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Pharmacokinetic Characteristics of Diclazuril in Japanese Quails (*Coturnix japonica*) and Domestic Pigeons (*Columba livia*)

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ABSTRACT

Coccidiosis, caused by the protozoan *Eimeria*, is a significant disease in poultry farms worldwide, leading to substantial economic losses. Triazines, benzene-aceto-nitrile derivatives, are widely employed in the field of veterinary healthcare to combat the hazardous impacts of protozoan parasite infestation comprising coccidiosis. The current research was designed to investigate the pharmacokinetic profile of diclazuril, a member of triazines, in Japanese quails (*Coturnix japonica*) and domestic pigeons (*Columba livia*) following single oral administration at 0.3 mg/kg body weight. 78 Quails (male: female, 1:1, 7 weeks old) and 78 pigeons (male: female, 1:1, 4 weeks old) were randomly divided into 13 groups for each species (n=6 birds/ group). Plasma samples were obtained at various time intervals (at time 0 [preceding diclazuril administration], and 0.5, 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after diclazuril administration) to determine its concentration utilizing high-performance liquid chromatography (HPLC). The non-compartmental approach was applied to assess the pharmacokinetic parameters via the aid of WinNonlin 8.3 software. In quails and pigeons, the peak plasma concentrations were 5.35 and 9.14 µg/mL attained at 8 hours, respectively. Additionally, the elimination half-lives ($T_{1/2\lambda z}$) were 30.74 and 26.48 hours, and the area under the plasma concentration-time curve from time zero to the last sample ($AUC_{0\text{-last}}$) values were 155.67 and 343.57 µg h/mL, respectively. The mean residence time was 30.71 hours in quails and 39.68 hours in pigeons. Diclazuril exhibited favorable pharmacokinetic characteristics after oral administration at a dose of 0.3 mg/kg in quails and pigeons. However, to adjust the dosage regimen for curing coccidiosis, a future study is warranted to determine the clinical efficacy against coccidia infection. Moreover, further investigation is needed to evaluate the tissue residues and calculate the withdrawal time of diclazuril in quails and pigeons.

Keywords: Diclazuril, High-performance liquid chromatography, Japanese quail, Pharmacokinetic, Pigeon

INTRODUCTION

Avian coccidiosis, a parasitic disease caused by apicomplexan protozoan of the genus *Eimeria*, is one of the most serious diseases affecting poultry, causing significant economic losses worldwide (Blake and Tomely, 2014). It causes massive injury in the intestinal epithelial lining of the bird, resulting in impaired feed conversion and growth retardation. The clinical signs of avian coccidiosis may be hidden or manifested by weakness, diarrhea, the presence of blood or mucus in the feces, loss of appetite, reduced egg production, and increased mortality (Chapman, 2003; Christaki et al., 2004). The principal approach for controlling coccidiosis, besides rigorous hygiene and biosecurity techniques, is via the administration of the appropriate dose of anticoccidial therapy (Kadykalo et al., 2018). Triazines are extensively utilized in the veterinary field to combat the deleterious effects of protozoan parasites including coccidiosis (Stock et al., 2018).

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Diclazuril (2,6-dichloro-a-[4-chlorophenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2{3H}yl] benzeneacetonitrile), belongs to triazine family, is a chemical compound derived from the benzeneacetonitrile class that is developed successfully as an anticoccidial remedy for sheep, poultry, and rabbits (Hu et al., 2009). This compound exhibited a potent action against all pathogenic *Eimeria* species affecting poultry (Conway et al., 2002, Gadelhaq et al., 2017). Although the actual mechanism of the antiprotozoal action has not been fully elucidated yet, diclazuril has been claimed to perform its anticoccidial activity by attacking the sexual and asexual stages of *Eimeria* (Zhou et al., 2010; Wang et al., 2013, El-Ashram et al., 2019). Moreover, prior researchers have indicated that diclazuril may accomplish its anticoccidial action by suppressing serine/ threonine protein phosphatase type 5 expression (Zhou et al., 2013).

