Pharmacokinetics And Residues Of Ciprofloxacin In Broiler Chickens

Zaki. R.H. and Fatma El-Sayed Gaber
Animal Health Research Institute, Zagazig Branch

ABSTRACT

The pharmacokinetic properties of ciprofloxacin were determined in broiler chickens after single I.V. and orally administered doses of 10 mg/kg b. wt . After I.V. and oral administration the plasma concentration-time curve was characteristic of two compartment open model. After single oral administration, ciprofloxacin was absorbed slowly by time to reach maximal plasma concentration of 2.45 ± 0.07 ug/ml after 1.65 ± 0.05 hours. Oral bioavailability was found to be 65% ± 0.3. Significant difference between the two routes of administration was found for the pharmacokinetic variables, half- lives of the distribution and elimination phase and apparent volume of distribution.

Residues of ciprofloxacin in plasma, fat, kidney, liver, lung, muscle, and skin were measured in chicken that received an oral dose of 10 mg/kg once daily for four days. The results indicated, that ciprofloxacin residues were cleared slowly. Mean liver concentration was 0.025 ug/g, persisted up to day 12 in chickens after dosing .

INTRODUCTION

Ciprofloxacin is a new fluoroquinolone antimicrobial developed exclusively for use in animals. Similar to other quinolones the bactericidal activity of ciprofloxacin is mediated by affecting bacterial DNA gyrase, *(1)* Ciprofloxacin inhibits DNA gyrase by interacting with DNA *(2)* Because of its broad spectrum activity, ciprofloxacin has potential therapeutic application for many types of infection, *(3)* The antimicrobial properties of ciprofloxacin indicated that it might have advantages for use in poultry. A major use of this drug is for treatment of pasteurellosis, secondary respiratory colibacillosis and Mycoplasmal infection in chickens and turkeys, *(4)* Limited information is available on pharmacokinetic of ciprofloxacin in chickens, *(5).*

The objectives of the study were to determine plasma disposition of ciprofloxacin after I.V and oral administration in chickens and tissue depletion.

MATERIALS AND METHODS

Chickens

Thirty four, 35 day old (2kg) Hubbard broiler chickens were used They were placed individually in cages. Chickens were apparently healthy showing no clinical signs of disease .

Drug

Ciprofloxacin was donated by Bayer AG, Lever Kusen, Germany .

(doses 10 mg / kg b. wt.). ciprofloxacin chlorhidrate was dissolved in distilled water to a total volume of 0.5 ml or 2 ml before I.V. and oral administration, respectively .

Experimental design

The birds were divided in to 3 groups chickens of groups 1 and 2 (8 chicken/ group) were given singl 1.V and oral doses of 10 mg ciprofloxacin/kg body weight. Chickens of group 3 (n:18) were given daily dosage of 10 mg ciprofloxacin/ kg orally for 4 successive days.

Ciprofloxacin was administered IV into the right brachial vein of group I chickens and was administered orally directly into the crop of chickens of group 2 and 3.

Blood samples were taken from the left brachial vein of each chicken of group 1 and 2 and collected in heparinized syringes at 0.16 , 0.25 , 0.5 , 1. 2, 4, 6, 8, 12 and 24 hours after drug administration. Plasma was separated after centrifugation and was stored frozen until analyzed. Ciprofloxaicin concentration in the plasma of chickens was measured.

All chickens in group 3 were slaughtered (6 chicken at each time) on the 1st, 6th and 12th days after the last dose.

Blood, fat, kidney, liver, lung, muscles and skin specimens were obtained . Each of the tissue specimens was weighed and kept frozen until assay for ciprofloxacin concentration.

Drug assay

Plasma and tissue concentration of ciprofloxacin was measured by use of an agar – well diffusion biological assay with *Bacillus subtilis* as the test organism *(6)* . A standard curve of 10 to 0.003 ug of ciprofloxacin / ml of chicken plasma was used to calculate plasma and tissues concentrations in the treated chickens .The value of parmacokinetic parameters was calculated *(7& 8)*.

RESULTS

Plasma concentrations of ciprfloxacin obtained are single IV and oral administration of 10mg/kg were determined (Fig. 1). After each route of administration, the plasma concentration-time curve indicated a biphasic decrease. Good fit of the observed data to a two- compartiment open model was obtained. The values for the kinetic parameters that described the absorption and disposition kinetics of ciprofloxacin in chickens were determined Table (1).

