Received: 24 February 2020 | Revised: 13 May 2020 | Accepted: 13 May 2020

DOI: 10.1111/jvp.12882

PHARMACOKINETIC REPORT

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

Pharmacokinetics and bioavailability of tildipirosin in rabbits following single-dose intravenous and intramuscular administration

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Funding information
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Abstract

The objective of this study was to determine the pharmacokinetics of tildipirosin in rabbits after a single intravenous (i.v.) and intramuscular (i.m.) injection at a dose of 4 mg/kg. Twelve white New Zealand rabbits were assigned to a randomized, parallel trial design. Blood samples were collected prior to administration and up to 14 days postadministration. Plasma concentrations of tildipirosin were quantified using a validated ultra-high-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method. The pharmacokinetic parameters were calculated using a noncompartmental model in WinNonlin 5.2 software. Following i.v. and i.m. administration, the elimination half-life ($T_{1/2\lambda}$) was 81.17 ± 9.28 and 96.68 ± 15.37 hr, respectively, and the mean residence time (MRT_{last}) was 65.44 ± 10.89 and 67.06 ± 10.49 hr, respectively. After i.v. injection, the plasma clearance rate (Cl) and volume of distribution at steady state (V_{dss}) were 0.28 ± 0.10 L kg^{-1} h^{-1} and 17.78 ± 5.15 L/kg, respectively. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}) after i.m. administration were 836.2 ± 117.9 ng/ml and 0.33 ± 0.17 hr, respectively. The absolute bioavailability of i.m. administration was 105.4%. Tildipirosin shows favorable pharmacokinetic characteristics in rabbits, with fast absorption, extensive distribution, and high bioavailability. These findings suggest that tildipirosin might be a potential drug for the prevention and treatment of respiratory diseases in rabbits.

KEYWORDS

bioavailability, pharmacokinetics, rabbit, respiratory infection, tildipirosin

1 | INTRODUCTION

Macrolides are useful antibacterial drugs that are mainly used in veterinary medicine to treat bacterial infections. Tildipirosin (TD) is a novel semisynthetic macrolide antibiotic derivative from the chemical modification of tylosin, which is exclusively used in veterinary practice for the treatment of respiratory infections. In Europe, TD is currently approved to prevent and treat bacterial respiratory diseases in pigs and cattle caused by bacteria such as *Actinobacillus pleuropneumoniae*, *Haemophilus parasuis*, and *Pasteurella* (*P.*) *multocida* (EMA, 2010).

Due to the extensive use of TD, the pharmacokinetic behavior of TD has been investigated in several animal species including pigs (Rose et al., 2013), cattle (Menge et al., 2012), goats (Elazab & Badawy, 2020), and dogs (Wang et al., 2018). The pharmacokinetic profile of TD is characterized by rapid absorption, long elimination half-life, and extensive distribution into tissues, in which the concentrations are multifold higher than those observed in

corresponding plasma samples (Menge al., 2012; Rose et al., 2013). Experimental data from radioactive labeling studies in pigs and cattle show that TD is mainly excreted through feces and urine (EMA, 2012). However, there are currently no data on the pharmacokinetics of TD in rabbits.

Respiratory diseases are responsible for severe economic losses in the rabbit industry, especially rhinitis caused by *P. multocida* (Langan, Lohmiller, Swing, & Wardrip, 2000). The main clinical symptoms include snuffle, nasal discharge, sneezing, fever, and conjunctivitis (Deeb & DiGiacomo, 2000). Unfortunately, the choice of antibiotics in rabbits is limited, as many oral antibiotics disrupt the intestinal flora and cause clostridial enterotoxemia (Borriello & Carman, 1983). Therefore, parenteral administration of antibiotics appears to be an ideal alternative strategy for controlling respiratory infections in rabbits. The advantages of TD injection include a rapid onset and long duration of action, and the single-dose injection regimen can decrease stress from excessive handing and improve compliance with treatment interventions. Clinical field trials have demonstrated that a single injection at a recommended dose of 4 mg/kg body weight is effective for both the prevention and treatment of respiratory diseases in pigs and cattle (EMA, 2012).

