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Pharmacokinetics of oral terbinafine in horses and Greyhound dogs

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Abstract

The objective of the study was to assess the pharmacokinetics of terbinafine administered orally to horses and Greyhound dogs. A secondary objective was to assess terbinafine metabolites. Six healthy horses and six healthy Greyhound dogs were included in the pharmacokinetic data.

The targeted dose of terbinafine was 20 and 30 mg/kg for horses and dogs, respectively. Blood was obtained at predetermined intervals for the determination of terbinafine concentrations with liquid chromatography and mass spectrometry.

The half-life (geometric mean) was 8.1 and 8.6 hours for horses and Greyhounds, respectively. The mean maximum plasma concentration was 0.31 and 4.01 µg/mL for horses and Greyhounds, respectively. The area under the curve (to infinity) was 1.793 hr*µg/mL for horses and 17.253 hr*µg/mL for Greyhounds. Adverse effects observed in one study horse included pawing at the ground, curling lips, head shaking, anxiety and circling, but these resolved spontaneously within 30 minutes of onset. No adverse effects were noted in the dogs. Ions consistent with carboxyterbinafine, n-desmethylterbinafine, hydroxyterbinafine and desmethylhydroxyterbinafine were identified in horse and Greyhound plasma after terbinafine administration. Further studies are needed assessing the safety and efficacy of terbinafine in horses and dogs.

Keywords

terbinafine; antifungal; pharmacokinetics; horse; dog

Introduction

Fungal infections are problematic in many domestic animal species, including horses and dogs, as they can cause severe illness and are both difficult and expensive to treat. A variety of fungal organisms can cause systemic, localized, and cutaneous infections in dogs, including *Blastomyces* spp., *Cryptococcus* spp., *Coccidioides* spp., *Histoplasma* spp., *Aspergillus* spp., *Trichophyton* spp., *Microsporum* spp., and *Malassezia* spp. (Kerl, 2003). *Aspergillus* spp. is an important fungal organism affecting horses (Tell, 2005). Systemic *Aspergillus* spp. infections are difficult to treat in horses due to the limited therapeutic options, high cost, and poor oral bioavailability of many of the available antifungal drugs.

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Terbinafine is an allylamine antifungal drug approved in humans to treat dermatophyte infections. The minimum inhibitory concentrations of terbinafine have been reported for a wide variety of fungal organisms, including dermatophytes, filamentous and dimorphic organisms, and some yeasts (Shadomy et al., 1985; Goudard et al., 1986; Petranyi et al., 1987). However *in vivo* studies have not been conducted to confirm clinical efficacy against many of these organisms.

Terbinafine is structurally unrelated to other systemic antifungal drugs, including azoles, and is fungicidal (Ryder & Dupont, 1985). It is a selective inhibitor of fungal squalene epoxidase, thereby increasing the extracellular concentration of squalene to levels toxic to fungal cells and inhibiting cell wall function due to decreased synthesis of ergosterol.

A pharmacokinetic study performed in humans administered 250 mg terbinafine PO resulted in maximum plasma concentrations of 1.34 ± 0.45 $\mu\text{g/ml}$ at 1.5 hours following a single administration (Kovarik et al., 1998). The elimination half-life was about 12 hours. Clearance of terbinafine from the body occurs primarily through biotransformation (Kovarik et al., 1998). Although fifteen metabolites have been identified thus far, none have shown to be active. The metabolites found in humans with the highest concentrations in plasma are carboxyterbinafine > n-desmethylterbinafine > desmethylcarboxyterbinafine. First pass metabolism results in less than complete oral bioavailability of terbinafine (Humbert et al., 1995). Multiple-dose and long-term administrations of this drug have been well-tolerated by patients, although a rare incidence of hepatobiliary dysfunction has been reported. A reactive metabolite, 7,7-dimethylhept-2-ene-4-ynal (TBF-A), has been proposed to be the cause of this hepatic dysfunction (Iverson & Utrecht, 2001).