After IV administration of ciprofloxacin (10mg/kgb.wt), drug concentration in plasma at 10 minutes was 24.06 ± 0.43 ug/ml and the concentration exceeding 0.5 ug/ml persisted about 12 hours. (Fig. 1) ciprofloxacin was distributed more quickly after IV than after oral dosing ($t_{1/2}\alpha$ 0.07 ± 0.001 and 1.43 ± 0.10 . hours $t_{1/2}\beta$ respectively). Values for obtained for IV and oral administration indicated final disappearance of the drug from blood ($t_{1/2}\beta$ 10.29 ± 0.45 and 14.23 ± 0.43 ug/ml respectively) Table (1).

Ciprofloxacin was slowly and partially absorbed after oral administration of 10mg/kg ($t_{1/2}$ a 0.67 ± 0.05 hour , F , 65.0 ± 0.03 %). The value for T_{max} in plasma was 1.65 ± 0.05 hour, and C max for the 10 mg/kg was 2.45 ± 0.07 ug/ml.

Ciprofloxacin (oral dose of 10 mg/kg for 4 days) was efficiently distributed to tissues. Residues of ciprofloxacin were determined in plasma and tissues after oral administration of the drug (Table 2). Ciprofloxacin was not detected in plasma on 6th and 12th day after treatment, but the drug was eliminated more slowly from tissues than from plasma. At the time of slaughter (12 days) ciprofloxacin residues was only detected in liver.

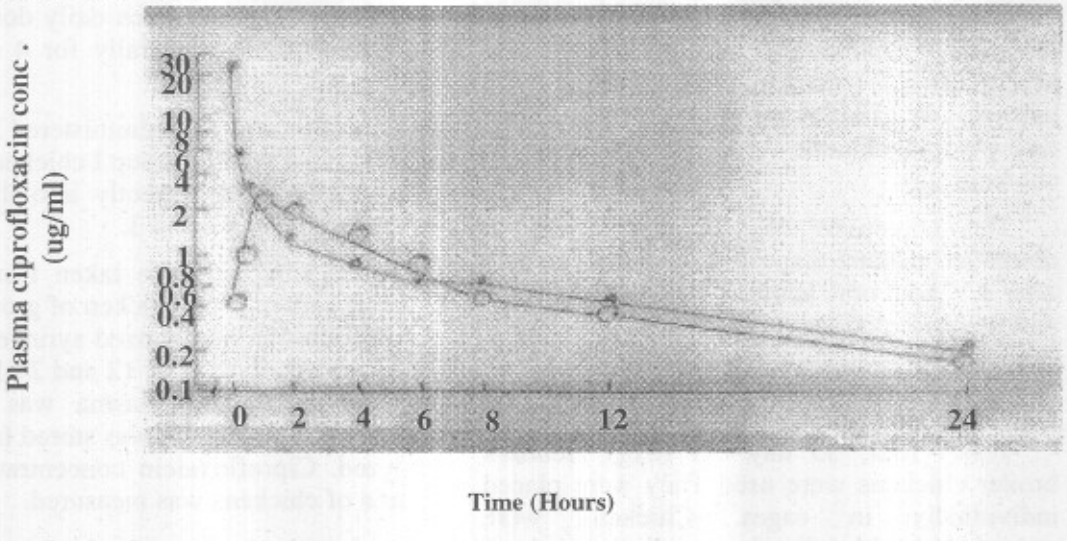

Figure 1. Plasma concentration of ciprofloxacin after single IV (•) and oral (o) administration of 10mg/kg of body weight.

Table 1. Ciprofloxacin pharmacokinetic parameters in 8 chickens after single IV and oral administration of 10 mg/kg of body weight.

Parameters	Route of administration	
	I.V	Oral
α (h^{-1})	9.72±0.18	0.50±0.03
β (h^{-1})	0.068±0.003	0.049 ±0.002
$t_{1/2}$ α(h)	0.07 ±0.001	1.43 ±0.10*
$t_{1/2}$ β	10.29 ±0. 45	-14.23 ±0.46*
$t_{1/2}$ a(h)		0.67 ±0.05
$Vd_{(area)}$ (L/kg)	4.31 ±0.15	5.94 ±0.20*
$Vd_{(ss)}$ (L/kg)	2.77 ±0.09	4.41 ±0.16*
K_{10}(h^{-1})	3.46 ±0.09	0.22 ±0.02
CL(L/h/kg)	0.29 ±0.01	0.288 ±0.001
F (%)		65.0 ±0.03
C_{max} (ug/ml)		2.45±0.07
T_{max} (h)		1.65 ±0.05

*** Significant at (P<0.05)**

α = hybrid rate constant for distribution phase.

β = hybrid rate constant for terminal elimination phase.