The pharmacokinetics of diclazuril have been described in several species such as cattle (Dirikolu et al., 2022), horses (Pusterla et al., 2023), rabbits (Hu et al., 2009), and chickens (Mortier et al., 2005; Zhang et al., 2020). Nevertheless, so far as the authors know, the pharmacokinetic features of diclazuril in quails and pigeons have not been studied and documented yet. Therefore, the purpose of the present study was to assess the pharmacokinetic behavior of diclazuril in Japanese quails (Coturnix japonica) and domestic pigeons (*Columba livia*) after single oral administration.

MATERIALS AND METHODS

Ethical approval

All procedures incorporating birds were reviewed and approved by the Research Ethics Committee of the Faculty of Veterinary Medicine, Mansoura University, Egypt (Approval No. R/139).

Chemicals

In this experiment, diclazuril (0.5% solution, Shandong Luxi Animal Medicine Share Co., Shandong, China) was obtained. The diclazuril standard, N, N-dimethylformamide (DMF), and tetrabutylammonium hydrogen sulfate were supplied from Sigma Aldrich Co. (St. Louis, MO. USA). Hexane, Acetonitrile, and methanol were bought from Thermo Fisher Scientific (Waltham, MA, USA). Acetic acid was provided by Merck (Darmstadt, Germany). All chemicals utilized in this work were of high-performance liquid chromatography analytical grade. The Milli–Q system (Waters Corp., Milford, MA. USA) was employed to obtain Purified water.

Animals

Quails

Seventy-eight clinically healthy adult Japanese quails (Coturnix japonica, male: female, 1:1), weighing 180 ± 10 g, were obtained from the Faculty of Agriculture, Mansoura University, Egypt. They were allotted into 13 groups (n= 6 birds/group/cage) and were offered medication-free ration and had unrestricted access to water. The quails underwent a 14-day acclimatization period before the initiation of the trial.

Pigeons

Seventy-eight adult healthy pigeons (*Columba livia*, 250 ± 10 g, male: female, 1:1) were procured from a pigeon farm (Dakahlia Governorate, Egypt) and were enrolled into 13 groups (n=6/group) and were kept in cages (one group (6 birds/cage). Medication-free diet and water were supplied during the study. A period of two weeks was considered for the pigeons to adapt to their surroundings before the commencement of the investigation

Experimental design

Quails and pigeons were divided into 13 groups for each species (n=6). All quails and pigeons received a single oral dose of 0.3 mg diclazuril/kg body weight (EPMAR, 2013; Said et al., 2019) directly into the crop employing a 1-cc, 26 G syringe. Each bird was subjected to blood sampling only once (the amount of blood sample was not more than 1% of body weight). According to the method of Turk et al. (2021), blood samples from various groups were withdrawn from the right brachial vein (1mL from each bird) using an insulin syringe (a 26-gage,½-inch needle) at time 0 (preceding diclazuril administration), and 0.5, 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168 h post drug administration (n = 6 birds of each species/time point, (Hunyadi et al., 2015; Zhang et al., 2020). After centrifugation of blood samples at 2000 x g for 15 minutes, plasma was preserved at −20 ˚C for further investigation.

Analysis of diclazuril in plasma samples

Standards and plasma specimen preparation

A solution of the diclazuril reference standard in DMF was prepared (1mg/ml). Then, it was diluted utilizing blank plasma collected either from quails and pigeons as a diluent to prepare diclazuril calibration

standards at concentrations of 0.025,0.05, 0.1, 0.25, 0.5, 1, 2.5, 5, 10 µg/mL.

Plasma samples were prepared as reported by Dirikolu et al. (1999). Briefly, the solid phase extraction (SPE) column (Bond Elut C18, 500 mg, 3 or 6 ml; Varian) was treated with 2 ml methanol followed by 2 ml of 0.1 M phosphate buffer (pH 6.0). The sample was pulled gradually through the column. The column was washed with 2 ml of 0.1 M phosphate buffer (pH 6.0), then 2 ml of 1.0 M acetic acid, and finally with 2 ml hexane. It was kept to dry for 5- 10 min after every wash. 4 ml elution solution consisted of methanol: HCl (conc); 95:5 was added to the column. The elute was collected and the solvent was evaporated at 40 ^{0}C under a nitrogen stream. The residue was reconstituted with 100 µl DMF. After vortex and sonication, 100 µl of water was added, and the resuspension process was repeated. 20 µL of the sample were introduced into the HPLC system.