There are little data available regarding the use of terbinafine in veterinary medicine. Terbinafine was effective and was well-tolerated in cats with *Microsporum canis* ringworm infections (Kotnik, 2002). Some vomiting and occurrence of soft stools were observed, which may have been due to an unpleasant taste of the drug and possible local gastrointestinal mucosal irritation. Two studies performed in dogs suggested terbinafine was well-tolerated and effective as a potential alternative to ketoconazole for treatment of *Malassezia* dermatitis in dogs (Guillot et al., 2003; Rosales et al., 2005). Toxicology studies in dogs have administered terbinafine for 26 weeks at 20, 60, and 200 mg/kg resulting in salivation and emesis in the mid and high dose groups with no changes in hematological parameters (Lamisil, Freedom of Information Summary). The high dose group had 3/4 dogs with liver abnormalities, lamellated intracytoplasmic inclusions, with 60 mg/kg determined to be the no-toxic-effect level. Studies investigating the pharmacokinetics of orally-administered terbinafine have not been reported for dogs or horses.

The purpose of this study was to assess the pharmacokinetics of terbinafine in horses and dogs. A secondary purpose of this study was to assess metabolites present in equine and canine plasma after oral administration of terbinafine.

Materials and Methods

Animals

The study was approved by the Institutional Animal Care and Use Committee at Kansas State University. Six healthy horses were used, ranging in age from 14 to 26 years and weight from 446 kg to 625 kg. The horses included three Quarter Horses, one Paint, one Thoroughbred, and one Hanoverian. Three of the horses were mares and three were geldings. The horses were acclimated to an indoor stall for the day prior to initiation of the investigation. Horses were offered brome hay and water ad libitum throughout the study and received 3 pounds of pelleted feed twice daily. The study duration was 24 hours.

Six healthy Greyhound dogs were used, ranging in age from 2 to 3 years. Weights of the dogs ranged from 24.8 kg to 41.9 kg. Three of the dogs used were neutered males, and three were intact females. The dogs were brought to the study site the evening before to acclimate to their environment. The dogs were fed normally throughout the study. The study duration was 24 hours.

Drug Dosing Protocols

The horses received a morning meal consisting of 3 pounds of pelleted feed with 30 mL of vegetable oil. Each horse received a dose of 20 mg/kg terbinafine (Terbinafine hydrochloride, 250 mg tablets, Actavis Elizabeth, LLC, Elizabeth, NJ, USA) orally. Tablets were crushed and combined with corn syrup in a 60 cc dosing syringe to a volume of 60 mL.

The dogs received a morning meal of dry dog food (amounts varied between individuals) prior to drug dosing. Each dog received a dose of 30 mg/kg terbinafine (Terbinafine hydrochloride, 250 mg tablets, Actavis Elizabeth, LLC, Elizabeth, NJ, USA) orally (dogs were pill) to the nearest whole tablet.

Blood sampling for plasma analysis of terbinafine

Jugular catheters were aseptically placed in each horse for collection of blood samples on the first morning of the study. Blood (10 mL) was aspirated and discarded prior to sample collection to ensure the sample was not contaminated with heparin flush. Whole blood, 9 mL sample per time point was obtained, and the catheter was flushed with 10 mL of heparinized saline. Whole blood was collected from each horse and transferred into tubes containing lithium heparin at times 0 (prior to drug administration), 30 and 45 minutes, and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours after drug administration. Plasma was separated by centrifugation, 15 minutes at 3 000 x g, and frozen at -70°C for later analysis.

Each dog received an aseptically placed jugular catheter for collection of blood samples on the first morning of the study. Blood (1 mL) was aspirated and discarded prior to sample collection to ensure the sample was not contaminated with saline. After aspiration of the 9 mL sample, the catheter was flushed with 3 mL of saline. Whole blood was placed into heparinized tubes at times 0 (prior to drug administration), 15, 30, and 45 minutes, and at 1, 2, 4, 6, 8, 12, and 24 hours after drug administration. Plasma was separated by centrifugation, 15 minutes at 3 000 x g, and frozen at -70°C for later analysis.

