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Research Article

Pharmacokinetics of Tilmicosin in Pigeons, an explorative study

Farmacocinética da Tilmicosina em Pombos: Um Estudo Exploratório

Mustafa A. Al-Jumaili *(ORCID 0000-0002-9634-7601), **Khudhair A. M. Abed Al-Ani** (ORCID 0000-0003-4931-0598)

University of Diyala, Iraq. *Corresponding author: mustafa.a@uodiyala.edu.iq

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ABSTRACT

Tilmicosin is a semisynthetic macrolide used in the veterinary field to treat various infections caused by gram-positive and gram-negative bacteria in different species. Therefore, this work focused on exploring the single and multiple pharmacokinetics of orally administered Tilmicosin in pigeons, as there is limited information available on this topic. For this study, six pigeons weighing about 0.35 kg were used as model; a single oral dose of Tilmicosin (15 mg/kg) was administered every 24 hours for three consecutive days. The microbiological assay was applied to measure plasma concentrations of Tilmicosin**.** The non-compartmental analysis revealed that the highest measured concentration was 0.258 µg/ml two hours after administration, the area under the curve was 2.119 µg/ml.h, the area under the moment curve was 36.069 µg/ml.h^2, the mean residence time was 13.893 hours, the half-life was 11 hours, and the terminal elimination rate constant was 0.063 h^{-1}. The pharmacokinetics of multiple doses of Tilmicosin showed that the estimated time to reach the steady state was 44 hours, the ratio of accumulation was 1.283, the remnant fraction was 0.22 µg/ml, and the total area under the curves was 8.77 µg/ml·h. The maximal, trough, and average concentrations at steady state were 0.331 µg/mL, 0.073 µg/mL, and 0.202 µg/mL, respectively. The study concluded that the pharmacokinetics of Tilmicosin in different administration patterns could provide sufficient tissue concentrations, influencing the contact time with tissue-invading bacteria in a manner similar to that observed in other animal species. This could qualify Tilmicosin as a viable option for the treatment of many bacterial diseases in pigeons.

KEYWORDS: Pharmacokinetics. Oral. Tilmicosin. Pigeons. Multiple doses. Non-compartmental.

RESUMO

A tilmicosina é um macrolídeo semissintético utilizado na medicina veterinária contra diversas infecções causadas por bactérias gram-positivas e gram-negativas em diferentes espécies. Portanto, o presente trabalho teve como objetivo explorar a farmacocinética de dose única e múltiplas doses da tilmicosina administrada por via oral em pombos, devido à escassez de informações disponíveis sobre essa espécie. Para este estudo, foram utilizados seis pombos com peso aproximado de 0,35 kg, aos quais foi administrada uma dose oral única de tilmicosina (15 mg/kg) a cada 24 horas por três dias consecutivos. Um ensaio microbiológico foi aplicado para medir as concentrações plasmáticas de tilmicosina. A análise não compartimental revelou que a maior concentração medida foi de 0,258 µg/ml, duas horas após a administração; a área sob a curva (AUC) foi de 2,119 µg/ml.h; a área sob a curva de momentos foi de 36,069 µg/ml.h²; o tempo médio de permanência foi de 13,893 horas; a meia-vida foi de 11 horas; e a constante de eliminação terminal foi de 0,063 h⁻¹. A farmacocinética das doses múltiplas de tilmicosina indicou que o tempo estimado para atingir o estado de equilíbrio foi de 44 horas; a razão de acúmulo foi de 1,283; a fração residual foi de 0,22 µg/ml; e a área total sob as curvas foi de 8,77 µg/ml.h. As concentrações máximas, mínima (vale) e média no estado de equilíbrio foram, respectivamente, 0,331 µg/ml, 0,073 µg/ml e 0,202 µg/ml. O estudo concluiu que a farmacocinética da tilmicosina, em diferentes regimes de administração, pode proporcionar concentrações teciduais suficientes para influenciar o tempo de contato com bactérias invasoras de tecidos, de forma semelhante ao que é observado em outras espécies animais. Isso pode qualificar a tilmicosina como uma opção viável para o tratamento de diversas doenças bacterianas em pombos.

