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Pharmacokinetic Profile of Norfloxacin in Pigeons

Perfil Farmacocinético da Norfloxacina em Pombos

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ABSTRACT

Through this work, the pharmacokinetics of Norfloxacin in pigeons were explored by using six healthy male pigeons as the subjects for this study. The pharmacokinetic indices of orally administered Norfloxacin were obtained by microbiological assay and then the data were fitted to the two-compartment pharmacokinetic open model to evaluate the distribution and excretion parameters. In the achieved results, the calculated absorption rate constant (K_{ab}) was 1.26 h^{-1}, the maximum achieved concentration of Norfloxacin was 2.75 µg/ml at 1.34 hr., the volume of distribution (Vd/F) was 3.15 L/kg. The half-life ($t_{1/2\beta}$) was 4.9 hrs., the calculated area under the curve of Norfloxacin (AUC_{0-t}) was 16.75 (h*µg)/ml, while the clearance of Norfloxacin (Cl/F) was 0.49 L/hr/kg. In conclusion, the pharmacokinetic parameters of Norfloxacin in pigeons are not far away from other birds like chickens, considering the differences among them. Norfloxacin is a valuable antibacterial agent against susceptible bacterial infections depending on the obtained pharmacokinetic profile.

KEYWORDS: Pharmacokinetics; compartmental analysis; Norfloxacin; pigeon.

RESUMO

Através deste trabalho, a farmacocinética da Norfloxacina em pombos foi explorada usando seis pombos machos saudáveis como sujeitos para este estudo. Os índices farmacocinéticos da norfloxacina, administrada por via oral, foram obtidos por ensaio microbiológico e, em seguida, os dados foram ajustados ao modelo aberto de farmacocinética de dois compartimentos para avaliar os parâmetros de distribuição e excreção. Nos resultados obtidos, a taxa constante de absorção (Kab) calculada foi de 1,26 h^{-1}, a concentração máxima alcançada da Norfloxacina foi de 2,75 µg/ml em 1,34 h, o volume de distribuição (Vd/F) foi de 3,15 L/kg. A meia-vida (t1/2β) foi de 4,9 h, a área calculada sob a curva de concentração da Norfloxacina (AUC0-t) foi de 16,75 (h*µg)/ml, enquanto a depuração da Norfloxacina (Cl/F) foi de 0,49 L/h/kg. Em conclusão, os parâmetros farmacocinéticos da Norfloxacina em pombos não estão muito longe de outras aves, como galinhas, considerando as diferenças entre eles. A norfloxacina é um agente antibacteriano valioso contra infecções bacterianas susceptíveis, dependendo do perfil farmacocinético obtido.

PALAVRAS-CHAVE: Farmacocinética; análise compartimental; Norfloxacina; pombo.

INTRODUCTION

Pigeons are one of the important bird species that were domesticated since 5000 years ago (HARLIN & WADE 2009). They are bred mainly for two purposes; meat production and sporting activities like flying and exhibition (KABIR 2020).

Bacterial infections like Salmonellosis and Colibacillosis can negatively affect the health state of pigeons and require antibacterial agents to be in use to treat these infections (KABIR 2010). Fluoroquinolones are a group of large, and expanding antibacterial agents and they are the most predominant DNA gyrase inhibitors in clinical use (EZELARAB et al. 2018). Broadly, they are used to manage bacterial infections of the respiratory tract, soft and hard tissues, and, urinary tract infections (HU et al. 2017). Fluoroquinolones are classified into five generations based on their antibacterial spectrum and pharmacokinetics (FAN et al. 2018, JONES et al. 2016). The bactericidal effect of Fluoroquinolones was an encouraging factor to be used in veterinary medicine; therefore, many members are extensively used in

different animal species, including birds (HRUBA et al. 2019).

Norfloxacin belongs to the second generation of Fluoroquinolones, and it is prescribed mainly for urinary tract infections, besides other general applications in treating enteric diseases (OIE 2015). Like other DNA gyrase inhibitors, it has a significant concentration-dependent bactericidal effect with a considerable post-antibiotic effect against most gram-negative bacteria especially Enterobacteriaceae with a distinctive bactericidal effect against Escherichia coli (AL-MUSTAFA & AL-GHAMDI 2000, HAQ et al. 2015)

Drug pharmacokinetics, besides pharmacodynamics, plays a crucial role in determining the accurate dose that ensures maximal antibacterial activity, minimal side effects, with no bacterial resistance (LEVISON & LEVISON 2009), so this study aims to find the pharmacokinetic parameters of Norfloxacin in pigeons to provide explorative information about Norfloxacin absorption, distribution and elimination for further utilization in clinical applications like dose optimization through PK-PD modeling.

