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Pharmacokinetics and bioavailability of ceftiofur following intravenous and intramuscular administrations in broiler chickens

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ABSTRACT

The study focussed on pharmacokinetics and bioavailability of ceftiofur (CFT) after receiving a single dose (2 mg/kg BW) through either intravenous (IV) or intramuscular (IM) injection. Eight broiler chickens, were used in a crossover design with a washout period of two weeks to analyze the behaviour of CFT. Ceftiofur concentrations in the plasma were determined by HPLC with UV detector. The pharmacokinetics of CFT was analyzed using non-compartmental analysis. Following IV injection, CFT elimination half-life ($t_{1/2\beta}$) was 2.43 h, volume of distribution at steady state (Vd_{ss}) was 0.63 L/kg, and total body clearance (Cl) was 0.24 L/h/kg. Following a single intramuscular (IM) injection of CFT at the same dose, the drug was quickly absorbed into the bloodstream with an absorption half-life ($t_{1/2ab}$) of 0.31 h. The maximum concentration of the drug in the plasma (C_{max}) was 2.85 µg/mL and reached at a time (T_{max}) of 0.57 h after injection and the bioavailability (F) of CFT was 96.25%. The results of the study revealed that CFT was absorbed rapidly and showed high bioavailability when administered by IM route. This suggests that CFT has a promising disposition in chickens, and its use could help determine the best dosage regimens for effective eradication of various infections in chickens.

Keywords: Bioavailability, Ceftiofur sodium, Chickens, HPLC, Pharmacokinetics

Ceftiofur is a third-generation cephalosporin antibiotic that belongs to the class of β-lactam antibiotics. It is classified as a time-dependent antibiotic and is approved for use in various veterinary species (Hooper *et al*. 2016, Kilburn *et al*. 2016, Bonilla *et al*. 2021). CFT is known for its broad-spectrum activity against a variety of bacteria, including gram-positive and gram-negative aerobes and some anaerobes. Its effectiveness against a wide range of bacterial infections in birds makes it a valuable antibiotic (Flammer 2006, Ambar *et al*. 2023).

Currently, several antibiotic dosage regimens for exotic avian species are not supported by actual pharmacokinetic studies conducted in those species. Instead, many of these regimens are either based on empirical observations or extrapolated from data obtained from closely related bird species, poultry, or even mammals (Flammer 2006, Soh *et al.* 2022). Inter-species differences in anatomy and physiology can vary significantly even between closely related avian species. As a result, extrapolating drug dosages from one species to another can lead to sub-optimal drug doses that can cause treatment failure and the development of resistant bacterial strains, if doses are too low, or toxicity and potentially fatal outcomes if doses are too high. It is preferable to determine drug dosage regimens based on pharmacokinetic studies conducted in the same species (Toutain *et al*. 2002). Ceftiofur is obtainable in various formulations, which include ceftiofur sodium, ceftiofur crystalline-free acid, and ceftiofur hydrochloride (Zhang *et al*. 2019).

The pharmacokinetic properties of ceftiofur sodium have been recorded in goats (Courtin *et al*. 1997), sheep (Craigmill *et al*. 1997), pigs (Brown *et al*. 1999), elephants (Dumonceaux *et al*. 2005), camels (Goudah 2007), cattle (Brown *et al*. 1996, Brown *et al*. 2000, Woodrow *et al*. 2016), water buffalo (Nie *et al*. 2016), fish (Khalil *et al*. 2016), horses (Macpherson *et al*. 2017), and in exotic and domestic avian species (Tell *et al*. 1998), chickens (Amer *et al*. 1998), and ducks (Chung *et al*. 2007).

Considering the above facts, this study aimed to examine the pharmacokinetic properties of ceftiofur sodium in broiler chickens following a single intravenous (IV) or intramuscular (IM) dose administration.