PALAVRAS-CHAVE: Farmacocinética. Oral. Tilmicosina. Pombos. Doses múltiplas. Não compartimental.

INTRODUCTION

Pigeons are considered a companion animal species to humans throughout different ages; they are domesticated for their food value or entertainment activities like races and shows. (MIA et al. 2022). Like other avian species, pigeons can be exposed to various bacterial infections, including salmonellosis, colibacillosis, chlamydiosis, mycoplasmosis, and other bacterial pathogens. (SANTOS et al. 2020).

Treating bacterial infections and improving growth are the main points that call for using antibiotics in pigeons. (DAI et al. 2025). Different antibiotics are currently used to treat bacterial infections in pigeons, including penicillin, tetracyclines, sulfonamides, fluoroquinolones, and macrolides (BALDREY 2020).

Macrolides are secondary metabolites derived from various *Streptomyces spp.* With antimicrobial and cytotoxic properties (AL-FADHLI et al. 2022). The chemical structure of most pharmacologically distinguished macrolides is a macrocyclic lactone ring composed mostly of 14-16 carbon atoms attached to sugars (JANAS & PRZYBYLSKI 2019).

One of the most clinically efficient macrolides is Tilmicosin, a 16-membered macrocyclic-lactone that is semi-synthesized from Tylosin by aldehyde modifications. It presents a broad-spectrum, with mostly bacteriostatic properties against sensitive pathogenic bacteria (ARSIC et al. 2018, ELGENDY et al. 2024). It works by inhibiting the 50S ribosomal subunit, consequently ceasing bacterial protein translation during synthesis (ARSIC et al. 2018).

Tilmicosin is exclusive to veterinary therapeutic purposes; it is administered to fight various animal infectious respiratory diseases caused by gram-positive, gram-negative, and mycoplasma microbes (ZHANG et al. 2021). Additionally, the immunomodulatory impact of Tilmicosin via induction of Neutrophil apoptosis has been mentioned (BLONDEAU 2022).

The lack of avian-specific pharmacokinetic parameters of many antibiotics, especially those employed in determining their dosage regimens, led to the approach of dose extrapolation that is potentially insufficient or comes with a chance of toxicity (SOH et al. 2022). Therefore, this work intends to explore the pharmacokinetics of single and multiple orally administered Tilmicosin in pigeons which is considered the 1st providing data for the next works that involve determining the pharmacokinetic parameters of Tilmicosin in pigeons, also, this work provides potential exploratory data for establishing future dosage regimens that could be accredited as an potential treatment option against many bacterial species that possibly cause infectious diseases in pigeons.

MATERIAL AND METHODS

Animals

Six domestic pigeons were purchased from the local market in Diyala province/Iraq, with an average weight of 0.35 kg ($\pm$ 0.009) at the time of the experiment; a certified avian pathologist inspected all pigeons to ensure their integrity from diseases and lesions. All birds were housed in the laboratory animal house at the College of Veterinary Medicine/ University of Diyala. Pigeon antibiotics-free pellet diet (13% protein) and water were freely accessed; an adaptation period of 14 days was

implemented before the experimentation. The approval number issued by the ethical committee for scientific research in the College of Veterinary Medicine/ University of Diyala is (VM 405,10, 2024).

Drug administration

A single dose (15 mg/kg B.W.) of Tilmicosin (Macrotyl 25%, Interchemie-Holland) was orally administered every 24 hours for three consecutive days (EMEA 1998).

Sample collection

Blood samples (≤ 1 ml per time point) were obtained from the right or left basilic veins at 0.5, 1, 2, 4, 8, 12, and 24 hours; For the multiple doses analysis, collection of blood samples continued at 26, 28, 32, 36, 48, 50, 52, 56, 60, and 72 hours. To determine the sampling time points for single and multiple doses of the study followed the recommended pharmacokinetic protocols (EMA 2021). All samples were kept in lithium-heparin tubes for further plasma separation by centrifugation (AL-JUMAILI et al. 2023).