Chromatographic condition

Following the technique of Dirikolu et al. (1999), the levels of diclazuril in plasma samples were evaluated. The HPLC Agilent Series 1200 quaternary gradient pump, Series 1200 autosampler, Series 1200 UV VIS detector adapted at 280 nm, and HPLC 2D Chemstation software (Hewlett-Packard, Les Ulis, France) were employed. Chromatographic separation was accomplished with the aid of Phenomenex C18 column (5 µm, 150 mm x 4.6 mm). The mobile phase comprised of solvent A (80% [0.5% ammonium acetate, 0.01 M tetrabutylammonium hydrogen sulphate in water]: 20% acetonitrile) and solvent B (80% methanol, 20% acetonitrile, A: B, 46:54 v/v). The flow rate was 1 ml/min. The retention time was 13.7 min. The validation of the HPLC analytical assay was performed by evaluating recovery, sensitivity, precision, and linearity (Table 1). The linearity of the method was identified ($R^2 > 0.99$) in the range of 0.025–10 µg/ml plasma. The lower limits of detection and quantification of diclazuril were 0.008 and 0.025 µg/ml.

Pharmacokinetic analysis

The mean plasma concentration of diclazuril for every sampling time point was estimated for each species of bird (quails and pigeons). The non-compartmental approach was applied to analyze the mean concentrations of diclazuril utilizing the WinNonlin 8.3 software (Certara, USA) (Dirikolu et al., 2022). The area under the plasma concentration-time curve ($AUC_{0\text{-last}}$) assessed employing the linear up/log down trapezoidal method, the elimination half-life (T1/2λz), mean residence time (MRT), volume of distribution scaled by bioavailability (Vz_F_obs), clearance divided by bioavailability (Cl_F_obs) were among the pharmacokinetic parameters calculated. The values of the peak plasma concentration (C_{max}) and the time needed to achieve C_{max} (T_{max}) were identified from the data on the plasma concentration-time plot.

Table 1. Validation parameters of the high-performance liquid chromatography technique used for measuring diclazuril in plasma samples of Japanese quails (*Coturnix japonica*) and domestic pigeons (*Columba livia*) after its administration at a level of 0.3 mg/kg of body weight

Matrix	Average recovery (%)	Intra-day RSD (%)	Inter-day RSD (%)	LOD (µg/mL)	LOQ (µg/mL)
Quails' plasma	102.91 ± 4.87	2.06	2.65	0.008	0.025
Pigeons' plasma	99.48 ± 8.08	4.43	3.72	0.008	0.025

Data for recovery are elucidated as mean ± Standard deviation, LOQ: Limit of quantification, LOD: Limit of detection, RSD: Relative standard deviation. Intra-day RSD and Inter-day RSD % (n = 6, 0.025µg/mL). Average recovery % (utilizing spiked concentrations in the range of 0.025–10µg/mL in triplicate investigation).

RESULTS

No noticeable side effects from diclazuril were recorded in experimental birds throughout the study. The plasma concentration-time plots of diclazuril after being administered once at 0.3 mg/kg to quails and pigeons are illustrated on a semilogarithmic graph in Figure 1. The plasma levels of diclazuril were higher than the LOQ (0.025µg/ml) up to 168 h post-administration in quails and pigeons. The plasma concentration versus time curves revealed that quails had lower drug concentrations relative to pigeons. Table 2 demonstrates the pharmacokinetic features of diclazuril in quails and pigeons. The C_{max} values of diclazuril were identified to be 5.35 and 9.14 µg/mL at 8 h after oral administration in quails and pigeons, respectively. Diclazuril was eliminated with elimination half-lives ($T_{1/2\lambda z}$) of 30.74 and 26.48 h in quails and pigeons, respectively. The $AUC_{0\text{-last}}$ of the drug was 155.67 µg *h/mL in quails and 343.57 µg *h/mL in pigeons. The calculated MRT values in quails and pigeons were 30.71 and 39.68 h, respectively.

