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ORAL BIOAVAILABILITY OF CEFADROXIL IN HEALTHY BROILER CHICKENS

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ABSTRACT

The pharmacokinetic parameters of cefadroxil (20 mg/kg bwt) were studied following single intravenous (IV) and oral (PO) administrations in healthy broiler chickens. Following a single IV injection of cefadroxil at a dose of 20 mg/kg bwt in healthy chickens, cefadroxil could be detected therapeutically for 24 h. The serum concentration–time curve of cefadroxil following IV injection showed that, the drug obeyed a two compartments open model and the elimination half-life ($t_{0.5\beta}$) was 4.85 h, volume of distribution (Vd_{ss}) was 629 ml/kg and total body clearance (CL_{tot}) of cefadroxil was 0.185 L/h/kg). Following a single PO administration of 20 mg cefadroxil /kg bwt in healthy chickens, the peak serum concentration (C_{max}) was 15.59 µg/ml was achieved at a maximum time (T_{max}) of 1.47 h. The oral bioavailability of cefadroxil in healthy chickens was 77.18%.

KEYWORDS: Pharmacokinetics, cefadroxil, chickens.

INTRODUCTION

Cephalosporins antibacterial group acts by inhibition of bacterial cell wall synthesis and are typically more resistant to deactivation by β-lactamases.[1] The efficacy of cephalosporins, in common with other b-lactam compounds, is closely related to the time over which the active drug concentration exceeds the bacterial minimum inhibitory concentration (t > MIC).[2] 1Cefadroxil, is a first generation semisynthetic cephalosporin intended for oral administration. *In vitro*, it exhibits activity against most strains of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, Klebsiella sp., and both penicillin-susceptible and

resistant *Staphylococcus aureus*.[3] Cefadroxil has long-acting therapeutic effect, high solubility and relatively broad spectrum of anti-bacterial activity.[4] It is used to treat urinary tract infections,[5] skin and soft tissue infections,[6] pharyngitis,[7] and tonsillitis.[8] Cefadroxil has low plasma protein binding (~20%) and good oral bioavailability of at least 90%.[9,10] Renal excretion is the primary route of elimination, with more than 90% of the orally administered drug being excreted unchanged in urine over 24 hours.[11] However, this study was done to investigate several data about pharmacokinetics of cefadroxil in chickens. Therefore, the aim of present work was undertaken to study the pharmacokinetic parameters of cefadroxil after IV injection and PO administration in healthy chickens. Also, the bioavailability of cefadroxil was calculated after PO administration in healthy chickens.

MATERIAL AND METHODS

Drug

Cefadroxil was used in this study was obtained as a pure powder (98% purity) from SmithKline Beecham, Giza, Egypt. One gram of cefadroxil monohydrate powder was dissolved in 2.5 ml of methanol, then complete till 10 ml by sterile water for injection; each 1 ml of the final solution contains 100 mg cefadroxil.

Experimental birds

Five clinically Healthy Hubbard chickens weighting about 1500 to 2000 gm. Chickens were chosen randomly from poultry farm from Qalubia government, Egypt. Chickens were feed balanced ration free from antibiotics and were kept two weeks before starting the experiment to ensure a complete excretion of any drug from bodies of used chickens. Feed and water free from antibacterial additives were provided *ad-libitum.*

Experimental design

Five healthy chickens were injected cefadroxil at a dose of 20 mg/kg bwt by IV route into the right wing vein. These chickens were left for 15 days after the IV injection to ensure complete elimination of cefadroxil from their bodies and then administered the same dose by PO route to determine the bioavailability of cefadroxil in healthy chickens.

Blood samples

About one milliliter of blood was taken from the left wing vein, following administration of cefadroxil. Blood samples were collected at 5, 10, 25, 30 minutes, 1, 2, 4, 6, 8, 12, 24 hours after single IV and PO administration of cefadroxil. All blood samples were collected in

sterilized test tubes and allowed to clot. Serum was separated by centrifugation for 15 minutes at 3000 r.p.m. Sera were kept frozen until assayed.

