/min/kg) is larger than both the Olsen et al., 2007 (8.2 ml/min/kg) and Knych et al., 2016 (9.2 ml/min/kg serum) repeated dose cetirizine studies.

Examination of the plasma PK profiles from the single oral dose hydroxyzine Knych et al., 2019 study shows that all 12 horses have serum concentrations below a possible plasma hydroxyzine SL (0.5 ng/ml) by the proposed DT of 96 hours. Application of the Toutain approach to the 2007 and 2016 cetirizine oral studies affords EPC values of 68 and 60 ng/ml, respectively. This corresponds to cetirizine IPC values of 0.14 and 0.12 ng/ml which are comparable but slightly less than a possible plasma SL for cetirizine of 0.3 ng/ml as a marker of hydroxyzine administration. The 2007 and 2016 cetirizine administration studies only managed to quantify plasma concentrations out to 48 hours post last administration, however, for both cases the majority of horses at 48 hours had concentrations below 1 ng/ml. Therefore, a DT of 96 hours post last administration using a possible plasma cetirizine SL of 0.3 ng/ml appears to be consistent with all these studies.

As mentioned previously, there is limited urine PK data available in horse for either hydroxyzine or cetirizine. However, for many equine sports regulators, urine is the matrix of choice for regulating the use of medications in equine sports competitions. Neither the 2007 nor 2016 cetirizine studies investigated the urine PK of cetirizine. Furthermore, the Knych et al., 2019 hydroxyzine

study only measured urine concentration from 4 time points post single dose administration. Nonetheless, all 12 horses had urine hydroxyzine concentrations below a possible urine SL of 5 ng/ml by a DT of 96 hours. Application of the Rss value determined for cetirizine in the herein study (220) to the IPC values estimated from the 2007 and 2016 cetirizine studies affords an IUC of approximately 30 ng/ml. This is comparable but less than a possible urine SL for cetirizine of 100 ng/ml as a marker of hydroxyzine administration. All 12 horses in the Knych et al., 2019 study had cetirizine urine concentrations below a possible urine SL of 100 ng/ml by a DT of 96 hours.

A compartmental NLME model has been developed that holistically describes both plasma and urine concentrations of hydroxyzine and cetirizine, either from administration of each individually or cetirizine as a metabolite of hydroxyzine. Combining this model with Toutain methodology affords possible SLs that can regulate for a DT of 4 days in either plasma or urine. Furthermore, a DT of 4 days affords statistical protection of at least the 80^{th} percentile in a population of horses for the possible urine SLs and can be used to aid veterinary surgeons in determining a corresponding WT. However, it is down to the individual racing authorities to apply their own risk management with regard to SLs, DTs and WTs.

Animal welfare and Ethics

The study was approved by the British Horseracing Authority's Centre for

Racehorse Studies Animal Welfare and Ethics Review Board, with the horses and personnel involved licensed under the UK's Animals (Scientific Procedures) Act.

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Conflict of interest

The authors have no commercial conflict of interests; however, the authors are either employed by, working on behalf of or consulting to a regulatory agency.

Data availability statement

The data that support the findings of this study are available from the British Horse Racing Authority (BHA). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the BHA.

Authors' contribution

AGG contributed to the analytical development method, validation and sample analysis. TM led the administration study, PH performed project management, TM and PH performed manuscript editing. SP and MA co-ordinated the data

and performed pharmacokinetic analysis. All authors contributed to the writing of the manuscript, and have read and approved the final manuscript.

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Table 1: NLME typical value (TV) and post hoc parameter estimates from compartmental model for 500 mg Atarax® (hydroxyzine hydrochloride) and 190 mg Allacan® (cetirizine hydrochloride) dosed orally twice daily for four and a half days (9 doses)(Figure 1).

Parameter	Typical Value* (TV)	Post Hoc Empirical Bayes Estimate	
		Mean	CV%
$V1/F_H$ (L/kg)	0.095	0.098	5
Ka_H (hr^{-1})	0.12	0.13	32
$V2/F_H$ (L/kg)	0.50	0.51	21
CLD/F_H (ml/min/kg)	0.090	0.092	8
$V1^*_C$ (L/kg)	6.5	8.1	71
$V2^*_C$ (L/kg)	0.20	0.20	5
CLM/F_H (ml/min/kg)	9.80	10.0	10
CLR^*_C (ml/min/kg)	20	23	59
CLD^*_C (ml/min/kg)	0.032	0.008	125
CLR/F_H (ml/min/kg)	0.25	0.25	5
VU (L/kg)	0.004	0.008	100
Ka_C (hr^{-1})	0.23	0.23	6
UF (ml/min/kg)	0.091	0.090	49

*TV for 500 kg horse

Figure Legends

Figure 1: Compartmental model describing plasma and urine concentrations of hydroxyzine and cetirizine, either from administration of each individually or cetirizine as a metabolite of hydroxyzine.