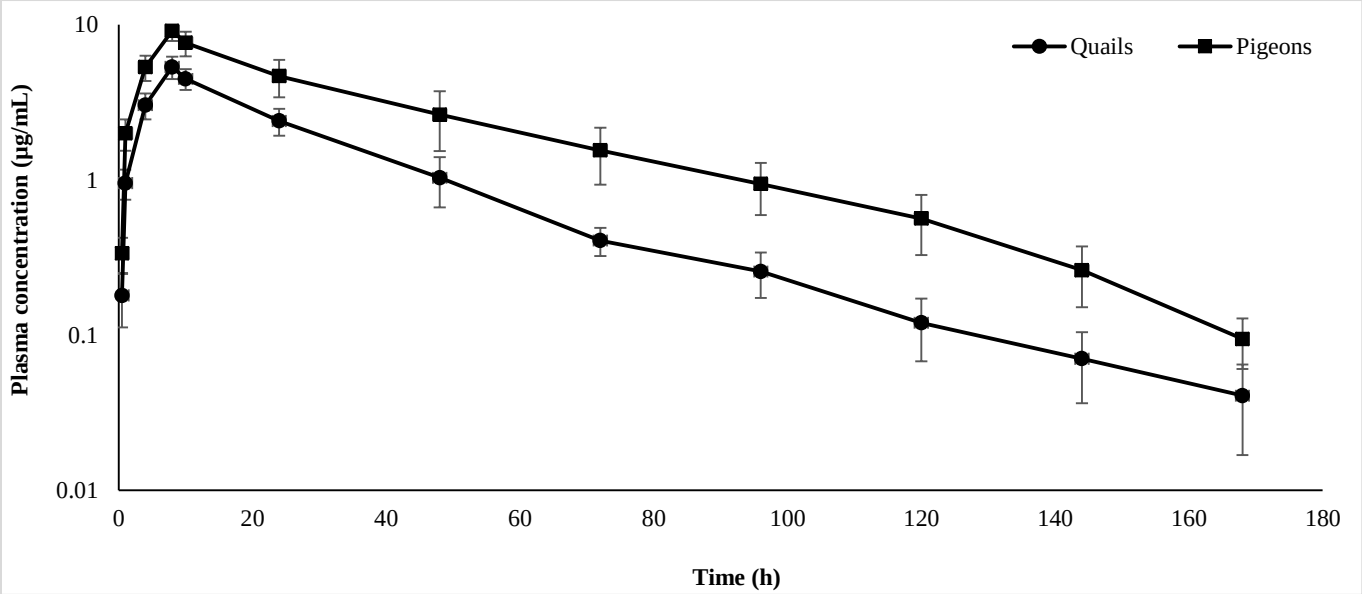

Figure 1. Mean plasma concentrations of diclazuril in Japanese quails (*Coturnix japonica*) and domestic pigeons (*Columba livia*) after a single oral administration at a dose of 0.3 mg/kg. Values are shown as mean ± SD (n=6)

Table 2. Pharmacokinetic parameters of diclazuril following its single oral administration in Japanese quails (*Coturnix japonica*) and domestic pigeons (*Columba livia*)

Parameters	Japanese quails	Domestic pigeons
C_{max} (µg/mL)	5.35	9.14
T_{max} (h)	8.00	8.00
λz (1/h)	0.022	0.026
$T_{1/2}$ λz (h)	30.74	26.48
$AUC_{0\text{-}last}$ (µg*h/mL)	155.67	343.57
Vz_F_ obs (ml/kg)	84.51	33.01
Cl_F_obs (ml/hr/kg)	1.91	0.86
MRT (h)	30.71	39.68

C_{max}: Maximum concentration in plasma; T_{max}: Time to achieve maximum concentration; λz: The first order rate constant; $T_{1/2\ \lambda z}$: Elimination half-life; $AUC_{0\text{-}last}$: Area under the plasma concentration-time curve from 0 to last time; Vz_F_obs: Volume of distribution scaled by bioavailability; Cl_F_obs: Clearance divided by bioavailability; MRT: Mean residence time.

