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Some pharmacological studies of cephradine in broilers

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The pharmacokinetic aspects of cephradine were studied after intravenous (IV), intramuscular (IM), subcutaneous (SC) and oral administration of a single dose of 50 mg kg-1 b.wt. in chickens. Tissue distribution and residues of cephradine after repeated oral administration for 5 consecutive days were also estimated. After IV injection of cephradine in a dose of 50 mg kg-1 b.wt., the serum concentration time curves were best described by a two compartment-open model. The drug was rapidly distributed with a distribution half-life (t0.5(α)) of 0.120 h and apparent volume of distribution (Vdss) was 2.187 L kg-1. The drug was rapidly eliminated with a half-life of elimination (t0.5(β)) of 1.047 h and the body clearance (ClB) was 2.35 L kg-1 h-1. The drug was rapidly absorbed after IM, SC and oral administration as indicated by short half-lives of absorption (t0.5(ab)) of 0.154, 0.364 and 0.65 h., respectively. While the elimination half-lives (t0.5(el)) and systemic bioavailabilities were 0.859, 2.652, 1.74 h and 59.386, 84.5, 97.97 %, respectively. Repeated oral administration of cephradine (50 mg kg-1 b.wt twice daily) for 5 consecutive days caused no change in serum enzyme activities of ALT and AST but induced a significant increase in serum uric acid concentration at 72 to 120 hours post administration.

Cephalosporins are well known and very useful classes of antibiotics widely used in veterinary medicine for preventing and treating bacterial infections (Becker *et al*., 2004). They are described as *β*-lactam antibiotics, based on their common structural feature, containing the *β*-lactam ring. A major advantage of the *β*-lactam antibiotics is the high degree of safety in the target animal (Preston, 1992). Cephradine is first generation cephalosporin that can be administered by the oral route. It has been used successfully in treating of the respiratory tract, soft tissue and urinary tract infections (Quintilani *et al*., 1982). The present work is under taken to study the pharmacokinetics of cephradine after single IV, IM, SC and oral dose in chickens and to determine the tissue residues of the drug after repeated oral doses and to examine its effect on liver and kidney functions. The effect on some field bacterial isolates affecting chicken was also investigated.

Materials and methods

Drug. Cephradine was obtained from Bristol-Myers Squibb Company, Cairo, Egypt as (velocef)®.

Chickens. Fourty eight birds of both sexes with an average body weight from 1.280-2.800 kg and from 4-12 months old were used for pharmacokinetic studies and twenty four one-day old Fayoumy chicks were used for pharmacodynamic studies. These birds were obtained from El-Azab project for poultry production in Fayoum Governorate. The chickens were fed on a balanced commercial ration and water *ad-libitum*. They were kept under good hygienic conditions and left for 15 day before the experiment for acclimatization and ensuring complete clearance of their bodies of any antibacterial drug.

Experimental protocol. Single dose pharmacokinetic studies were done on fourty eight chickens which classified into four groups (each of 12 chickens). The 1st, 2nd, 3rd and 4th groups were administered cephradine in a single dose of 50 mg kg^{-1} b.wt. (Oishi et al. 1976) via oral, intramuscular, subcutaneous and intravenous routes, respectively. Blood samples (1ml each) were taken from wing vein just before and 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8,12 and 24 hours post drug administration. Blood samples were left to clot then centrifuged at 3000 rpm for 15 minutes to obtain clear serum that was kept frozen at -20 °C until assayed.

Repeated dose pharmacokinetics were performed on twenty four birds where the birds were given 50 mg kg^{-1} b.wt cephradine orally twice daily for five consecutive days. The blood samples were collected just before and 1 hour after dose (peak and trough). Three chicken were slaughterd at 4, 8, 12, 24 hours and 7th, 8th, 9th, 10th days after the last dose.