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MATERIALS AND METHODS

Reagents and chemicals: The sterile powder for injection under the trade name Respifur® was supplied by ATCO PHARMA Co, Egypt. Each vial contained 1.105 g of ceftiofur sodium which is equivalent to 1.06 g of ceftiofur base. All other chemicals and reagents used in the study were of analytical reagent grade.

Experimental birds: The study used eight healthy Hubbard breed broiler chickens that were 40 days old and weighed between 1.9 to 2.4 kg. The chickens were obtained two weeks prior to the study and were acclimatized during this time period to ensure that they were free from residual drugs. During the acclimatization and treatment periods, the birds were fed a balanced commercial diet free from antibacterial agents and had access to water. The study was approved by the Research Ethical Committee of the Faculty of Veterinary Medicine at Cairo University, Egypt (Vet CU 01122022621).

Experimental design: Before drug administration, broiler chickens were weighed individually and given a precisely calculated dose of ceftiofur sodium. The study used a crossover design with a two-week washout period. Chickens were first given a single IV dose of CFT at 2 mg/kg BW, which was the same dose given to ducks and hens in other studies (Chung *et al*. 2007, Knafo *et al*. 2019). The injection was given into the left brachial vein. Two weeks later, the same chickens were given a single intramuscular (IM) injection of the same dose into the thigh muscles. Blood samples were collected from the right brachial vein at various time points, including immediately before medication (time = 0) and at several intervals afterward (0.08, 0.16, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h). Blood samples were gathered into tubes containing heparin, and the plasma was isolated by spinning it at 1,600 g for 10 min. The plasma was then taken out with a suction device and kept at a temperature of -20°C until it was analyzed.

Analytical method: HPLC with UV detector was employed to determine the presence of ceftiofur sodium and its associated metabolites in plasma samples. The separation process was carried out using a PLRP-S column with specific dimensions. Before usage, the mobile phase (composed of water with 0.1% formic acid and acetonitrile) underwent filtration and sonication and an injection volume of 20 µl was utilized alongside a flow rate of 0.3 mL/min. Peak detection was performed by scanning the eluate at 266 nm, while maintaining the column oven temperature at 40°C. The retention time for the eluted substances was around 11 min.

The method previously described by Altan *et al*. (2017) was used to measure CFT and desfuroylceftiofur (DFC) in plasma samples.

The average plasma recovery rate for CFT was 92%, while the intra-day and inter-day CV values ranged from 4.01 to 4.47% and 4.64 to 5.11%, respectively (measured three times over three days). The assay was found to be linear across concentrations ranging from 0.05 to 20 µg/mL, and the LOQ (0.1 µg/mL) and LOD (0.02 µg/mL) of the method were determined in plasma.

Pharmacokinetic analysis: The average plasma concentrations of CFT for each chicken at different sampling times following IV and IM administrations were expressed as mean±SE. The statistical moment theory was utilized to perform a non-compartmental analysis of the average concentrations (Gibaldi and Perrier 1982) using the computer program WinNonlin 6.1 (Pharsight, Mountain View CA, USA) to calculate the pharmacokinetic parameters. Pharmacokinetic parameters such as CL, V_{dss}, and MRT were calculated. The trapezoidal method was employed to determine the area under plasma concentration-time curve (AUC) and area under moment curve (AUMC):

$$MRT = AUMC/AUC \text{ and } CL = Dose/AUC$$

For each chicken, the plasma concentration vs. time curve was used to determine the C_{max} and T_{max} following IM injection. The bioavailability (F) was calculated using the equation:

$$F = AUC_{IM}/AUC_{IV} \times 100$$

RESULTS AND DISCUSSION

The pharmacokinetic profile of CFT following a single IV and IM injection of 2 mg/kg BW is depicted in Fig. 1 using semi-logarithmic plasma concentration-time curves. The mean±SE values of the pharmacokinetic parameters obtained from the curve fitting are presented in Table 1. The results showed that CFT had a positive disposition profile in chickens, and no adverse reactions such as tissue irritation, pain, or lameness were observed.