Figure 2: Pharmacokinetic profiles for 500 mg Atarax® (hydroxyzine hydrochloride) and 190 mg Allacan® (cetirizine hydrochloride) dosed orally twice daily for four and a half days (9 doses): (A) plasma cetirizine; (B) urine cetirizine; (C) plasma hydroxyzine; (D) urine hydroxyzine concentrations (red circles). Lines represent model individual fits to each horse.

Figure 3: Pharmacokinetic profiles from last administration for 500 mg Atarax® (hydroxyzine hydrochloride) and 190 mg Allacan® (cetirizine hydrochloride) dosed orally twice daily for four and a half days (9 doses): (A) plasma cetirizine; (B) urine cetirizine; (C) plasma hydroxyzine; (D) urine hydroxyzine concentrations (blue circles). The upper black dotted, solid and dashed lines represent hydroxyzine and cetirizine concentration prediction intervals for the 80^{th}, 95^{th} and 99^{th} percentiles (10,000 simulations)

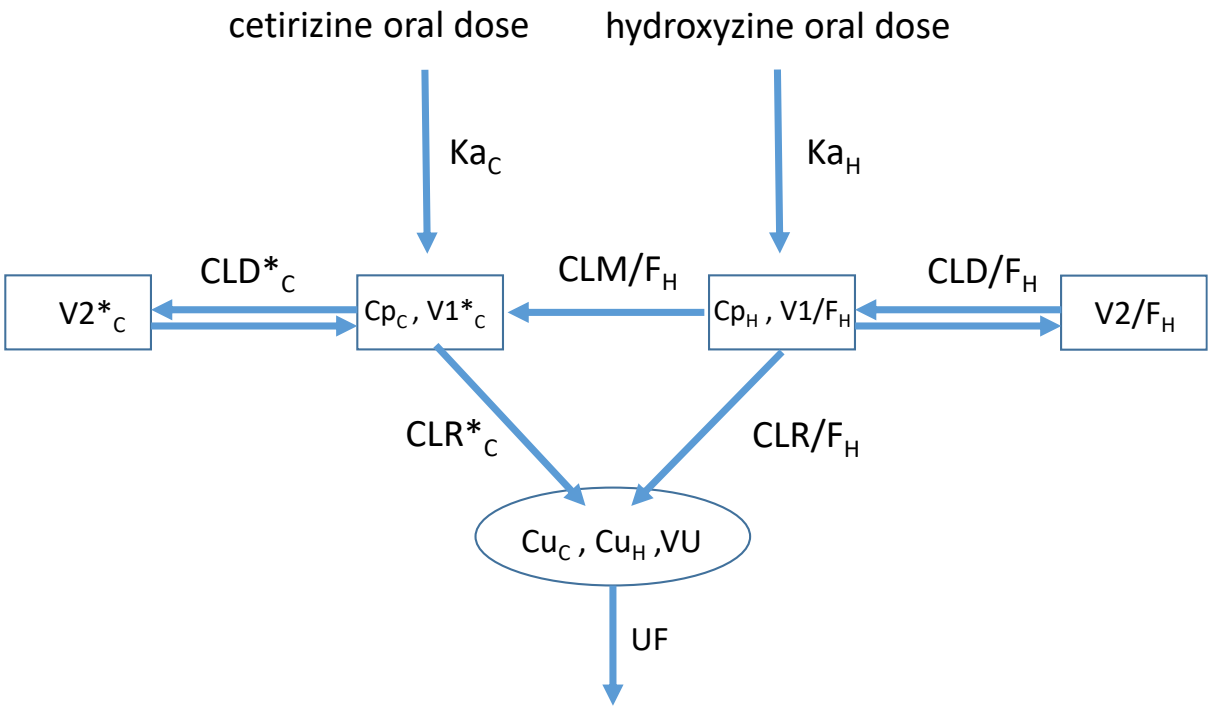
cetirizine oral dose
hydroxyzine oral dose
Ka_C
Ka_H
CLD*_C
CLM/F_H
CLD/F_H
V2*_C
Cp_C , V1*_C
Cp_H , V1/F_H
V2/F_H
CLR*_C
CLR/F_H
Cu_C , Cu_H ,VU
UF