Terbinafine analysis

LC/MS analysis—Determination of terbinafine in plasma was performed by liquid chromatography (Shimadzu Prominence, Shimadzu Scientific Instruments, Columbia, MD, USA) with mass spectrometry (API 2000, Applied Biosystems, Foster City, CA, USA) (LC/MS). Terbinafine (m/z 292.19→141) concentrations were determined with tolinaftate (m/z 308.08→148.1) as the internal standard after protein precipitation. The metabolites carboxyterbinafine (m/z 322→141), desmethylhydroxyterbinafine (m/z 294→141), hydroxyterbinafine (m/z 308→141), and n-desmethylterbinafine (m/z 278→141), were assessed qualitatively as reference standards were not available. Standard curves for terbinafine were constructed by adding terbinafine (Sigma-Aldrich, St Louis, MO, USA) dissolved in 50% methanol to blank equine and canine plasma respectively at concentrations of 0, and 0.005, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5, 1, 2.5, and 5 µg/mL. Standard curves were accepted if the measured concentrations were within 15% of the actual concentrations and the standard curve was linear with a correlation coefficient of at least 0.99. Concentrations above the highest concentration were diluted 1:4 and re-analyzed. The lower and upper limits of quantification were 0.005 and 5 µg/mL, respectively and defined as the lowest and highest concentrations on the linear standard curve with a measured concentration within

15% of the actual concentration. The signal to noise ratio at the lower limit of quantification (0.005 µg/mL) was greater than 13 for both canine and equine plasma. The accuracy of the analytical assay in canine plasma was $101 \pm 11.2\%$ and $101 \pm 8\%$ in equine plasma. The coefficient of variation was 9% in canine plasma and 3% in equine plasma.

Plasma samples and standards were prepared by adding 0.1 mL plasma to 0.4 mL tolinaftate (Sigma-Aldrich, St Louis, MO, USA), 500 ng/mL dissolved in acetonitrile, in a microcentrifuge tube. The samples were vortexed and centrifuged at $16,000 \times g$ for 10 minutes. The supernatant was transferred to an injection vial and 10 µL was injected. The mobile phase consisted of acetonitrile (A) and 0.1% formic acid (B) with a flow rate of 0.4 mL/minute using a linear gradient starting at 95% B from 0 to 0.1 minutes, to 0% B at 2 minutes and then back to 95% B at 4 minutes with a 5 minute total run time. Separation was achieved with a C18 column (Zorbax-C18 XDB, 50mm $\times$ 2.1 mm, 5 µm, Agilent Technologies, Wilmington, DE, USA).

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was performed using computer software (WinNonlin 5.2, Pharsight Corporation, Mountain View, CA, USA). The noncompartmental pharmacokinetic variables determined were the area under the curve from time 0 to infinity (AUC) using the linear trapezoidal rule, area under the first moment curve from time 0 to infinity (AUMC), plasma clearance per fraction of the absorbed dose (Cl/F), apparent volume of distribution (area method) per fraction of the dose absorbed (Vd/F), first-order terminal rate constant (λ_z), terminal half-life ($T_{1/2} \lambda_z$), maximum plasma concentration (C_{MAX}), time to maximum plasma concentration (T_{MAX}), and mean residence time (MRT). The relative bioavailability of terbinafine in horses compared to dogs was determined with the following equation:

$$\frac{AUC_{horse} \bullet Dose_{dog}}{AUC_{dog} \bullet Dose_{horse}}$$

using the mean values for each species.

Results

Adverse effects were observed in one of the horses. The adverse effects included opening and closing of its mouth several times with some head shaking, curling of its lips, and pawing at the ground. The adverse effects resolved spontaneously. No observable lesions were present in the mouth. Terbinafine was well-tolerated following oral administration in dogs with no adverse effects noted.

The plasma concentrations of terbinafine are presented in Table 1 and the calculated pharmacokinetic parameters are presented in Table 2. The $T_{1/2} \lambda_z$ (geometric mean) following oral administration was similar in horses and Greyhounds, 8.10 and 8.63 hours, respectively. The T_{MAX} (geometric mean) was comparable between horses and Greyhounds, 1.73 hours and 2.00 hours, respectively (Figure 1). The C_{MAX} (geometric mean) was substantially lower in the horses compared to the Greyhounds, 0.31 µg/mL and 4.01 µg/mL, respectively (Table 2). Large differences were noted in the AUC for horses, 1.793 hr·µg/mL, and Greyhounds, 17.253 hr·µg/mL. The mean dose administered to horses, 20.1 mg/kg was lower than administered to the Greyhounds, 30.6 mg/kg, but the relative bioavailability of terbinafine in horses was only 16% compared to Greyhounds.