$t_{1/2}$ α= half life at α phase- $t_{1/2}$ β= half life at β phase.

$t_{1/2}$ a absorption half life $Vd_{(area)}$ = apparent volume of distribution

$Vd_{(ss)}$ = volume of distribution at steady state, K_{10} = elimination rate constant, Cl= total plasma clearance, F= bioavailability, C_{max}= Maximal Conc. in plasma after oral administration and T_{max}= time needed to reach C_{max}

Table 2. Plasma and tissue concentrations (ug/g) of ciprofloxacin administered orally at a dose of 10mg/kg for 4 successive days (mean ± SE).

Time after last dose	Plasma	Fat	Kidney	Liver	muscle	skin	lung
1st day	0.22±0.04	0.35± 0.04	0.91±0.08	0.99± 0.11	0.54± 0.4	0.79± 0.23	0.66± 0.11
6th day	-	-	0.32±0.05	0.41± 0.10	-	0.30± 0.04	0.15± 0.1
12th day	-	-	-	0.025±0.003	-	-	-

DISCUSSION

Disposition of ciprofloxacin after IV and oral administration in chickens could be described adequately by a two- compartment model.

Experiments were performed by others in birds *(9)* and in mammals *(10)*. The disappearance of the drug from the plasma of chickens was characterized by an initial rapid distribution phase followed by a slower eliminiation phase.

Ciprofloxacin was distributed rapidly and widely in the body, as evidenced by large $t_{1/2}$ α ,$Vd_{(area)}$ and $Vd_{(ss)}$ values (Table 1). Ciprofloxacin has a longer $t_{1/2}$ β in chickens

than in other species of birds. The $t_{1/2}\beta$ of ciprofloxacin after oral administration to chickens at dosage of 10 mg/kg was greater than the value reported in turkeys *(5)*. In this study, the rate of elimination was influenced by the route of administration. With oral dosing, the $t_{1/2}\beta$ estimated (14.23 hours) was significantly greater than that (10.29 hours) obtained after I.V. dosing. This difference is probably the result of continued absorption of ciprofloxacin from the gastrointestinal tract during the elimination phase, thereby, prolonging the $t_{1/2}\beta$ of the drug.

The $t_{1/2}\beta$ for oral dosing of ciprofloxacin was more than three folds greater than that in calves *(10)*. This finding is in agreement with that reported for norfloxacin treated broiler chicken *(11)*. The $Vd_{(area)}$ in chicken of this study was high (2.77 L/kg). This value differs greatly from that found in rabbits *(12)* it was 0.93 L/kg. In addition, estimation of $Vd_{(area)}$ (4.31 L/kg) for ciprofloxacin in chickens of this study was nearly similar to the calculated $Vd_{(area)}$ in poultry *(5)*. The large $Vd_{(area)}$ of ciprofloxacin in chickens indicates that the drug is widely distributed extra vascularly in chickens.

Ciprofloxacin when given orally was slowly and incompletely absorbed from the gastrointestinal tract.

The bioavailability of the drug was 65% after oral administration of 10mg/kg. The bioavailability reported here was considerably less than that previously reported in chickens (84%) *(13)*.

In our study, ciprofloxacin when given orally at a dosage of 10mg/kg resulted in C_{max} of 2.45 ug/ml (T_{max} 1.65 hours), drug concentration in plasma at 30 minutes of 1.06 $\pm$ 0.07 ug/ml persisting about 12 hours. On the basis of our findings, 10 mg of ciprofloxacin /kg given orally every 12 hours should provide ciprofloxacin tissue concentration effective against infective pathogens responsible for most of the morbidity and mortalilty.

We studied a dosing regimen of 10mg/kg once daily for 4 successive days to estimate tissues depletion of ciprofloxacin, Ciprfloxacin was high initially then decreased by time.

The preslaughter withdrawal time was more than 12 days, should be appropriate in the food- producing animals.

REFERENCES

1. ***Anadon A, and Martinez – Larrahaga MR,. (1992a):*** Pharmacology and Toxicology of quinolones In Sunshine 1st .ed Recent Development in Therapeutic Drug Monitoring and Clinical Toxicology. New York Marcel Dekker Inc, 193-198.

2. ***Shen LL, and Pemet Ag (1985):*** Mechanism of inhibition of DNA gyrase by analogues of nalidixic acid and the target of the drug is DNA proc Natl Acad Sci USA 82, 307-311.

3. ***King K, Riond JL, and wanner M.(1993):*** Pharmacokinetic of enrofloxacin and its metabolite ciprofloxacin after intravenous and oral administration of enrofloxacin in dogs J.Vet. Pharmacol Ther; 16-462-468.