Blood and tissue (lung, spleen, liver, kidney, breast, thigh muscle and intestine) samples were

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taken from the slaughterd chicken. About 1 gram was taken from each tissue sample, then thoroughly homogenized in 4 ml phosphate buffer pH 6. The homgenized tissue was centrifuged at at 3000 rpm for 15 minutes. The supernatent was transferred to sterilized tubes to be used in the assay of concentration. The collected serum samples were divided into two portions, the first to be used in the assay of concentration and the second for biochemical studies. The effect of cephradine on the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and concentration of uric acid were estimated according to Schmidt and Schmidt (1963) and Kageyama (1971), respectively.

Bacteriological samples were taken from 50 one-day old chicks for isolation of pathogenic bacteria according to Collee *et al*., (1996). The isolated microorganisms from the chicks were examined for antimicrobial sensitivity against cephradine using the disc and agar diffussion method as described by Collee *et al*., (1996). All the suspected microorganisms were subjected to serotyping by slide agglutination test using standard polyvalent and monovalent *E. coli* antisera and according to the method described by Edwards and Ewing (1972). The minimum inhibitory (MIC) and minimum bactericidal concentrations (MBC) were estimated according to Collee *et al*., (1996).

Drug bioassay. Cephradine concentrations were estimated in serum samples by microbiological assay according to the method of Arret *et al*. (1971) using *Micrococcus luteus* (ATCC 9341) as a test organism. Standard cephradine concentrations of 0.25, 0.5, 1, 2, 4, 8, 16ug ml^{-1} were prepared in antibiotic-free chicken's serum and also in phosphate buffer solution of pH 6. Semi-logarithmic plots of the inhibition zone diameters versus standard cephradine concentrations in serum and phosphate buffer were linear with typical correlation coefficient of 0.989 (for the standard curve). The difference of inhibition zone diameter between the solutions of the drug in serum and phosphate buffer was used to calculate the *in-vitro* protein binding tendency of the drug according to Lorian (1980) by the following equation :

$$\text{Protein binding \%} = \frac{\text{zone of inhibition in buffer} - \text{zone of inhibition in serum}}{\text{zone of inhibition in buffer}} \times 100$$

Pharmacokinetic analysis.

Serum concentrations of cephradine for each chick after IV, IM, SC and oral administration were subjected to a compartmental analysis using a non linear least-squares regression analysis using a computerized curve-stripping program (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA). For IV, IM, SC and oral data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) (Yamaoka *et al*., 1978).

Following IV injection, the serum concentration-time relationship was best estimated as a two-compartment open model system (Baggot, 1978) according to the following bi-exponential equation: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$, where C_p is the concentration of drug in the serum at time t; A is the intercept of the distribution phase with the concentration axis expressed as ug ml^{-1}; B is the intercept of the elimination phase with the concentration axis expressed as ug ml^{-1}; α is the distribution rate constant expressed in units of reciprocal time (h^{-1}); β is the elimination rate constant expressed in units of reciprocal time (h^{-1}); and e is the natural logarithm base.

After IM, SC and oral administration, data was analyzed by adopting a one-compartment open model. This program also calculated non-compartmental parameters using the statistical moment theory (Gibaldi and Perrier, 1982). The C_{max} (maximum serum concentration) and t_{max} (time of maximum serum concentration) were taken directly from the curve. The terminal elimination half-life ($t_{0.5(el)}$) and absorption half-life ($t_{0.5(ab)}$) were calculated as $\ln 2/K_{el}$ or $\ln 2/K_{ab}$, respectively, where K_{el} and K_{ab} are the elimination and absorption rate constants, respectively. The area under serum concentration-time curve (AUC) was calculated by the method of trapezoids and extrapolation to infinity was performed. The total body clearance (Cl_B) was calculated as Cl_B = Dose/AUC and the absolute bioavailability (F) as $F = AUC_{i.m}/AUC_{i.v} \cdot 100$. Results were expressed as mean and standard error (S.E). Standard errors were calculated from the mean data according to Snedecor (1969).