Analytical Procedure

Cefadroxil was assayed in chicken's serum and distilled water by using microbiological method using *Bacillus subtilis* ATCC 6633 as test organism for cefadroxil.[12] The test organism was obtained from Department of Microbiology, Animal Health Research Institute, Dokki, Giza, Egypt. Three plates were used for each sample. One well in each plate was filled with reference concentration (12.5 µg/ml of cefadroxil in distilled water or normal chicken's serum). The plates were incubated at 37^{o}c for 24 h then the diameter of inhibitory zones was measured. The average diameter of inhibition zone of the samples was corrected by using the diameter of the reference concentration. From the standard curve, the concentration corresponding to the correct values of the zone diameter were obtained.

Pharmacokinetic analysis

Pharmacokinetics parameters were calculated by WinNonlin 6.3 program (Pharsight, Mountain View CA, USA).

RESULTS

Following a single IV injection of 20 mg/kg bwt in healthy chickens, cefadroxil could be detected therapeutically for 24 h post IV injection. The plasma concentration-time curve of cefadroxil following IV injection showed that the drug obeyed a two compartments open model. The disposition kinetics of cefadroxil following a single IV and PO administration were recorded in table (1) and showed in figure (1).

Table 1: Mean ± SE serum pharmacokinetic parameters of cefadroxil in healthy chickens following IV and PO administration of 20 mg/kg bwt (n=5).

Parameter	Unit	V	PO
α (k_{ab})	h^{-1}	3.85 ± 0.11	0.98±0.03
$t_{1/2\alpha}$ ($t_{1/2ab}$)	h	0.18 ± 0.005	0.71 ± 0.02
β (k_{el})	h^{-1}	0.14 ± 0.005	0.124 ± 0.003
$t_{1/2\beta}$ ($t_{1/2el}$)	h	4.85 ± 0.17	5.58 ± 0.15
AUC	µg ml^{-1} h^{-1}	108.17 ± 3.31	83.43 ± 2.21
AUMC	µg ml^{-1} h^{-2}	366.87±12.04	472.44±25.36
MRT	h	3.39±0.02	5.64±0.17
MAT	h	—	2.25±0.16
V_{dss}	L kg^{-1}	0.629±0.01	—
Cl_{tot}	l kg^{-1} h^{-1}	0.185±0.005	—
C_{max}	µg ml^{-1}	—	15.59 ± 0.12
t_{max}	h	—	1.47 ± 0.009
F	%	—	77.18±0.78

α; β hybrid rate constant representing the slope of distribution and elimination phase after IV injection; K_{ab}; Kel absorbtion and elimination rate constant after PO administratin; $t_{1/2(\alpha)}$ distribution half-life after IV injection; $t_{1/2(ab)}$ absorption half-life after po administration; $t_{1/2(\beta)}$ elimination half-life after IV injection; $t_{1/2(el)}$ elimination half-life after po administration; AUC area under concentration-time curve; AUMC area under moment curve; MRT mean residence time; MAT mean absorption time; V_{dss} volume of distribution at steady state; Cl total body clearance. C_{max} maximum serum concentration; T_{max} time to peak serum concentration; F fraction of drug absorbed systemically after po adminstration.

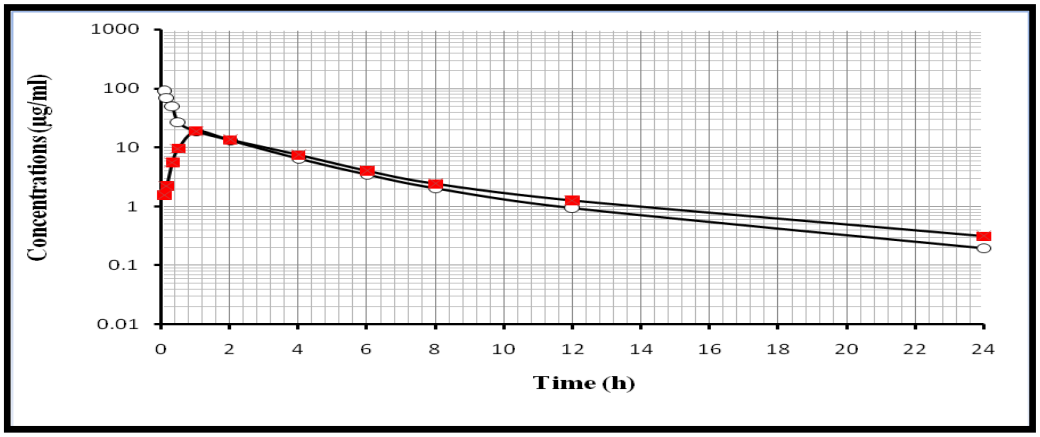

Figure 1: Semi-Logarithmic graph depicting the time-concentration of cefadroxil in serum of broiler chickens after a single IV (○) and PO (■) administration of 20 mg/kg bwt (n=5).