After IV injection in chickens, the half-life ($t_{1/2\beta}$) of CFT in chickens' plasma was 2.43 h, indicating a rapid elimination from the body. These data is quite similar to that reported for ceftiofur in lactating goats 2.86 h (Courtin *et al*. 1997), but longer than that of cefquinome in ducks 1.57 h (Yuan *et al*. 2011), chickens 1.29 h (Xie *et al*. 2013), gosling 1.73 h (Cheng *et al*. 2020), turkey 1.56 h (Elbadawy *et al.* 2021). In contrast, the half-life of

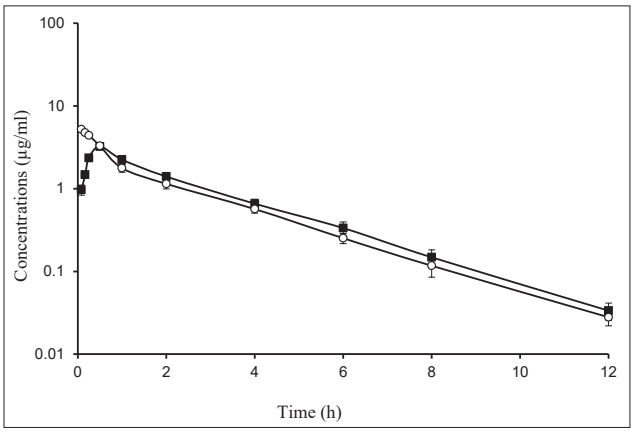

Fig.1. Semi-Logarithmic graph depicting the time-concentration of ceftiofur in broiler chickens following IV (○) and IM (■) administration of 2 mg/kg BW (n=8).

Table 1. Mean±SE plasma pharmacokinetic parameters of ceftiofur in broiler chicken following intravenous (IV) and intramuscular (IM) administration of 2 mg/kg body weight (n=8)

Parameter	Unit	IV	IM
C^0	µg/mL	5.95±0.13	—
$t_{1/2ab}$	h	—	0.31±0.005
$t_{1/2\beta(el)}$	h	2.43±0.08	2.45±0.05
AUC	µg·h/mL	8.21±0.27	7.90±0.27
AUMC	µg·h/mL	21.23±0.82	24.29±1.28
MRT	h	2.58±0.04	3.06±0.07
MAT	h	—	0.47±0.08
Vd_{ss}	L/kg	0.63±0.02	—
Cl_{tot}	L/kg/h	0.24±0.009	—
C_{max}	µg/mL	—	2.85±0.06
T_{max}	h	—	0.57±0.006
F	%	—	96.25±1.34

C^0, concentration at zero time (immediately after single IV injection); $t_{1/2ab}$, absorption half-life after IM administration; $t_{1/2\beta}$, elimination half-life after IV injection; AUC, area under plasma concentration-time curve; AUMC, area under moment curve, MRT, mean residence time; MAT, mean absorption time; Vd_{ss}, volume of distribution at steady-state; Cl_{tot}, total body clearance; C_{max}, maximum plasma concentration, T_{max}, time to peak plasma concentration; F, absolute bioavailability.

CFT in chickens is shorter than that of ceftiofur in sheep 4.86 h (Craigmill *et al*. 1997), camel 3.18 h (Goudah 2007), cat 11.29 h (Zhang *et al*. 2019), dogs 7.40 h (Yang *et al*. 2020), and black-bone silky fowl 3.19 h (Yang *et al*. 2021). These findings suggest that CFT is eliminated rapidly in chickens following IV administration.