4. ***Bauditz R. (1987):*** Result of clinical studies with Baytril in poultry Vet Med Rev. 2; 130-136.

5. ***Conzelman GM, McMillan R.A. and Baggot JD(1986):*** Pharmacokinetics of 1-Cyclopropyl – 6- fluoro 1.4 dilydro-4- oxo – 7- (4-ethyl 1- piperiazinyl) –3- quinl carboxilic acid in chickens Pro West Pharm Soc; 30,393-395.

6. ***Arret B; Johansan D and Kirshown A (1971):*** outline of detail for microbiology assay of antibiotics. Second resision J. of Pharm. Science 60,1689-1994.

7. ***Baggot J.D. (1977):*** principles of Drug Disposition in Domestic Animals. The Basis of Veterinary Clinical Pharmacology P34 saunders. Philadelphia.

8. ***Yamaka K, Nakagawa T, and Uno, T (1978):*** Application of Akaike's information criterion (A/C) in the

evaluation of linear pharm-acokinetic equation. J. Pharmacokientic Biopharm 6, 165-175.

9.Flammer K, Aucoin Dp, and Whitt DA. (1991): Intramuscular and oral disposition of enrofloxacin in African Grec Parrots following single and multiple doses . J Vet Pharmacol Ther, 14; 359-366.

10.Davidson JN, Conzelman GM, and Baggot JD (1986): Pharmacokinetics of 1-Cyclopropyl –6- Fluoro- 1.4 dihydro – 4-oxo – 7- (4-ethyl – 1- piperazinyl) –3-quinoline carboxylic acid (CFPQ) in preruminant and ruminant calves Proc West pharmacol Soc 29; 129-132.

11.Anadon A, Martinez-Larrahaga MR. and Velez C., (1992[b]): Pharmacokinetics of norfloxacin and its N-desethyl and oxy metabolites in broiler chickens Am J.Vet. Res 53-2084-2089.

12.Boome Rl, Books DL, and Babish JG (1991): Pharmacokinetic properties of enrofloxacin in rabbits Am. J vet Res; 52; 1835-1841

13.Conzelman GM, Babish JG, and Davidson jn, (1987): Pharma- cokinetics of 1-Cyclopropyl –6- fluoro, 1.4 dihydro – 4-Oxo – 7-(4- ethyl –1- piperzing L)-3-quinolone – carboxylic acid in chicken Proc West Pharmacol Soc; Zg, 321-323.

الملخص العربي

دراسة مسار السيبروفلوكساسين ومتبقياته في دجاج التسمين

رضا حسن زكي ، فاطمة السيد جابر
معهد بحوث صحة الحيوان بالزقازيق

تم دراسة الخواص الفارماكوكينيتيكية لعقار السيبروفلوكساسين في دجاج التسمين بعد إعطاء جرعة واحدة بالوريد و أخرى بالفم بمعدل ١٠ مليجرام/ كيلوجرام من وزن الجسم.

وقد وجد إنه بعد الحقن الوريدي والفم السيبروفلوكساسين سلك منحنى التركيز في الدم مقابل الزمن مسلك النموذج ثنائي الحجرات. وكان امتصاص الدواء بعد الحقن الفمي بطيئاً حيث وصل أعلى منسوب للعقار في الدم (C_{max}) ٠,٠٧ ± ٢,٤٥ ميكروجرام/ مللي بعد (T_{max}) ٠,٠٧ ± ١,٦٥ ساعة وكانت الإتاحة الحيوية ٠,٣% ± ٦٥% وقد وجد أن هناك إختلاف معنوى بعد الحقن بالوريد وإعطائه بالفم في كل من فترة عمر النصف لتوزيع وإخراج العقار $t_{1/2}\ \alpha$ ، $t_{1/2}\ \beta$ وحجم توزيع العقار بطرق $Vd_{(area)}$ ، $Vd_{(ss)}$ وتم قياس تركيز متبقيات عقار السيبروفلوكساسين في دجاج التسمين بالدم والدهون والكبد والكليتين والرئة والعضلات والجلد بعد إعطاء العقار بمعدل ١٠ملجرام/كيلو جرام من وزن الجسم مرة يومياً لمدة ٤ أيام بالفم.

وقد أثبتت الدراسة ان عقار السيبروفلوكساسين انسحب ببطء من الجسم حيث بلغ معدل تركيز العقار بالكبد ٠,٠٢٥ ميكروجرام/ جرام في اليوم الثاني عشر من أخر جرعة .