DISCUSSION

Dilcazuril is effective against intestinal *Eimeria* species in avians, all pathogenic *Eimeria* species affecting poultry and turkeys, intestinal and hepatic coccidiosis in rabbits, and toxoplasmosis in mice, and possesses extended-spectrum anticoccidial activity in many other mammalian species (El- Banna et al., 2005; Kotra, 2007; Vereecken et al., 2012; Noack et al., 2019). Limited data are available concerning the pharmacokinetic features of diclazuril in quails and pigeons. The evaluation of the pharmacokinetic characteristic designated that diclazuril was quickly absorbed following oral ingestion in quails and pigeons, with peak plasma level achieved at 8 hours (T_{max} was 8 hr in both species). This finding is consistent with the report of Dirikolu et al. (2022) who demonstrated rapid absorption of diclazuril after oral administration in cattle at 2.2 mg/kg with T_{max} of 8 h. Similarly, Giorgi et al. (2010) recorded a T_{max} of 9.4 h for diclazuril in lambs following a single oral administration at 5mg/kg. The C_{max} of diclazuril in quails and pigeons were 5.35 and 9.14 µg/ml, respectively. The C_{max} value in quails was comparable to that announced for horses who received diclazuril orally at 2.2 mg/kg (4.2 µg/mL, Dirikolu, 2001). In contrast, the C_{max} values in quails and pigeons were less than that revealed in rabbits administered diclazuril at 10

mg/kg (16.42 µg/ml, Hu et al., 2009). Meanwhile, they were higher than those observed in chickens who received diclazuril at 0.5 mg/kg (21.6 ng/mL, Zhang et al., 2020), and in sheep and lambs who received diclazuril at 5 mg/kg (0.9 and 1.3 µg/mL, Giorgi et al., 2010). These variations may be owed to species and dose differences.

Moreover, the current study declared that the $T_{1/2\lambda z}$ of diclazuril in quails and pigeons were 30.74 and 26.48 h, respectively. These findings were relatively similar to those of Zhang et al. (2020) and Giorgi et al. (2010) who reported that the values of $T_{1/2\lambda z}$ of diclazuril were 37.6, and 27.3 h in chickens administered diclazuril orally at 1 mg/kg, and lambs received diclazuril at 5 mg/kg, respectively. On the contrary, the $T_{1/2\lambda z}$ found in rabbits (9.23 h, Hu et al., 2009) was shorter than that recorded in this research for quails and pigeons. Furthermore, in this research, the quails and pigeons had longer MRT (30.71 and 39.68 h, respectively) than that revealed by Hu et al. (2009) in rabbits (10.41 h). Conversely, The MRT announced for horses (113.6 h) by Dirikolu (2001) was longer than that computed in this study. The Vz_F_ obs for diclazuril was 84.51 mL/kg in quails and 33.01 mL/kg in pigeons. To the best of the authors' knowledge, no data are documented about the Vz of diclazuril in other species.

CONCLUSION

Diclazuril displayed favorable pharmacokinetic properties after oral administration at a dose of 0.3 mg/kg in quails and pigeons. Nevertheless, to determine the appropriate dosage regimen for treating coccidiosis in clinical practice, future study is required to assess the clinical effectiveness against coccidial infection. In addition, further research is warranted to evaluate the residues in tissues and estimate the withdrawal period of diclazuril in pigeons and quails.

DECLARATIONS

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Authors' contributions

Sara T. ELazab; Conceptualized the idea and methodology, conducted the experiment, analyzed the data, and wrote the draft and final manuscript. Iqra Zafar contributed to the data analysis and review of the manuscript. Nahla S. Elshater performed the laboratory analysis of plasma samples using HPLC and reviewed the draft of the manuscript. All authors have read and approved the final manuscript.

Availability of data and materials

The data sets generated for this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflict of interest.

Ethical consideration

All authors confirmed that the research adheres to ethical issues such as avoiding plagiarism, getting permission before publishing, avoiding misconduct, preventing data fabrication or falsification, refraining from double publication or submission, and avoiding redundancy.

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