The V_{dss} value reflects the extent of drug diffusion in the body tissues. According to the results of the current study, the V_{dss} value for CFT in broiler chickens was 0.63 L/kg. The value obtained for CFQ in the present study was similar to the value reported for cefquinome in turkeys, which was 0.54 L/kg (Elbadawy *et al*. 2021). The obtained value was higher than that recorded for ceftiofur in lactating and non-lactating goats, which were 0.31 L/kg and 0.25 L/kg, respectively (Courtin *et al*. 1997), camel 0.13 L/kg (Goudah 2007), cat 0.24 L/kg (Zhang *et al*. 2019), dogs 0.34 L/kg (Yang *et al*. 2020), black-bone silky fowl 0.33 L/kg (Yang *et al*. 2021), and cefquinome in ducks 0.41 L/kg (Yuan *et al*. 2011), chickens 0.49 L/kg (Xie *et al.* 2013), and gosling 0.43 L/kg (Cheng *et al*. 2020). These results imply that CFT has a restricted distribution in chickens after IV injection. Ceftiofur sodium is a weak acid with a pKa value of 3.7. When present in the bloodstream with a *p*H of 7.4, it exhibits limited lipid solubility, which may explain its inability to penetrate milk and the consequent restricted volume of distribution observed (Fernández-Varón *et al*. 2016).

The clearance (CL_{tot}) of CFT from the body was estimated to be 0.24 L/h/kg, which is comparable to the value reported for cefquinome in ducks at 0.22 L/h/kg (Yuan *et al*. 2011), longer than ceftiofur in camel 0.03 L/h/kg (Goudah 2007), cat 0.014 L/h/kg (Zhang *et al*. 2019), dogs 0.039 L/kg (Yang *et al*. 2020), black-bone silky fowl 0.073 L/kg (Yang *et al*. 2021), and shorter than cefquinome in chickens 0.35 L/h/kg (Xie *et al*. 2013), and gosling 0.45 L/h/kg (Cheng *et al*. 2020) and turkey 0.32 L/h/kg (Elbadawy *et al*. 2021). Taken together, the results suggest that CFT is rapidly cleared from the plasma of chickens after IV injection, indicating a fast elimination rate.

Following IM injection, CFT was rapidly absorbed in chickens as the $t_{1/2ab}$ was 0.31 h. This value closely resembles that of CFT in camels, which was 0.34 h (Goudah 2007), newborn calves 0.37 h (Altan *et al*. 2017), longer than ceftiofur in lactating goats 0.26 h (Courtin *et al*. 1997), cefquinome in ducks 0.12 h (Yuan *et al*. 2011), chickens 0.07 h (Xie *et al*. 2013), turkey 0.25 h (Elbadawy *et al*. 2021), and shorter than ceftiofur in pigs 1.45 h (Li *et al*. 2019). These results suggest that CFT is quickly absorbed and reaches a therapeutic level in the bloodstream of chickens, allowing for rapid onset of action.

The obtained value for the elimination half-life ($t_{1/2el}$) of CFT in chickens was 2.45 h, which is very similar to the value reported for ceftiofur in lactating goats 2.60 h (Courtin *et al*. 1997), cefquinome in ducks 1.79 h (Yuan *et al*. 2011), chickens 1.35 h (Xie *et al*. 2013), gosling 1.40 h (Cheng *et al*. 2020), turkey 1.71 h (Elbadawy *et al*. 2021), and shorter than ceftiofur in sheep 7.65 h (Craigmill *et al*. 1997), dogs 7.40 h (Yang *et al*. 2020), and black-bone silky fowl 3.36 h (Yang *et al*. 2021).

The administration of a single IM dose of ceftiofur sodium at 2 mg/kg resulted in plasma concentrations that surpassed the MIC_{90} for the majority of susceptible pathogens. The maintenance of antibiotic concentrations above the MIC in both plasma and tissues is the pharmacodynamic factor that is associated with the clinical effectiveness of ceftiofur, as stated (Toutain *et al*. 2002).

The C_{max} 2.85 µg/mL and T_{max} 0.57 h of CFT in chickens were found to be similar to those reported for cefquinome in turkeys (Elbadawy *et al*. 2021), lower than those of ceftiofur in lactating goats 4.57 µg/mL at 1.17 h (Courtin *et al*. 1997), sheep 7.31 µg/mL at 0.81 h (Craigmill *et al*. 1997), camel 10.34 µg/mL at 1.22 h (Goudah, 2007), pigs 11.23 µg/mL at 2.35 h (Li *et al*. 2019), and black-bone silky fowl 3.36 µg/mL at 1.67 h (Yang *et al*. 2021), and for cefquinome in ducks 9.38 µg/mL at 0.38 h (Yuan *et al*. 2011), gosling 3.40 µg/mL at 0.20 h (Cheng *et al*. 2020).