Ions consistent with the metabolites carboxyterbinafine (m/z 322→141), desmethylhydroxyterbinafine (m/z 294→141), hydroxyterbinafine (m/z 308→141), and n-desmethylterbinafine (m/z 278→141), were detected in both horses and Greyhounds after oral terbinafine administration, but not prior to terbinafine administration. Authentic reference standards were not assessed therefore definitive metabolite identification was not possible and interpretation has to be cautious. The magnitude of the detector response was the greatest for carboxyterbinafine, followed by n-desmethylterbinafine, and hydroxyterbinafine and desmethylhydroxyterbinafine with the latter 2 metabolites being of similar magnitude in horses. In Greyhounds, the magnitude of the detector response was the greatest for carboxyterbinafine, followed by n-desmethylterbinafine, and hydroxyterbinafine with a much lower response from desmethylhydroxyterbinafine suggesting different metabolite profiles.

Discussion

To the authors' knowledge, this is the first report of terbinafine pharmacokinetics in either dogs or horses. The pharmacokinetics of other antifungal drugs including ketoconazole (Prades et al., 1989; KuKanich & Hubin, 2010), itraconazole (Yoo et al., 2002, Davis et al., 2005), fluconazole (Humphrey et al., 1985; Latimer et al., 2001), and voriconazole (Roffey et al., 2003; Davis et al., 2006) have been described in dogs and horses.

Terbinafine was well tolerated in 5/6 horses following oral administration. However, similar adverse effects were also seen in 1 of 2 horses used in a pilot study (data not presented). This may indicate that the drug may have an unpleasant taste, may cause irritation to the oral cavity of some horses, or may simply be due to an aversion of some horses to oral administration of drugs. It is also possible the adverse effects were due to colic, but the rapid onset and recovery from clinical signs suggest a transient response. Potential oral irritation or palatability issues should be a consideration with oral dosing of terbinafine in horses as well as the potential for colic in some horses, especially with multiple doses. The drug was otherwise well-tolerated with no further adverse effects noted and no treatment for the adverse effects was administered. However, the safety of long-term or multiple dose administration was not evaluated in horses.

Terbinafine was well tolerated in Greyhounds following oral administration. Adverse effects were not observed in any of the dogs. The lack of an adverse response in Greyhounds compared to the horse may be due to the dogs being administered whole tablets rather than receiving crushed tablets, providing less opportunity for them to notice a bitter taste or irritating reaction to the tablets. Additionally, no signs of abdominal discomfort were noted, and the Greyhounds appeared to behave normally throughout the entire 24 hours of the study. However, the safety of long-term or multiple dose administration of terbinafine to Greyhounds was not evaluated in this study.

Multiple potential metabolites were detected with the mass spectrometer for both the equine and canine samples, suggesting terbinafine is extensively metabolized in both species. Although similar metabolites were detected between these two species in this study, the magnitude of the detector response suggested different abundance of the metabolites between species. The detected metabolites, hydroxyterbinafine, n-desmethylterbinafine, desmethylhydroxyterbinafine, and carboxyterbinafine, are similar to those detected in previously conducted human studies. However, all possible metabolites were not assessed, just those most commonly reported in humans. Additionally, the metabolites were detected as quickly as the terbinafine itself (15 minute sample in dogs and 30 minute sample in horses), which is suggestive first pass metabolism of this drug occurs as has been described in humans (Humbert et al., 1995).

A large variability of pharmacokinetic parameters within horses was observed, indicating variable effects may be seen if the antifungal effects are related to the AUC or CMAX. The mean AUC was 1.793 hr·µg/mL, but the range was 1.179 – 2.515 hr·µg/mL, a 2.1 fold difference in these 6 healthy horses. Similarly the range in the CMAX was large, 0.21 – 0.61 µg/mL a 2.9 fold difference. The large variability in the healthy horses included in this study is expected to reflect an even larger variability in a larger population of horses, including those with clinical disease. Since this was only a single dose, it is unclear if the variability is between animal variability, or if a similar variability would be observed within the same animal administered multiple doses. Further studies assessing multiple doses in horses are indicated to evaluate the variability with a multi dose regimen.