DISCUSSION

The kinetic parameters of cefadroxil following a single intravenous injection of 20 mg/kg b.wt. in normal chickens indicated that serum concentration of cefadroxil obeyed two compartments open model; a compartment of serum and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for cefquinome in chickens,[13] and cefequinome in sheep and goats,[14] cefotaxime in muscovy ducks,[15] cephradine in chickens,[16,17] and cefoperazone in camels.[18] Cefadroxil was transferred from central to peripheral compartment at a higher rate (K_{12}=2.04 h^{-1}) than its passage from peripheral compartment to central compartment (K_{21}=0.92 h^{-1}). On the other hand, these values were higher than that reported for ceftiofur in cows (K_{12}=0.47 h^{-1}) and (K_{21}=0.96 h^{-1}).[19] And ceftiofur in chickens (K_{12}=0.27 h^{-1}) and (K_{21}=0.99 h^{-1}).[20]

The elimination half-life [$t_{0.5(\beta)}$] of cefadroxil following a single intravenous injection of 20 mg/kg b.wt. was equal to 4.85 h. This observation was nearly similar to data reported for cefepirome in cow calves (2.41 h).[21] On the other hand, it was shorter than those showed for ceftiofur in chickens (5.47 h).[20] The V_{dss} is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions**.** The V_{dss} for cefadroxil was 629 ml/kg (0.62 L/kg) suggesting higher penetration through biological membranes and tissue distribution after intravenous administration in broiler chickens. The obtained value was higher than the data reported after intravenous administration of cephradine in goat (142.4 ml/kg).[22]

The rate of total body clearance [CL_{tot}] of cefadroxil following intravenous injection was 0.185 L/kg/h. This value was higher to the values reported for ceftiofur in cows (0.051 L/kg/h),[19] and cefepime in goats (0.098 L/kg/h).[14]

Following a single oral administration of 20 mg/kg b.wt. the drug reached its maximum concentration (18.91 µg/ml) at 1 hour and could be detected in serum in therapeutic level 0.31 µg/ml for 24 hours. In the present study, cefadroxil was rapidly absorbed from gastrointestinal tract of chickens after single oral administration with a short absorption half-life [$t_{0.5(ab)}$=0.71 h] . This value higher than that reported for cefquinome in rabbits (0.26 h)**.**[23]

Maximal serum concentration (C_{max}) (15.59 µg/ml) achieved at (t_{max}) 1.47 h. These value were higher to those recorded for cefquinome in rabbits (C_{max}; 8.12 µg/ml) and (t_{max}; 1.01 h).[23]

The elimination half-life **[**$t_{0.5(el)}$] expresses the overall rate of elimination of the drug and allows the predication of drug accumulation. The $t_{0.5(\beta)}$ after oral administration was 5.58 h**.** These value is longer than those reported for cefquinome in rabbits (2.32 h).[23]

The bioavailability of cefadroxil in normal chickens, which estimated the rate and extent of the dose entered the systemic circulation after oral administration was 77.18%. This percent indicated a good absorption of cefadroxil after oral administration. This value was lower to those recorded for ceftiofur in ducks (89.54%).[24] On the other hand, this value was higher than the bioavailabilities recorded for cephalosporins as cephradine in goats (73.9%).[22] Protein binding has long been considered one of the most important physicochemical

characteristics of drugs, playing a potential role in distribution, excretion, and therapeutic effectiveness as a low protein binding generally enables a rapid and extensive distribution into the intracellular and extracellular space. In this study, the *in vitro* plasma protein binding experiment showed that cefadroxil displayed a low level of binding to plasma proteins (10.09%) to broiler chicken serum. The results of *in vitro* protein binding of antibiotics vary considerably depending upon the method and experimental conditions**.** This value was nearly similar to these reported value of 13.3% for ceftazidime in rabbits.[25]

CONCLUSIONS

The oral bioavailability of cefadroxil is excellent, so it is recommended to be used against bacterial infection in chickens.

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