Figure 1

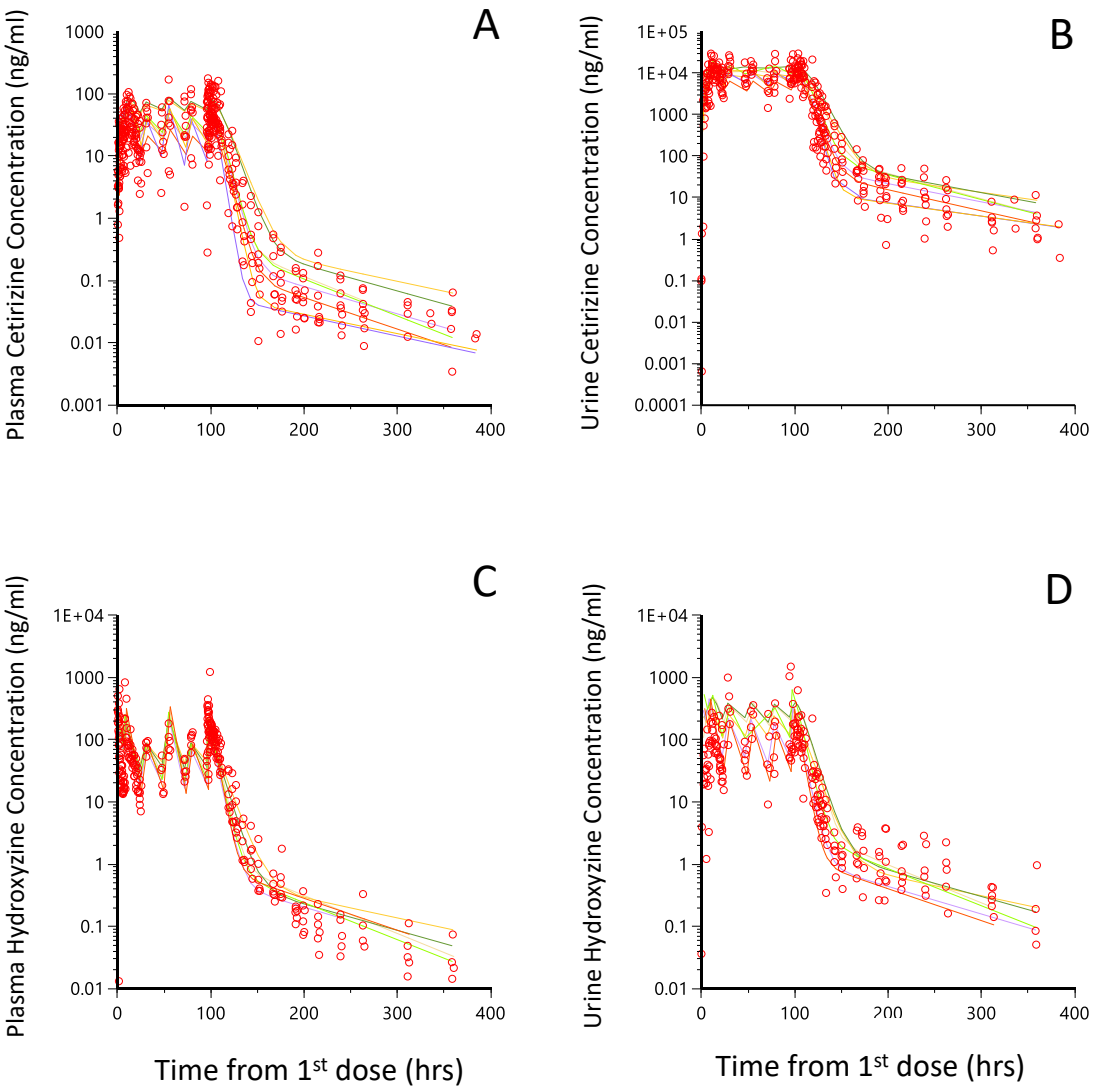
A
B
C
D
Plasma Cetirizine Concentration (ng/ml)
Urine Cetirizine Concentration (ng/ml)
Plasma Hydroxyzine Concentration (ng/ml)
Urine Hydroxyzine Concentration (ng/ml)
Time from 1st dose (hrs)
Time from 1st dose (hrs)