MATERIAL AND METHODS

Materials

Six healthy pigeons of a local breed with an average weight of 300 g were caged in 100x60x 80 cm cages in the laboratory animal facility at the College of Vet. Med. at Diyala University, the ethics of laboratory animal handling and sample collection that was adopted by the scientific research ethics committee in the College of Vet. Med. /Diyala University were followed (AKINS et al. 2005); The pigeons had been kept for a week for adaptation with ad libitum providing of water and food. The study used Norfloxacin (Noroxin® tablets, Merck Sharp & Dohme, Italy) as a drug in the study.

Methods

Drug Administration and Blood Sampling

A single dose of 10 mg/kg of Norfloxacin (Noroxin® tablets, Merck Sharp & Dohme, Italy) was administered orally; one milliliter of blood was obtained from the wing vein on 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hrs then kept in lithium heparin tubes. Blood samples were centrifuged at 3000 rpm/min for 15 minutes to obtain plasma that was kept at -20Co for further drug analysis (AL-JUMAILI & IBRAHIM 2021)

Pharmacokinetic Analysis

The Microbiological assay was used for drug analysis; a locally sensitive bacterial isolate of Klebsiella pneumoniae was used as a biological sensor to trace the concentrations of Norfloxacin (BLAND et al. 1983). The standard curve of Norfloxacin was constructed in drug-free plasma, and the degree of Norfloxacin engagement to plasma proteins was determined by calculating Norfloxacin partitioning between two different phases (AL-JUMAILI & IBRAHIM 2021, CRAIG 1986).

The pharmacokinetic parameters were calculated by Microsoft Excel® spreadsheet algorithm (ROSENBAUM 2016). The weighing factor of the collected data was 1/C2; whereas (C) is the predicted Norfloxacin concentration in the plasma of pigeons (BIDGOOD & PAPICH 2002), the Aikake criterion (AIC) was applied to choose the suitable compartmental model for fitting the obtained data points (YAMAOKA et al. 1978).

RESULTS

Results of the Norfloxacin standard curve revealed that the variation coefficient of inter-assay (CV %) equals 2.7%, the coefficient of determination (R^2) was 0.97, and the detection limit (LOD) was 0.23 µg/ml. In contrast, the lowest quantification limit (LLOQ) was 0.52µg/ml. The ratio of Norfloxacin binding to plasma proteins was 13.3%, which resembles a low binding tendency toward albumin. According to the fitted concentration-time data points of Norfloxacin in plasma of that depicted in Figure (1), besides the calculated value of the AIC, we found that the two-compartmental analysis is the most suitable model for the calculation of pharmacokinetic parameters.

The maximum achieved concentration (C_{max}) of Norfloxacin was 2.75 µg/ml at 1.34 hr., and the calculated absorption rate constant of Norfloxacin (K_{ab}) listed in Table (1) was 1.26 h^{-1}. At the same time, the volume of distribution (Vd/F) of orally administered Norfloxacin was 3.15 L/kg. The half-life ($t_{1/2\beta}$) of Norfloxacin was 4.9 hrs., and the calculated area under the curve (AUC_{0-t}) that indicates the total exposure of the body Norfloxacin was 16.75 (h*µg)/ml., while the clearance (Cl/F) of the orally administered Norfloxacin was (0.49 L/hr/kg).

Table 1. pharmacokinetic analysis of Norfloxacin (Single oral administration) in pigeon's plasma.

Index	Unit	$\bar{x}$	SE.
C_{max}	µg/ml	2.75	0.22
AUC_{0-t}	(h*µg)/ml	16.75	1.06
Vd/F	L/kg	3.15	0.11
Cl/F	L/hr/kg	0.49	0.03
T_{max}	h	1.34	0.09
MRT	h	7.17	0.16
Cp^0	µg/ml	N.A	N.A
$t_{1/2\alpha}$	h	0.64	0.05
$t_{1/2\beta}$	h	4.93	0.10
K_{ab}	h^{-1}	1.26	0.09
K_{10}	h^{-1}	0.25	0.01
K_{12}	h^{-1}	0.37	0.04
K_{21}	h^{-1}	0.63	0.06
A	µg/ml	19.89	1.19
α	h^{-1}	1.10	0.09
B	µg/ml	2.88	0.18
β	h^{-1}	0.14	0.003
Protein binding	%	13.3	0.67

No. of pigeons = 6. Weighing by 1/C2.