Considering the pharmacokinetic and pharmacodynamic features of TD, understanding the pharmacokinetics of TD in rabbits will be beneficial for designing future studies to explore the potential use of TD in the treatment of respiratory infections. The objective of this study was to evaluate the pharmacokinetic profiles of TD in rabbits following single-dose intravenous (i.v.) and intramuscular (i.m.) administration.

2 | MATERIALS AND METHODS

2.1 | Animals

All animal experiments in this study were approved by the Laboratory of Animal Use and Care Committee of the China Agricultural University (Beijing, China). Twelve 10- to 12-week-old white New Zealand rabbits, six males and six females (mean weight 3.0 ± 0.2 kg), were used in this study. Prior to the study, all rabbits were allowed to acclimate for 1 week. Animals were fed antibiotic-free food and had free access to water. The animal house temperature and relative humidity were kept at 25 ± 2°C and 45%–65%, respectively.

2.2 | Experimental design and sample collection

Tildipirosin injection (Zuprevo® 40 mg/ml, MSD Animal Health) was used in this study. Rabbits were randomly divided into two groups of six animals each. In a parallel design, rabbits in the i.v. group were administered a single dose of 4 mg/kg into the marginal vein of the left ear. Rabbits in the i.m. group were injected into the left thigh at same dose. Blood samples (1 ml) were collected from the ear contralateral vein of each rabbit into heparinized tubes before and 5, 15, and 30 min; 1, 2, 4, 8 and 12 hr; and 1, 2, 3, 4, 6, 8, 10, 12, and 14 days after administration. Blood samples were separated by centrifugation at 3,000 *g* for 10 min and stored at −20°C for further investigation.

2.3 | Analysis of tildipirosin concentrations

Plasma concentrations of TD were determined using a previously reported ultra-high-pressure liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method with slight modification (Wang et al., 2018). TD plasma samples were taken from to −20°C and melted in room temperature, the plasma sample (200 μl) was added with 800 μl acetonitrile for protein precipitation, and then were adequately shaken for 3 min. The mixture was centrifuged at 10,000 *g* for 10 min at 4°C. The supernatant was transferred into a new tube and evaporated at 50°C under nitrogen stream. After that, the residue was resuspended with 0.4 ml of acetonitrile/0.1% formic acid–water (v/v 1:9). Subsequently, the samples were vortexed for 3 min and centrifuged at 10,000 g for 10 min at 4°C. Ultimately, the supernatants were filtered with 0.22 μm organic membranes and 10 μl of final samples was injected into the UPLC-MS/MS system to analyze.

The standard and plasma samples were quantified by using an Acquity UPLC-MS/MS system. A BEH C18 column (2.1 × 100 mm, 1.7 μm) was used for chromatographic separation, and the column temperature was kept at 30°C. The mobile phase consisted of 0.1% formic acid–water (mobile phase A) and acetonitrile (mobile phase B) with gradient elution at a flow rate of 0.3 ml/min. The gradient elution conditions were reported as follows: 0–0.5 min 95% solvent A; 0.5–2.5 min 20% solvent A; 2.5–3 min, 20% solvent A; and 3–3.5 min, 95% solvent A, and 3.5–5 min, 95% solvent A. The analysis was performed by electrospray ionization in positive ion detection mode, and the data were collected through multiple reaction monitoring (MRM) mode. Other typical conditions were reported as follows: capillary voltage 3 kV, source temperature 120°C, and desolvation temperature, 350°C. The parent ion m/z was 735.36, and the qualified and quantified ions were m/z 174.48 and m/z 98.23. The cone voltage and collision energy were 65 V, 35 eV, respectively.