Results

The diagrammatic relationship between the time and the observed concentrations of cephradine after intravenous, intramuscular, subcutaneous and oral administration (50 mg kg^{-1} b.wt) was demonstrated in figure (1). The pharmacokinetic parameters of cephradine after

the different routes are presented in table (1). Serum concentration time curve of cephradine following IV injection was best described by a two compartment open-model. Cephradine was rapidly distributed with a half life of distribution ($t_{0.5(\alpha)}$) of 0.120 h and eliminated with an elimination half-life ($t_{0.5(\beta)}$) of 1.047 h. The apparent volume of distribution at steady state (Vd_{ss}) was 2.187 L kg^{-1}. The total body clearance of the drug was calculated as (Cl_B) of 2.350 L kg^{-1} h^{-1}.

Following IM and SC injection, cephradine was rapidly absorbed with a half-lives of absorption ($t_{0.5(ab)}$) of 0.154 and 0.364 h and the peak serum concentrations (C_{max}) were 8.863 and 8.773 ug ml^{-1}., respectively. The elimination half-lives ($t_{0.5(el)}$) were 0.859 and 2.652 h, respectively. After oral administration, cephradine was rapidly absorbed with $t_{0.5(ab)}$ of 0.65 h and C_{max} of 5.79 ug ml^{-1} achieved after 1.38 h post administration. The elimination half-life ($t_{0.5(el)}$) was 1.74 h. The systemic bioavailabilities of cephradine were 59.386, 84.50 and 97.97 % after the three routes, respectively. *In-vitro* protein binding percent in chicken's serum was ranged from 2.66-26.24 (mean 10.03) %.

Serum concentrations of cephradine following multiple oral administration of 50 mg kg^{-1} b.wt. twice daily in chickens for 5 consecutive days were illustrated in figure (2). Multiple dose studies have demonstrated that cephradine was non-cumulative over 5 days with a 12 hour dosing regimens. Table (2) demonstrates the serum and tissue concentration of the drug after multiple dosing. Cephradine produced a detectable level in intestine but not detected in the other tissues after 48 hours following the last dose. Repeated oral administration of cephradine (50 mg kg^{-1} b.wt twice daily) for 5 consecutive days caused no change in serum enzyme activities of ALT and AST but induced significant increase in concentration of uric acid at 72 to 120 hours post administration.

From the bacteriological study, the microorganisms recovered from the chicks were *Escherchia coli* O78 *serogroup, Proteus mirabilis and Pseudomonas aeroginosa*. Cephradine inhibit the growth of *Proteus mirabilis* at concentration of 30 ug/disc, but *Pseudomonas aeroginosa* and *Escherchia coli* O78 were resistant. The minimum concentrations of cephradine which inhibited the growth of *Escherchia coli* O78, *Proteus mirabilis* and *Pseudomonas aeroginosa* were 32, 128 and >128 ug ml^{-1}., respectivelly. The minimum bactericidal concentrations (MBC) of cephradine against the tested microorganisms were 64, 128 and > 128 ug ml^{-1}.