Drug Analysis

The microbiological assay used *Micrococcus luteus* as a bio-detector (provided by Baqubah General Hospital, Diyala/Iraq). The bacteria were cultivated on Mueller-Hinton agar and incubated for 24 hours (36-37°C). The Tilmicosin concentration in plasma samples was determined based on the change in the zone of inhibition of bacterial growth as a response to different drug concentrations (COLEMAN et al. 1995). The zone of inhibition diameter of three replicates for each sample was measured using a digital vernier caliper.

The Standard curve was constructed by dissolving analytical grade (90% purity) of Tilmicosin (Solarbio Beijing, PRC) in 1:9 Methanol: Distilled water to produce a 0.1% stock solution, then, fresh serial dilutions of 1, 0.5, 0.25, 0.125, 0.0625, 0.031, and 0.0156 µg/ml were made (AL-JUMAILI et al. 2024). All related calculations and quality control for the standard curve were done according to ICH guidelines (BORMAN & ELDER 2017).

Pharmacokinetic Analysis

Non-compartmental (NCA) and multiple-dose analyses for extravascular administration were applied to calculate the pharmacokinetic parameters. The analysis was done using PKSolver, a Microsoft Excel® add-in tool, and spreadsheets (Microsoft® Excel 2021, USA) to calculate the pharmacokinetic parameters for extravascular single and multiple administrations of Tilmicosin (CHAMBERLAIN 2003, MEINEKE & BROCKMÖLLER 2007, ZHANG et al. 2010). The linear trapezoidal method was applied to calculate the area under the curve (AUC). The other parameters, including the maximal concentration (C_{max}), time to reach peak concentration (T_{max}), area under the moment curve (AUMC), mean residence time (MRT), half-life ($t_{1/2}$), and terminal elimination constant (λ_z), were derived from the time-concentration graph (GABRIELSSON & WEINER 2012).

The multiple-dose pharmacokinetic parameters such as the required time for the drug to reach steady state (t_{ss}), fraction of remaining drug after administration (fr), ratio of drug accumulation (R_{ac}), maximal concentration of drug at steady state ($C_{max,ss}$), trough concentration of drug at steady state ($C_{min,ss}$), average concentration of drug at steady state ($C_{avg,ss}$), and total area under the curve (AUC_{0-t}) were calculated using

spreadsheets (Microsoft® Excel 2021, USA) according to the mentioned analysis algorithms in the considerable texts (ROSENBAUM 2017, DERENDORF et al. 2020). The acquired data for both analyses were subjected to descriptive statistical analysis and tabulated as mean, standard deviation, and standard error (GAD 2005).

RESULTS

Based on clinical observations, no adverse effects were recorded from oral administration of Tilmicosin to the pigeons in single and multiple oral administrations. The linearity of the constructed standard curve of Tilmicosin was acceptable for analytical purposes based on the resultant determination coefficient (r^2=0.972). Detection and quantification limits (LOD & LOQ) of Tilmicosin in the plasma of pigeons were 0.012 and 0.03 µg/ml, respectively (Table 1).

Table 1. Standard curve of Tilmicosin (Microbiological assay).

Parameter	Value
CV%	11.8%
Slope	12.342
Intercept	6.887
r ²	0.972
LOQ (µg/ml)	0.032
LOD (µg/ml)	0.014

Abbreviations: *CV%;* Variation coefficient, *r ²;* Determination coefficient, *LOD;* Detection limit, *LOQ*; Quantification limit.

The gathered pharmacokinetic data of a single oral administration of Tilmicosin by the non-compartmental analysis is presented in Figure 1 and summarized in Table 2, revealing that the highest measured concentration (C_{max}) was 0.258 µg/ml, two hours after administration (T_{max}).