2.4 | Method validation

The analytical method was successfully established and validated, with a low limit of detection at 0.5 ng/ml and a quantification limit of 2 ng/ml. The calibration curve of TD in plasma samples ranged from 2 to 1,000 ng/ml, with a high correlation coefficient of 0.9991. The mean recovery of TD ranged from 90.86 ± 4.33% to 100.56 ± 2.60%, while intra- and interday coefficients of variation at three different concentrations (5, 50, and 500 ng/ml) were all under 5.22%. The method reported herein satisfied the criteria for bioanalytical method validation guidance for industry (FDA, 2013).

2.5 | Pharmacokinetic analysis

All of the pharmacokinetic parameters were analyzed using the noncompartmental model 200 (intravenous or extravascular dosing, linear/log trapezoidal method, 1/y weighting) in WinNonlin Professional software (version 5.2.1; Pharsight). After i.v. administration, the following parameters were calculated: $T_{1/2\lambda z}$ was calculated as 0.693/λz; λz, the first-order rate constant, was measured from the terminal slope of the plasma concentration time curve; and the area under the plasma concentration–time curve (AUC) and area under the first moment curve (AUMC) were calculated using the trapezoid method. The plasma clearance rate (Cl) was calculated by the equation Cl = dose/AUC. The mean residence time (MRT) was calculated by the equation MRT = AUMC/AUC. The volume of distribution at steady state (V_{dss}) was calculated by the equation V_{dss} = Cl × MRT. Following both i.m. and i.v. administration, the λz, $T_{1/2\lambda z}$, AUC, AUMC, and MRT were calculated. The maximum plasma concentration (C_{max}) and time to reach maximum concentration (T_{max}) were calculated for each animal. The mean absorption time (MAT) was calculated by the equation $MAT = MRT_{i.m.} - MRT_{i.v.}$; the apparent volume of distribution (Vz/F) was calculated as Vz/*F* = Cl/F/λz; and the plasma clearance rate (Cl/F) was calculated as Cl/*F* = dose/AUC/F. The absolute bioavailability (*F*%) of TD after i.m. administration was calculated using the mean values for the corresponding $AUC_{0\text{-}t}$:

$$F(\%) = \left(AUC_{0-t}\text{i.m.}/AUC_{0-t}\text{i.v.}\right) \times 100.$$

2.6 | Statistical analysis

All pharmacokinetic parameters were calculated for each rabbit, and data were expressed as the mean ± standard deviation (mean ± *SD*). A Kolmogorov–Smirnov test was used to determine for normal distribution of PK parameters. Student's *t* test was used to analyze significant differences in pharmacokinetic parameters associated with the two routes of administration. *p*-values of $p < .05$ and $p < .01$ were considered to be significant and highly significant, respectively. Differences in TD plasma concentrations following both routes of administration were analyzed by repeated-measures analysis of variance (ANOVA). The concentration–time profile of TD was generated using Prism 5.0 software (GraphPad Software). All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc.).

3 | RESULTS

After i.v. and i.m. administration of TD at a dose of 4 mg/kg, all rabbits were clinically healthy, and no adverse reactions were observed during the experimental period. The mean plasma concentration profiles of TD in rabbits after i.v. and i.m. administration are presented on a semilogarithmic graph in Figure 1. The pharmacokinetic parameters and absolute bioavailability are shown in Table 1. After i.v. and i.m. administration, plasma concentrations of TD could be quantified until 12 and 14 days postadministration, respectively, based on the limit of quantification (2 ng/ml). The C_{max} of TD was 836.2 ± 117.9 ng/ml at 0.33 ± 0.17 hr after i.m. administration. After i.v. injection, the V_{dss} and Cl were 17.78 ± 5.15 L/kg and 0.28 ± 0.10 L kg^{-1} hr^{-1}, respectively. The $AUC_{0\text{-}t}$ was 4.46 ± 1.10 and 4.54 ± 0.57 μg·hr/ml after i.v. and i.m. administration, respectively. The absolute bioavailability of i.m. administration was 105.4%. Regarding TD elimination, the $T_{1/2\lambda z}$ was 81.17 ± 9.28 and 96.68 ± 15.37 hr following i.m. and i.v. administration, respectively, which was equivalent to 3.38 and 4.03 days. No statistically significant differences in pharmacokinetic parameters were observed between the two routes of administration.