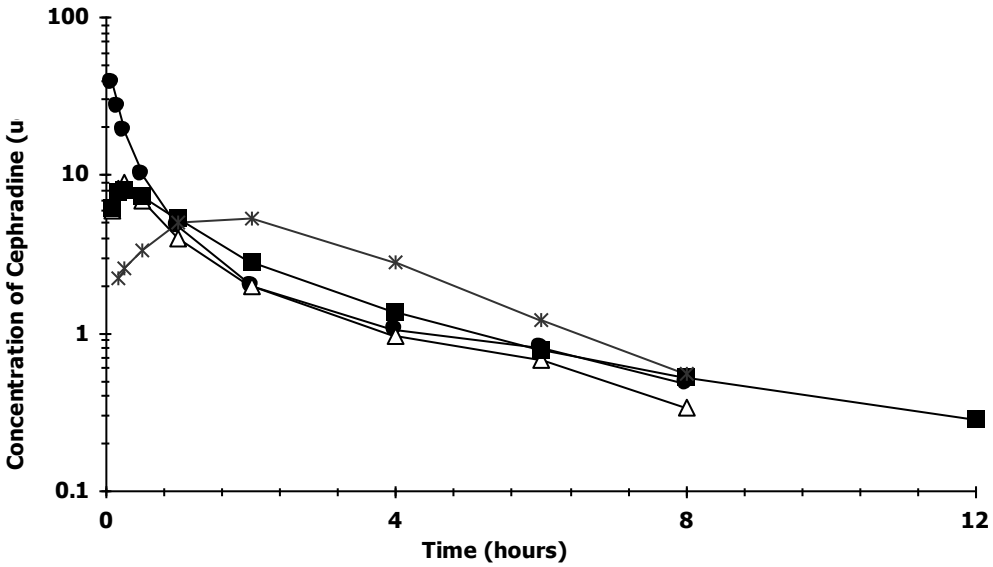

Figure (1): Semi-logarithmic graph depicting the time-concentration of cephradine in serum of chicken after a single IV (●), IM (Δ), SC (■) and oral (∗) administration of 50 mg kg^{-1} b.wt.

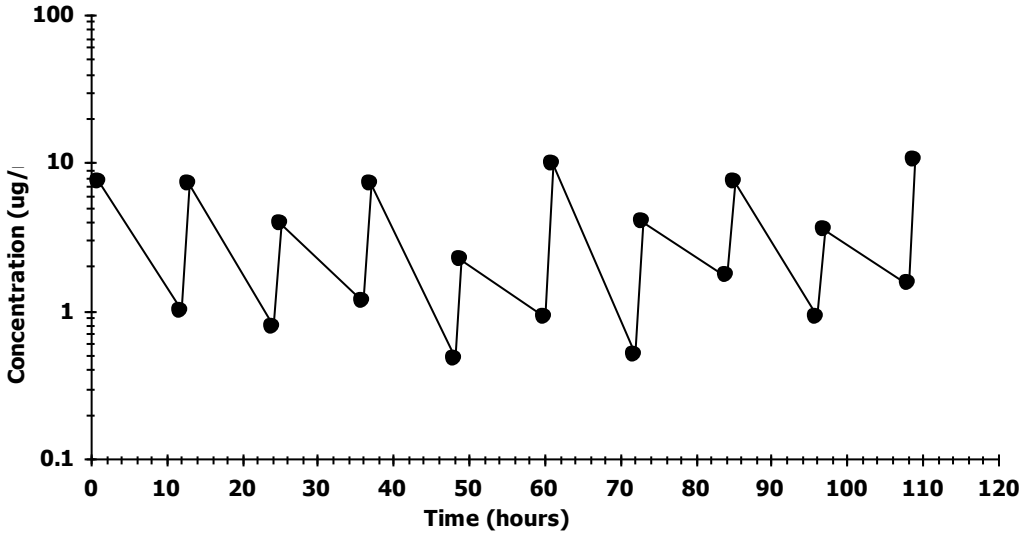

Figure (2): Semi-logarithmic plot depicting the time-course of cephradine in serum of chicken after repeated oral administration of 50 mg kg^{-1} b.wt. twice daily for 5 consecutive days.

Table (1): Mean (± SE) kinetic parameters of cephradine (50 mg kg^{-1} b.wt) following a single intravenous (IV), intramuscular (IM), subcutaneous (SC) and oral administration in chicken (n=12).

Parameter	Unit	IV	IM	SC	Oral
C_p^o	ug ml^{-1}	60.529 ± 2.091			
A	ug ml^{-1}	50.006 ± 2.79			
B	ug ml^{-1}	10.523 ± 1.743			
α	h^{-1}	6.549 ± 0.738			
β	h^{-1}	0.778 ± 0.075			
k_{21}	h^{-1}	1.746 ± 0.204			
K_{el}	h^{-1}	2.855 ± 0.205			
k_{12}	h^{-1}	2.721 ± 0.531			
$t_{0.5(\alpha)}$	h	0.120 ± 0.012			
$t_{0.5(\beta)}$	h	1.047 ± 0.149			
MRT	h	0.991 ± 0.131			
AUC	ug ml^{-1} h^{-1}	24.13 ± 1.589			
V_c	L kg^{-1}	0.836 ± 0.028			
Vd_{ss}	L kg^{-1}	2.187 ± 0.208			
Cl_B	L kg^{-1} h^{-1}	2.350 ± 0.151			
k_{ab}	h^{-1}		16.376 ± 4.67	3.056 ± 0.759	1.198 ± 0.58
K_{el}	h^{-1}		0.974 ± 0.104	0.342 ± 0.062	0.44 ± 0.04
$t_{0.5(ab)}$	h		0.154 ± 0.09	0.364 ± 0.066	0.65 ± 0.088
$t_{0.5(el)}$	h		0.859 ± 0.14	2.652 ± 0.346	1.74 ± 0.16
C_{max}	ug ml^{-1}		8.863 ± 0.254	8.773 ± 0.338	5.79 ± 0.38
t_{max}	h		0.129 ± 0.018	0.291 ± 0.048	1.38 ± 0.146
AUC	ug ml^{-1} h^{-1}		14.33 ± 0.73	20.39 ± 0.776	23.64 ± 1.17
MRT	h		1.267 ± 0.166	3.097 ± 0.276	3.34 ± 0.17
F	%		59.386 ± 4.11	84.50 ± 7.53	97.97 ± 8.11