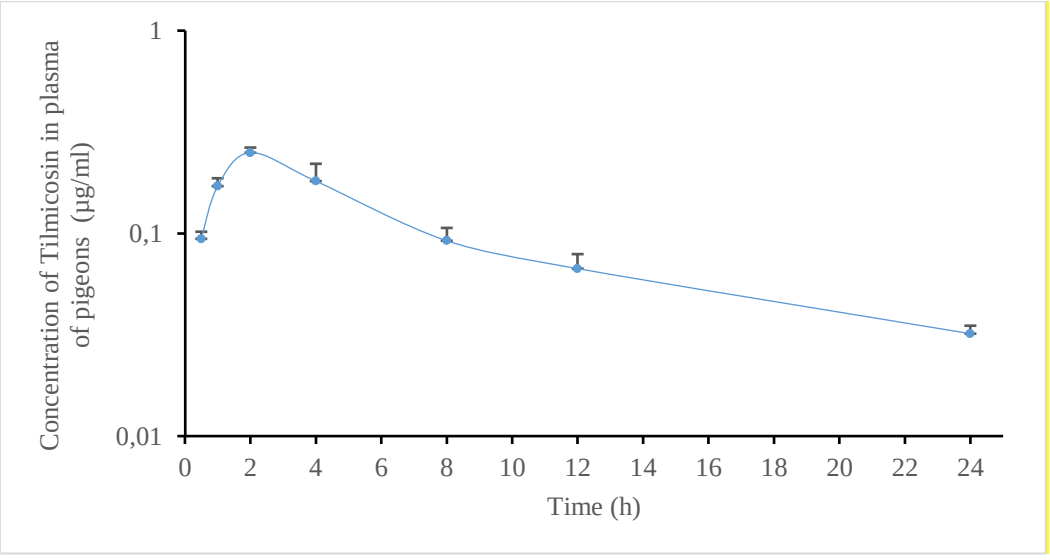

Figure 1. Tilmicosin concentration in the plasma of pigeons after a single oral administration (15mg/kg).

Table 2. Pharmacokinetics of Tilmicosin (Single oral dose) in the plasma of pigeons.

Parameter	Unit	Mean	STDEV	±SEM
λ_z	h^{-1}	0.063	0.004	0.001
$t_{1/2}$	h	11	0.783	0.319
T_{max}	h	2	0	0
C_{max}	µg/ml	0.258	0.015	0.006
AUC_{0-24}	µg/ml.h	2.119	0.322	0.131
$AUC_{0-\infty}$	µg/ml.h	2.612	0.333	0.136
$AUMC_{0-\infty}$	$\mu g/ml.h^2$	36.069	2.463	1.005
MRT	h	13.893	0.858	0.35

Abbreviations: $\boldsymbol{\lambda z}$; Terminal elimination rate constant, $\boldsymbol{t_{1/2}}$; Elimination half-life, T_{max} ; moment the drug reaches maximum concentration, $\boldsymbol{C_{max}}$ **;** maximum concentration, $\boldsymbol{AUC_{0-t}}$ **;** Area under the curve from time zero to the last measurable concentration, $\boldsymbol{AUC_{0-\infty}}$; Area under the curve from time zero to infinity, $\boldsymbol{AUMC_{0-\infty}}$; Area under the moment curve from time zero to infinity, ***MRT*** ; Mean residence time.

The calculated area under the curve (AUC) was 2.119 µg/ml.h, the area under the moment curve (AUMC) was 36.069 $\mu g/ml.h^2$, the mean residence time (MRT) of tilmicosin in the body was 13.893 hours, the half-life ($t_{1/2}$) was 11 hours, and the terminal elimination rate constant (λ_z) was 0.063 h^{-1} as listed in Table 2.