In humans, the mean CMAX after a single approved dose (250 mg) was 1.3 µg/mL (Kovarik et al., 1998). Multiple doses in humans resulted in minimal drug accumulation (27% increase in CMAX) when administered for 30 days. The half-life in horses (8.1 hours) and Greyhounds (8.6 hours) were similar to that in people, 12.6 ± 4.7 hours. It is also anticipated that minimal drug accumulation will occur in dogs and horses administered terbinafine once daily due to the relatively short half-lives in horses and dogs. The predicted drug accumulation in horses and dogs is 15 and 17%, respectively based on the equation:

$$\text{accumulation} = \frac{1}{1 - e^{\left(\frac{-0.693 \times t}{t_{1/2}}\right)}}$$

The relative oral bioavailability was only a 16% in horses compared to Greyhounds. The reason for the lower bioavailability in horses was not determined. Terbinafine metabolites were detected at the first time point after drug administration suggesting first pass metabolism may be occurring. Further studies assessing routes of administration which avoid first pass metabolism, such as intramuscular or intravenous administration, may produce higher plasma drug concentrations in horses. Additionally, studies investigating higher doses and multiple doses per day of terbinafine are indicated to obtain a more extensive understanding of the potential use of orally dosed terbinafine as a clinical treatment for fungal diseases in horses

Studies in dogs administering terbinafine, 30 mg/kg PO q 24h, to dogs for 3 weeks reported no adverse effects (Guillot et al., 2003, Rosales et al., 2005), which were consistent with toxicology studies. Both clinical studies were evaluating terbinafine as a treatment for *Malassezia* dermatitis in otherwise healthy dogs. Clinical improvement was noted in each study. The high plasma concentrations achieved in this study after oral administration warrant further investigation of terbinafine for the treatment of other fungal organisms in dogs such as *Blastomyces* spp., *Cryptococcus* spp., *Coccidioides* spp., *Histoplasma* spp., *Aspergillus* spp., *Trichophyton* spp., and *Microsporum* spp., in addition to *Malassezia* spp. However it is important to note plasma concentrations are not in themselves indicative that terbinafine will be effective as the drug must reach the site of infection and remain active in order to achieve a clinical cure, which has not been demonstrated for most fungal organisms in dogs.

Greyhound dogs were used in the study. Previous studies have indicated that some drugs may be metabolized differently in Greyhounds compared to Beagles. However it is unclear if Greyhounds metabolize drugs differently than other dog breeds or mongrels. *In vitro* studies assessing propofol indicated Greyhound purified hepatic microsomes metabolized propofol slower than Beagle microsomes (Court, et al, 1999; Hay Krause, et al, 2000). In comparison to mixed-breed microsomes, Greyhounds were not different, which may suggest

Greyhounds are not slow metabolizers of propofol, but Beagles are ultra-metabolizers of propofol.

Antipyrine is a probe substrate for cytochrome P450 (CYP) mediated metabolism and a marker for drug distribution to total body water. A direct comparison of the pharmacokinetics of antipyrine in Greyhounds (GH) and Beagles (B) (KuKanich, et al, 2007) resulted in significant differences in the clearance (GH = 8.33 mL/min/kg, B = 13.42 mL/min/kg), volume of distribution (GH = 760 mL/kg, B = 613 mL/kg), and elimination half-life (GH = 1.09 hr, B = 0.55 hr). Unrelated studies examined the pharmacokinetics of antipyrine in mongrel dogs with the clearance (9.1 mL/min/kg), volume of distribution (640 mL/kg), and elimination half-life (1.13 hr) similar to the clearance and terminal half-life in Greyhounds (Gugler, et al, 1975). Similarly, a study examining the pharmacokinetics of antipyrine in Coonhounds resulted in a clearance (6.2 mL/min/kg), volume of distribution (668 mL/kg), and elimination half-life (1.24 hr) similar to the clearance and terminal half-life in Greyhounds (Gurley, et al, 1997). Therefore, a reasonable conclusion is that for most drugs metabolized by CYP, Greyhounds are more similar to other dog breeds, whereas Beagles may be ultra-metabolizers.

The pharmacokinetics of intravenous propofol boluses in mixed-breed dogs and Greyhounds were examined (Zoran, et al, 1993). The terminal half-lives were not significantly different, similar to the *in vitro* metabolism studies. However the volume of distribution was significantly smaller and clearance proportionally less in Greyhounds relative to mixed-breed dogs suggesting metabolism is not a differing parameter, but a smaller distribution within the body. In contrast, the volume of distribution of antipyrine, a marker of total body water, in Greyhounds was larger compared to Coonhounds, Beagles, and mixed-breed dogs (Gugler, et al, 1975; Gurley, et al, 1997; KuKanich, et al, 2007). The volume of distribution of morphine in Greyhounds has been reported as 3.1 L/kg (KuKanich & Borum, 2008), similar to the volume of distribution in Beagles, 3.6 L/kg (KuKanich, et al, 2005). Therefore extrapolations of the relative difference in the volume of distribution to other drugs may not be accurate as the calculated volume of distribution of specific drugs has varied from less, to similar, to greater than other dog breeds or mixed-breed dogs.