Figure 2

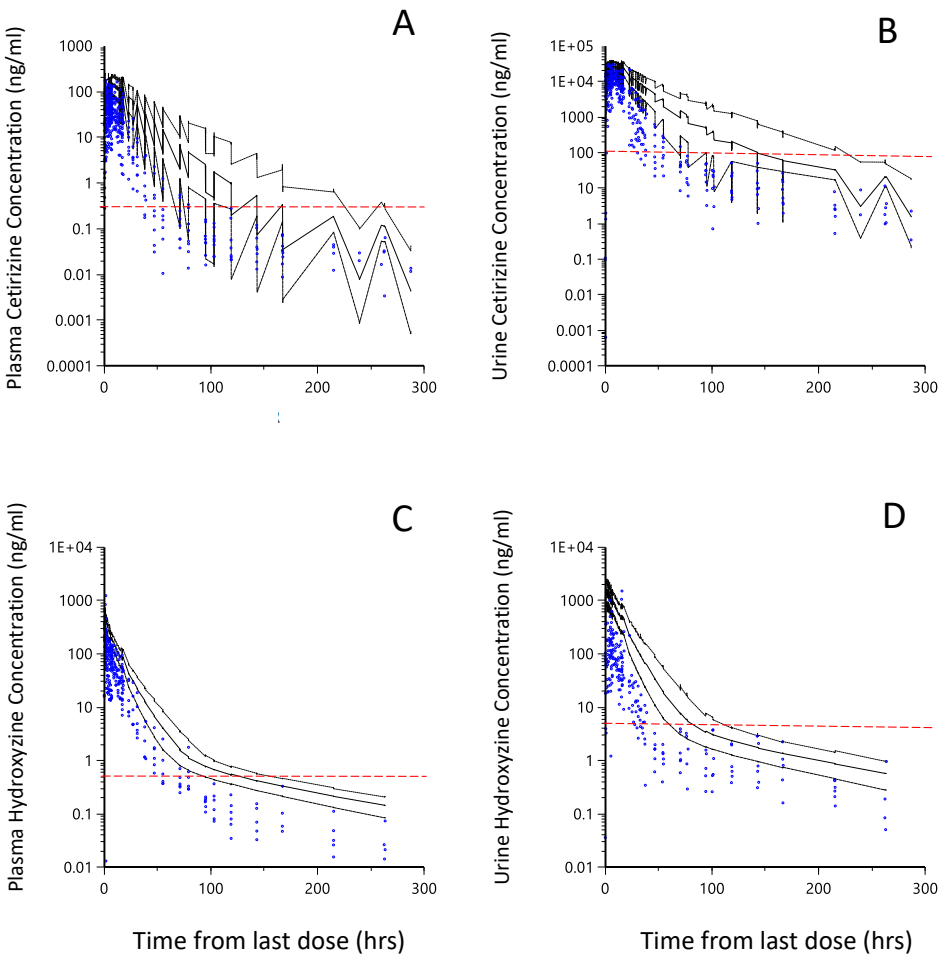
A
B
C
D
Plasma Cetirizine Concentration (ng/ml)
Urine Cetirizine Concentration (ng/ml)
Plasma Hydroxyzine Concentration (ng/ml)
Urine Hydroxyzine Concentration (ng/ml)
Time from last dose (hrs)
Time from last dose (hrs)

Figure 3

Supplementary

Table S1 Omega Correlation

Scenario	Label	nCLD*C	nCld/FH	nClR/FH	nV2*C	nClR*C	nUF	nClM/FH	nV2/FH	nV1/FH	nV1*C	nKaH	nVU	nKaC
	Omega													
	nCLD*C	20.82019												
	nCld/FH	-0.01949	0.029053											
	nClR/FH	-0.01005	-2.8E-05	4.98E-06										
	nV2*C	0.033464	-0.00031	-1.6E-05	5.65E-05									
	nClR*C	0	0	0	0	0.274786								
	nUF	0	0	0	0	0.134526	0.108014							
	nClM/FH	0	0	0	0	0	0	0.01248						
	nV2/FH	0	0	0	0	0	0	0	0.065338					
	nV1/FH	0	0	0	0	0	0	0	0	0.104121				
	nV1*C	0	0	0	0	0	0	0	0	0	0.439848			
	nKaH	0	0	0	0	0	0	0	0	0	0.191697	0.104715		
	nVU	0	0	0	0	0	0	0	0	0	0	0	1.407454	
	nKaC	0	0	0	0	0	0	0	0	0	0	0	0.077308	0.004486
	Correlation													
	nCLD*C	1												
	nCld/FH	-0.02506	1											
	nClR/FH	-0.98751	-0.07386	1										
	nV2*C	0.975526	-0.24161	-0.94273	1									
	nClR*C	0	0	0	0	1								
	nUF	0	0	0	0	0.780853	1							
	nClM/FH	0	0	0	0	0	0	1						
	nV2/FH	0	0	0	0	0	0	0	1					
	nV1/FH	0	0	0	0	0	0	0	0	1				
	nV1*C	0	0	0	0	0	0	0	0	0	1			
	nKaH	0	0	0	0	0	0	0	0	0	0.893223	1		
	nVU	0	0	0	0	0	0	0	0	0	0	0	1	
	nKaC	0	0	0	0	0	0	0	0	0	0	0	0.972865	1
	Shrinkage	0.77287	0.418881	0.779375	0.724667	0.005871	0.032061	0.315224	0.284824	0.797483	0.033736	0.055675	0.204513	0.224462