The percentage of CFT that enters systemic circulation (F) following IM injection in chickens was found to be 96.25%, which is comparable to the reported value of 97.4% for ceftiofur in camels (Goudah 2007), and black-bone silky fowl 93.03% (Yang *et al*. 2021), and for cefquinome in chickens 95.8% (Xie *et al*. 2013), ducks 93.3% (Yuan *et al*. 2011), turkey 95.6% (Elbadawy *et al*. 2021), higher than for cefquinome in duckling 67.5% (Cheng *et al*. 2020), black swans 74.2% (Zhao *et al*. 2017), and lower than for cefquinome in goslings 113.9% (Cheng *et al*. 2020). The results of this study indicate that CFT is rapidly and effectively absorbed following

IM administration in chickens. This is likely due to its zwitterionic property, which allows it to easily traverse cell membranes.

Variations in the disposition of CFT by different species of poultry are often observed, and can be attributed to differences in factors such as metabolism, measurement techniques, dosage, time intervals between blood samples, as well as the health and age of the animals (Toutain *et al*. 2010).

Beta-lactam antibiotics such as CFT exhibit time-dependent killing activity, and the MIC is an indicator of their effectiveness against pathogens (Drusano 1998). The percentage of time that the drug concentration remains above the MIC is the most useful and reliable parameter for determining their therapeutic efficacy (Altan *et al*. 2017). Despite its potential benefits, the use of CFT in chickens has not been widely adopted in the field. This is because of the lack of pharmacokinetic studies and minimal inhibitory concentration (MIC) data for pathogenic bacterial strains in chickens. According to Drusano (2004), the duration of cephalosporin concentration exceeding the minimum inhibitory concentration (MIC) is crucial for achieving successful clinical outcomes. Different studies have proposed varying durations for maintaining plasma concentrations above the MIC, but it is generally accepted that the drug concentration should be above the MIC for half of the dosing interval (Drusano 2004). In a study conducted by Hope *et al*. (2012), the minimum inhibitory concentrations (MICs) of CFT for bacteria obtained from various bird samples were examined. They found that bacterial isolates such as *Enterobacter* spp*., Klebsiella* spp*., Pasteurella* spp*., Proteus* spp*., Serratia* spp., and *Staphylococcus aureus* had a ceftiofur MIC_{90} of ≤1.0 µg/mL. For *E. coli, Klebsiella* spp*., Proteus* spp*., Salmonella* spp., and *S. intermedius*, the ceftiofur MIC_{90} values ranged from 0.5 to 1.0 µg/mL. On the other hand, *Citrobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Pseudomonas* spp., coagulase-negative *Staphylococcus* spp. and *Streptococcus* spp. had ceftiofur MIC*90* values >4.0 µg/mL, according to previous studies by Watts *et al*. (1993) and Salmon and Watts (2000). Nonetheless, MICs of ≤0.6 µg/mL of CFT have been shown to have potent antibacterial effects against many pathogenic bacteria (Al-Kheraije 2013). Therefore, based on the results of the present study and this information, administering 2 mg/kg BW of CFT IM twice daily to broiler chickens would be effective against various susceptible bacterial strains.

The absence of adverse effects and local reactions, along with rapid absorption, high IM bioavailability, and concentrations exceeding the MICs for most of poultry pathogens, suggest that repeated IM administration of ceftiofur at a dose of 2 mg/kg twice daily may be effective against susceptible bacteria in chickens. More studies are required to develop a dosing regimen for multiple administrations, to assess the clinical effectiveness of the drug, and determine the drug's residue concentrations in chicken tissues.

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