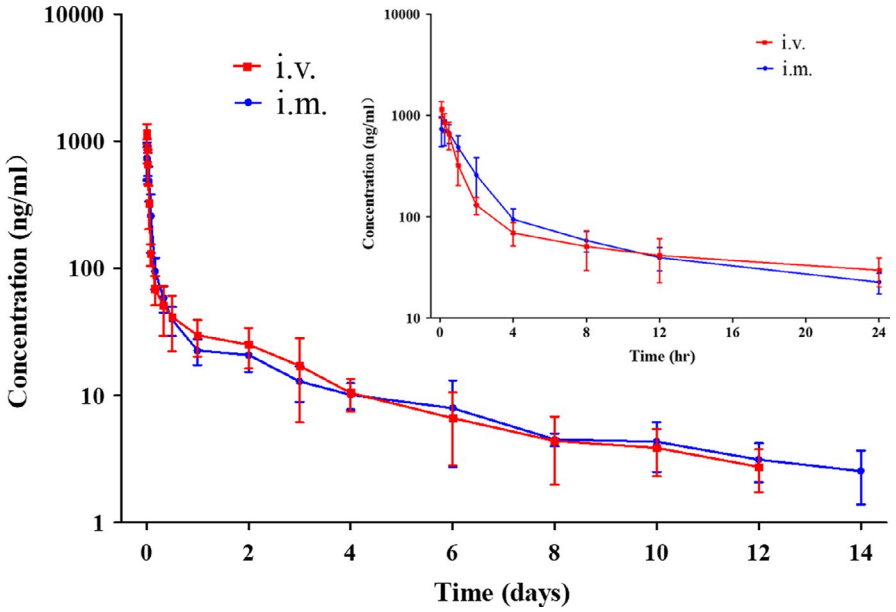

FIGURE 1 The semilogarithmic plot of plasma concentration–time curves of tildipirosin in New Zealand white rabbits following i.v. and i.m. administration at a single dose of 4 mg/kg body weight (mean ± *SD*, *n* = 6)

TABLE 1 Pharmacokinetic parameters of tildipirosin after i.v. and i.m. administration in rabbits at a dose of 4 mg/kg. Data are presented as mean ± *SD* (*n* = 6)

Pharmacokinetic parameters	i.v. 4 mg/kg	i.m. 4 mg/kg
λz (1/hr)	0.008 ± 0.001	0.007 ± 0.001
$T_{1/2\lambda z}$ (hr)	81.17 ± 9.28	96.68 ± 15.37
T_{max} (hr)	NA	0.33 ± 0.17
C_{max} (ng/ml)	NA	836.2 ± 117.9
AUC_{0-24} (μg·hr/ml)	1.98 ± 0.38	2.20 ± 0.35
AUC_{0-t} (μg·hr/ml)	4.46 ± 1.10	4.54 ± 0.57
$AUC_{0-\infty}$ (μg·hr/ml)	4.64 ± 1.12	4.91 ± 0.74
$AUMC_{0-t}$ (μg·hr^2/ml)	295.9 ± 99.2	308.1 ± 74.66
$AUMC_{0-\infty}$ (μg·hr^2/ml)	377 ± 123.8	486 ± 166.2
MRT_{last} (hr)	65.44 ± 10.89	67.06 ± 10.49
MAT (hr)	NA	1.61 ± 0.58
V_{dss} (L/kg)	17.78 ± 5.15	NA
Vz/*F* (L/kg)	NA	31.42 ± 5.76
Cl (L/kg/hr)	0.28 ± 0.10	NA
Cl/*F* (L/kg/hr)	NA	0.23 ± 0.06
F (%)	NA	105.4