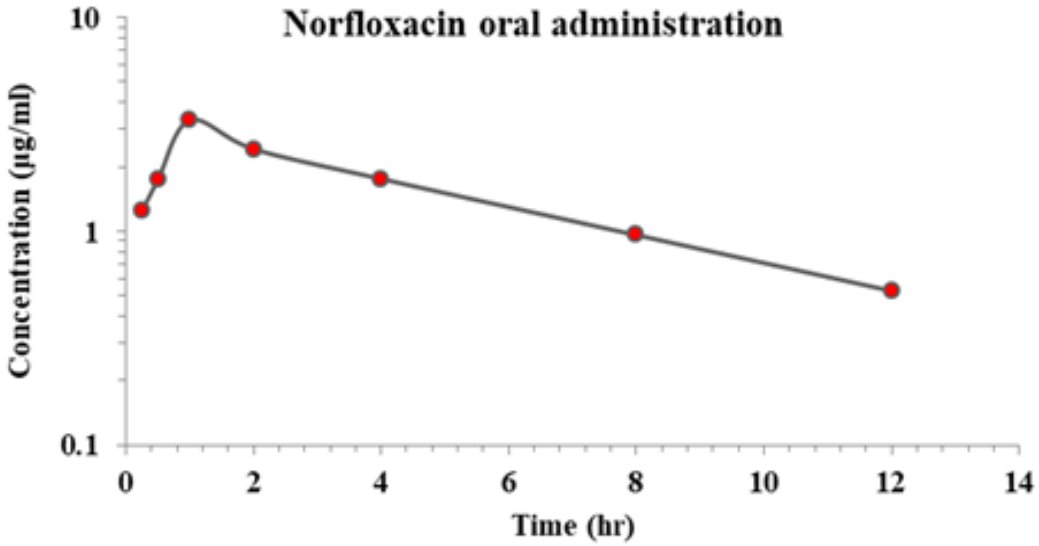

Figure 1. Norfloxacin concentrations in plasma of pigeons after oral administration (10 mg/kg).

DISCUSSION

Norfloxacin standard curve revealed that the variation coefficient of inter-assay (CV %), the coefficient of determination (R2), and the detection limit (LOD), in addition to the quantification low limit (LLOQ), showed a satisfying level of precision in the relationship between the dependent variables "the used concentrations of Norfloxacin" and the independent variables "the produced zones of inhibition" (SAUNDERS et al. 2012). Both achieved LOD and LLOQ values reflect a reliable limit of precision because they do not exceed 20% of the CV% calculated value for our applied analytical assay (UVAROVA et al. 2019). The degree of binding between drug molecules and plasma proteins has a critical role in the determination of PK-PD properties of that drug (ZLOTOS et al. 1998); in our in-vitro study, we found that Norfloxacin has a low binding tendency

toward albumin; such a low value will ensure a greater tissue distribution in addition to antimicrobial activity against sensitive bacteria (ZEITLINGER et al. 2004).

Based on fitted concentration-time data points of Norfloxacin in the plasma of pigeons depicted in Figure 1 beside the calculated value of the AIC, we found that the two compartmental analysis is the most suitable model for the calculation of pharmacokinetic parameters listed in Table 1 (SANDULOVICI et al. 2009).

The maximum achieved concentration of Norfloxacin has a low peak, which is a normal consequence of the large Vd/F because that implication will lower the achieved Cmax of that drug (RYU & HEBERT 2022).

As noticed from the calculated absorption rate constant (Kab), Norfloxacin (Noroxin®) is absorbed slowly from the gastrointestinal tract in comparison to other fluoroquinolones that are administered orally to the pigeons (DORRESTEIN et al. 1983, MOUTAFCHIEVA et al. 2009).

The volume of distribution (Vd/F) is another primary pharmacokinetic parameter, it describes how the molecules of the drug are distributed on the available anatomical spaces of the body (SMITH et al. 2015); we found that the Vd/F for oral administration of Norfloxacin was large, and finding is empowered by other studies that denoted to the large volume of distribution of Norfloxacin in different bird species (HARITOVA & LASHEV 2009), such large Vd/F will ensure more accessibility to different anatomical spaces including the intracellular compartment which considered a preferred choice against Norfloxacin sensitive bacteria (CHIFIRIUC et al. 2016).

The half-life (t1/2β) was found to be longer than the average in other species, and this finding is a reflection of the large Vd/F, also it could be attributed to some metabolic variations among birds. such long t1/2β may cooperate in increments of the duration of action, consequently increasing of reliability of Norfloxacin against complicated tissue-based infections (SMITH et al. 2015, HARITOVA & LASHEV 2009).

Based on the obtained concentration versus plasma curve of Norfloxacin, both the low peak and the flatly declined trough were characterized by the calculated area under the curve (AUC0-t), this logically attributed to the slow absorption, low achieved Cmax and the long half-life as a distinguished feature of oral administration (WISPELWEY 2005).

Our results revealed a low Cl/F of Norfloxacin, such a finding can be attributed to the inverse correlation between clearance and other pharmacokinetic parameters like MRT, t1/2β, and the AUC, which in turn reflects the large Vd of Norfloxacin on different body tissues of the pigeon (KHAFAJI et al. 1999, ROSENBAUM 2016).

CONCLUSION

In conclusion, the pharmacokinetic parameters of Norfloxacin in pigeons are close to those of other birds like chickens, considering the differences in species, more studies through different routes of administration are required to fully characterize the pharmacokinetics of Norfloxacin in pigeons, and these studies will promote using it as a therapeutic agent against bacterial infections like colibacillosis in pigeons based on future PK/PD trials.

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