Figure 2 illustrates the pharmacokinetics of multiple doses of Tilmicosin in pigeons after administration of 15 mg/kg of Tilmicosin for 3 consecutive days. The parameters were listed in Table 3, the estimated time to reach the steady state (t_{ss}) was 44 hours, the rate of accumulation (R_{AC}) was 1.283, the remnant fraction of Tilmicosin (fr.) was 0.22 µg/ml, the total area under the curves (AUC_{0-72}) was 8.77 µg/ml.h, the maximal concentration at steady state ($C_{max, ss}$) was 0.331 µg/ml, the trough concentration at steady state ($C_{min, ss}$) was 0.073 µg/ml, and the average concentration at steady state ($C_{avg, ss}$) was 0.202 µg/ml.

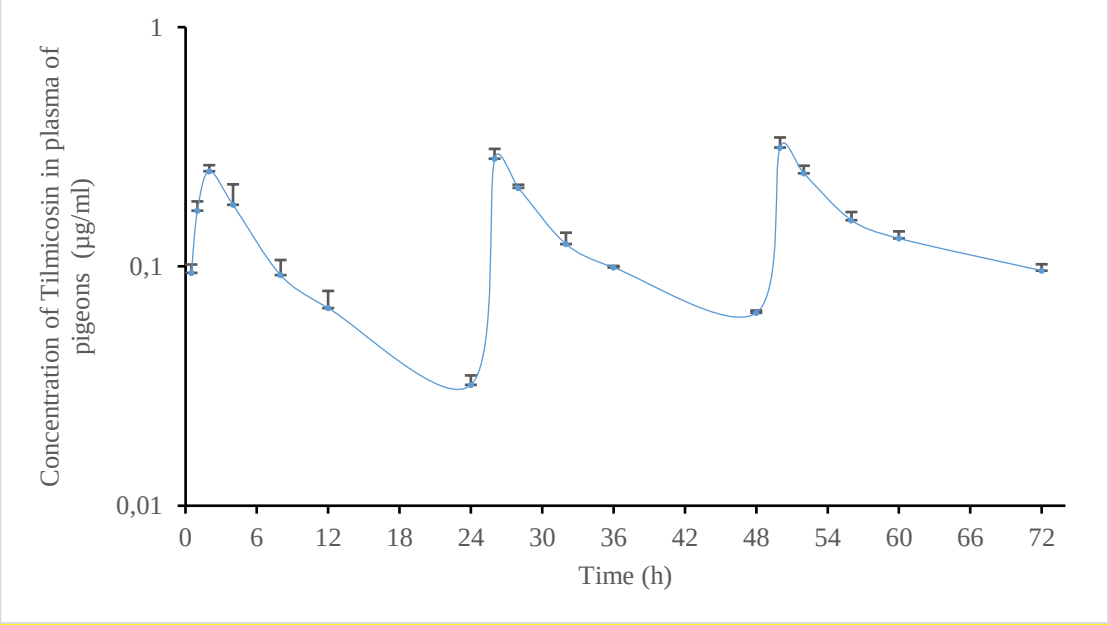

Figure 2. Tilmicosin concentrations in the plasma of pigeons after multiple oral administrations (15 mg/kg/ dose).

Table 3. Pharmacokinetics of Tilmicosin (Multiple oral doses) in the plasma of pigeons.

Parameter	Unit	Mean	STDEV	±SEM
t_{ss}	h	44	3.135	1.28
fr	µg/ml	0.22	0.023	0.009
R_{ac}	-	1.283	0.039	0.016
$C_{max,ss}$	µg/ml	0.331	0.012	0.005
$C_{min,ss}$	µg/ml	0.073	0.007	0.003
$C_{avg,ss}$	µg/ml	0.202	0.007	0.003
AUC_{0-72}	µg/ml.h	8.77	0.726	0.296

Abbreviations: t_{ss}; time to reach steady state *fr;* fraction of remaining drug, R_{ac} *;* rate of accumulation*;* $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, trough concentration at steady state, $C_{avg,ss;}$ Average concentration at steady state AUC_{0-72}; total area under the curve.