Abbreviations:: AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 hr; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; AUC_{0-t}, area under the plasma concentration–time curve from 0 to last point; $AUMC_{0-\infty}$, area under the first moment curve from 0 to infinity; $AUMC_{0-t}$, area under the first moment curve from 0 to last point; Cl, plasma clearance rate; C_{max}, maximum plasma concentration; F, the absolute bioavailability; MAT, mean absorption time; MRT_{last}, mean residence time from 0 to last point; NA, not available; $T_{1/2\lambda z}$, half-life of the elimination phase; T_{max}, time to reach maximum concentration; V_{dss}, volume of distribution at steady state; Vz/F, apparent volume of distribution of after extravascular route; λz, elimination rate constant.

4 | DISCUSSION AND CONCLUSION

To our knowledge, this is the first study to report the pharmacokinetics of TD in rabbits after i.v. and i.m. administration. In the current study, the pharmacokinetic profile of TD in rabbits was evaluated via both routes of parenteral administration at a single dose of 4 mg/kg. The values of $T_{1/2\lambda z}$ and MRT_{last} were 96.68, 67.06, 81.17, and 65.44 hr after i.m. and i.v. administration, respectively, which are similar to those reported in pigs (Rose et al., 2013), dogs (Wang et al., 2018), and goats (Elazab & Badawy, 2020), but significantly lower than in cattle (Menge et al., 2012). The time to reach C_{max} after i.m. administration was 0.33 hr, similar to pigs (0.38 hr; Rose et al., 2013) and goats (0.5 hr; Elazab & Badawy, 2020), shorter than that in cattle (0.69 hr; Menge et al., 2012), but significantly longer than in dogs (0.0833 hr; Wang et al., 2018) administered the same dose, which could be due to a difference in muscle vascularization between the species. The MAT of TD after i.m. injection was 1.61 hr, indicating that the absorption was quite fast. These rate parameters show that TD is rapidly absorbed in rabbits, is slowly eliminated from the body, and has a long drug persistence.

The pharmacokinetic parameters of AUC_{0-t} and $AUC_{0-\infty}$ were 4.54 ± 0.57 and 4.91 ± 0.74 μg·hr/ml after i.m. administration and 4.46 ± 1.10, and 4.64 ± 1.12 μg·hr/ml after i.v. administration, respectively. These values are lower than those reported in pigs (Rose et al., 2013), goats (Elazab & Badawy, 2020), and cattle (Menge et al., 2012), but similar to a previous report in dogs (Wang et al., 2018). According to the AUC_{0-t} values, the absolute bioavailability of i.m. administration was 105.4%. This high bioavailability indicates favorable absorption of TD in rabbits. The bioavailability reported in this work is similar to that previously reported in dogs (112%; Wang et al., 2018) and goats (96.64%; Elazab & Badawy, 2020), but higher than that reported in pigs (85.5%; Lei et al., 2018) and cattle (78.9%; Menge et al., 2012). This variation may be due to differences in the dietary habits and/or physiological characteristics of these animal species.

Following a single i.m. injection, the C_{max} (823.2 ng/ml) in rabbits in this study was similar to that reported in pigs (895 ng/ml; Rose et al., 2013), goats (720 ng/ml; Elazab & Badawy, 2020), and cattle (711 ng/ml; Menge et al., 2012) after i.m. or subcutaneous injection at the same dose, but slightly lower than in dogs (1,051 ng/ml; Wang et al., 2018). The low serum concentration may be attributed to a high Vz/F and low Cl/F, as the tissue levels were significantly higher than in serum. Previous studies have demonstrated that TD concentrations are 100 times higher in lungs, tonsils, and bronchial fluid than in serum (Menge et al., 2012; Rose et al., 2013; Torres et al., 2016). Due to its high lipid solubility and hydrophobic nature (EMA, 2012), TD administered parenterally is rapidly distributed into tissues and then released into the plasma. In addition to the long drug persistence, these characteristics would be efficacious for the treatment of systemic infections as a single injection therapy.