The differences in the calculated volumes of distribution in Greyhounds may be due the body composition in Greyhounds compared to other dogs. Greyhounds have significant differences in body composition as compared to non-Greyhound dogs. Greyhounds have a significantly larger percent body weight of muscle mass (57.1 ± 1.9 vs. $43.5 \pm 6\%$) a smaller percent body fat (0.28 ± 0.35 vs. $0.94 \pm 0.50\%$) and similar bone composition (12.2 ± 1.3 vs. $12.2 \pm 2.4\%$) (Gunn, 1978).

In conclusion, orally dosed terbinafine did not produce severe adverse effects when a single dose was administered to both horses and Greyhounds. Potential oral irritation, palatability or colic should be considered in horses. More studies are indicated examining the pharmacokinetics of multiple doses of terbinafine administered orally to horses and dogs. Further studies are also indicated to assess the efficacy of terbinafine for the treatment of fungal diseases in horses and dogs.

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Figure 1.
Mean and standard error plasma concentrations of terbinafine following oral administration at targeted doses of 20 mg/kg in horses and 30 mg/kg in dogs.

Table 1

Mean and standard error plasma concentrations of terbinafine in horses administered 20.0 mg/kg PO and dogs administered 30.6 mg/kg PO

Horses			Dogs		
Time (hours)	Mean Concentration (µg/mL)	Standard error	Time (hours)	Mean Concentration (µg/mL)	Standard error
0.50	0.077	0.024	0.25	0.057	0.021
0.75	0.125	0.038	0.50	0.597	0.160
1.00	0.121	0.019	0.75	2.097	1.025
1.50	0.235	0.051	1.00	3.240	1.578
2.00	0.274	0.068	2.00	4.132	0.885
4.00	0.169	0.023	4.00	1.642	0.127
6.00	0.134	0.033	6.00	0.715	0.114
8.00	0.075	0.015	8.00	0.392	0.091
12.00	0.031	0.005	12.00	0.230	0.030
24.00	0.011	0.001	24.00	0.092	0.012

Noncompartmental pharmacokinetic parameters of terbinafine administered orally to horses and dogs

Table 2

Parameter	Units	Horses				Dogs			
		Geometric Mean	Min	Median	Max	Geometric Mean	Min	Median	Max
Dose	mg/kg	20.1	20.0	20.1	20.3	30.6	28.5	30.3	32.7
AUC _{extrap}	%	6.9	1.8	8.8	12.6	6.4	3.6	6.8	9.9
AUC	hr·µg/mL	1.793	1.179	1.803	2.515	17.253	9.579	17.237	30.385
AUMC	hr·hr·µg/mL	15.2	11.5	16.2	19.5	122.2	75.0	118.9	188.5
Cl/F	mL/min/kg	187.1	132.5	186.5	282.7	29.6	17.8	29.7	56.9
C _{MAX}	µg/mL	0.31	0.21	0.28	0.61	4.01	1.78	4.72	10.68
T _{MAX}	hr	1.7	0.8	1.8	4.0	2.0	1.0	2.0	4.0
λ _z	/hr	0.086	0.060	0.072	0.179	0.080	0.063	0.071	0.148
t _{1/2} λ _z	hr	8.1	3.9	9.7	11.6	8.6	4.7	9.9	11.1
MRT	hr	8.5	7.1	8.5	10.3	7.1	6.1	7.0	8.6
V _z /F	L/kg	131.2	50.1	138.7	266.7	22.1	14.0	20.6	45.6

AUC: area under the curve from time 0 to infinity, AUMC: area under the first moment curve from time 0 to infinity, Cl/F: plasma clearance per fraction of the absorbed dose, V_z/F: apparent volume of distribution, area method per fraction of the absorbed dose, λ_z: first-order terminal rate constant, t_{1/2} λ_z: terminal half-life, C_{MAX}: maximum plasma concentration, T_{MAX}: time to maximum plasma concentration, MRT: mean residence time.