DISCUSSION

The goodness of fit test for the standard curve of Tilmicosin (Table 1) was achieved by calculating the r^2 value, which yielded an acceptable limit of accuracy. (CHICCO et al. 2021). No issues were found with the accuracy of the analysis since the LOD is lower than the LOQ for the constructed standard curve. (BARNETT et al. 2021).

The use of non-compartmental approach to analyze Tilmicosin pharmacokinetics (Table 2) was used because it is widely adopted due to no need for compartment assumptions for the drug or its metabolites and flexibility in oral dose pharmacokinetics without the need for bioavailability estimation, especially with drugs with a potential cardiovascular toxicity due to intravenous administration like Tilmicosin. (GABRIELSSON & WEINER 2012, SHABAN et al. 2019, OSIPOVA et al. 2023).

The low peak plasma concentration (C_{max}) of Tilmicosin after oral administration is a shared feature for most macrolide members due to limited absorption and tendency for the most absorbed fraction to be distributed majorly to the peripheral tissues as mentioned by (WANG et al. 2023) and recorded through different clinical studies that were made in adjacent bird species, where they ranged from. A reduced calculated AUC in this study was also recorded as a potential result of limited oral bioavailability that led to low plasma concentrations of Tilmicosin as previously mentioned (RASSOULI et al. 2016).

The prolonged $t_{1/2}$ in this study was a response to the assumed large V_d that was previously reported in many animal species. (ZHANG et al. 2021) in turn attributes to the high lipophilicity of Tilmicosin that incorporate the increment of its distribution to the peripheral tissues (ZHANG et al. 2022) with noted intracellular accumulation, especially in phagocytes (SCORNEAUX & SHRYOCK 1998). Both V_d and $t_{1/2}$ produced a large AUMC of Tilmicosin that proportionally correlated to MRT, which is also found to be long in this study. (BEREZHKOVSKIY 2009).

The follow-up pharmacokinetics of multiple doses of Tilmicosin in pigeons (Table 3) revealed that it tends to accumulate in the body (R_{ac}) due to its extensive distribution in tissues like the lung, liver, and kidney, besides the intracellular accumulation previously mentioned. (SCORNEAUX & SHRYOCK 1998, ELSAYED et al. 2014).

The average plasma concentration at a steady state ($Cp_{avg,ss}$) was influenced by the accumulation (R_{ac}) of Tilmicosin in peripheral tissues due to the direct

proportionality that led to a state of equilibrium between the two parameters. (BROCKS & MEHVAR 2010, BRUNO et al. 2021).

CONCLUSION

The pharmacokinetics study of single oral administration of Tilmicosin in pigeons found that it has an extensive volume of distribution depending on the measured low maximum concentration and the small area under the curve, While, both half-life and the residence time were found to be long as an indicator for the slow clearance that contributed to the accumulation of the drug as reported in the multiple doses administration.

The similarity of these properties to what is recorded in different animal species could qualify Tilmicosin as a potential option for the treatment of many bacterial diseases in pigeons.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, and formal analysis**, Al-Jumaili and Al-Ani**; software and validation**, Al-Jumaili and Al-Ani;** investigation**, Al-Jumaili and Al-Ani**; resources and data curation**, Al-Jumaili and Al-Ani**; writing-original draft preparation**, Al-Jumaili and Al-Ani**; writing-review and editing**, Al-Jumaili**; visualization**, Al-Jumaili**; supervision, **Al-Jumaili**; project management, **Al-Jumaili and Al-Ani**; fundraising, **Al-Jumaili and Al-Ani**. All authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The ethical committee for scientific research in the College of Veterinary Medicine/ University of Diyala approved this study according to the approval number (VM 405,10, 2024).

INFORMED CONSENT STATEMENT

Not applicable as this study did not involve humans.

DATA AVAILABILITY STATEMENT

The data can be made available upon request.

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CONFLICTS OF INTEREST

There is no conflict of interest, as declared by all authors.

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