Most macrolides have been classified as time-dependent killing drugs; therefore, the best descriptive PK/PD parameter is time above MIC (T > MIC). However, for newer macrolides such as azithromycin and clarithromycin, the plasma AUC/MIC ratio seems to strongly correlated with successful results (Lees, Concordet, Aliabadi, & Toutain, 2006). In addition, recent studies have demonstrated that the use of AUC/MIC as a PK/PD predictor of efficacy is feasible for previously approved veterinary macrolides such as tulathromycin and gamithromycin (Toutain et al., 2017; Zhou et al., 2020). At present, the minimum inhibitory concentration (MIC) of TD against *P. multocida* isolated from rabbits has not been determined. Previous studies have reported that TD shows high antibacterial activity against *P. multocida* isolated from pigs, cattle, and mice (Lei et al., 2018; Michael et al., 2012; Zeng et al., 2018). The MIC_{90} of TD against pig *P. multocida* has been reported to be 1 μg/ml (EMA, 2012). This value was used to predict the pharmacodynamic efficacy of TD in this work by calculating AUC_{0-24}/MIC ratios following i.m. administration. An AUC_{0-24}/MIC ratio of more than 30 hr indicates an optimum antibacterial effect of macrolides against Gram-negative bacteria; however, due to the different immune status of target animals and bacteria, these thresholds may vary for different drugs and different types of bacteria. (Lei et al., 2018). The AUC_{0-24}/MIC of TD after i.m. adminstration was calculated as

2.20 hr, which is much lower than the 11.0 hr and 21.0 hr reported in pigs and cattle, respectively (Menge et al., 2012; Rose et al., 2013). These values suggest that the current dosage (4 mg/kg) might not guarantee a bactericidal effect. Nevertheless, high clinical efficacy has been confirmed for TD in clinical field trials (EMA, 2012). The C_{max} of TD was clearly below the MIC_{90} for target pathogens, similar to other macrolides (Xiong, Zhu, Yang, et al., 2019; Xiong, Zhu, Zhao, et al. 2019). These results indicate that the MIC value determined in *vitro* could underestimate the practical efficacy of TD, and the complex interactions between drugs, hosts, and pathogens should be taken into account. It is noteworthy that the MIC of pig *P. multocida* in serum (ex vivo) was at least fourfold lower than that in an artificial medium (Lei et al., 2018). A large potentiation effect of tulathromycin in calf serum was also observed for *Mannheimia haemolytica* and *P. multocida* (Lees et al., 2016). Therefore, serum is a more clinically relevant matrix for establishing a PK/PD model to predict dosing regimens.

In conclusion, this preliminary pharmacokinetic study of TD in rabbits showed rapid absorption, extensive distribution, and high bioavailability following i.m. administration. These improved pharmacokinetic features, especially the rapid distribution and long elimination half-life, support the use of TD as a single-dose treatment against respiratory infections in rabbit. Further investigations including pharmacodynamic studies, multiple-dose research, and elimination residue tests are warranted to determine and evaluate the clinical efficacy of TD in rabbits, as well as to confirm the safety of the drug and the optimum dosage regimens.

ACKNOWLEDGMENTS

This work has been financially supported by Beijing Advanced Innovation Center for Food Nutrition and Human Health. We also sincerely appreciated the great assistance of students who took the course of veterinary pharmacokinetics at College of Veterinary Medicine, China Agricultural University.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Haiyang Jiang conceived, designed experiment, and revised the final manuscript. Yuliang Xu, Shuang He, and Yanfang Zhang conducted the animal experiment. Zile, Wang, and Sihan Wang determined the concentrations of tildipirosin in plasma samples. Jincheng Xiong involved in study execution and data analysis and drafted the manuscript.

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How to cite this article: Xiong J, Xu Y, He S, et al. Pharmacokinetics and bioavailability of tildipirosin in rabbits following single-dose intravenous and intramuscular administration. *J vet Pharmacol Therap*. 2020;00:1–6. https://doi.org/10.1111/jvp.12882