C_p^o cephradine concentration at zero time (immediately after single IV injection); **A, B** zero-time intercepts of the biphasic disposition curve; **α, β** hybrid rate constants representing the slopes of distribution and elimination phases, respectively; k_{12} first-order constant for transfer from central to peripheral compartment; k_{21} first-order constant for transfer from peripheral to central compartment; K_{el} elimination rate constant; $t_{0.5(\alpha)}$ distribution half-life; $t_{0.5(\beta)}$ elimination half-life; **MRT** mean residence time; AUC_{0-12} area under serum concentration-time curve; **Vc** apparent volume of the central compartment; Vd_{ss} volume of distribution at steady state; Cl_B total body clearance. k_{ab} first-order absorption rate constant; C_{max} maximum serum concentration; t_{max} time to peak serum concentration; $t_{0.5(ab)}$ absorption half-life; $t_{0.5(el)}$ elimination half-life; **F** fraction of drug absorbed systemically after IM, SC and oral administration.

Table (2): Mean serum and tissue concentrations (ug ml^{-1}) of cephradine (50 mg kg^{-1} b.wt twice daily) in chicken after the last dose of repeated oral administration (n=3).

Tissue	Time of slaughter (h)			
	4 h	12 h	24 h	48 h
Serum	1.98±0.62	0.51±0.09	0.53±0.01	0.496±0.03
Liver	2.09±0.07	0.293±0.29	ND	ND
Kidney	19.43±0.83	1.09±0.04	ND	ND
Spleen	0.92±0.02	ND	ND	ND
Lung	2.04±0.21	ND	ND	ND
Intestine	13.96±0.22	0.94±0.01	0.397±0.39	0.448±0.45
Breast muscle	ND*	ND	ND	ND
Thigh muscle	ND	ND	ND	ND

*ND: Not detected

Discussion

Following IV injection of cephradine in a single dose of 50 mg kg^{-1} b.wt. in chickens, the serum concentration time curve was best described by a two-compartment open model. This finding was consistent with that reported in goats (EL-Sayed *et al*., 1994). The drug was rapidly distributed with a half-life of distribution ($t_{0.5(\alpha)}$) of 0.120 h and this finding was closely similar to that observed in goat (0.22 h) by El-Sayed *et al*., (1994).

Cephradine was relatively slowly eliminated with a half-life of elimination ($t_{0.5(\beta)}$) of 1.047 h. This result is close to the result obtained in human (62 min) by Lode *et al*., (1975), 0.85 h by Rattie *et al*., (1976) and 1.12 h in young subjects by Schwinghammer *et al*., (1990), but was shorter than that reported in goat (4 h) by El-Sayed *et al*., (1994). The slow elimination of the drug from the body is coincident with low rate of clearance (Cl_B=2.35 L kg^{-1} h^{-1}). The slow elimination of cephradine from chicken body than other mammals could be explained on the basis of its weak acidic nature, the high acidity of poultry urine and on the basis of the different rates of its metabolic transformation in the bodies of different species. Also birds of higher metabolic rates would be expected to produce shorter $t_{0.5(\beta)}$ value. The apparent volume of distribution at steady state (Vd_{ss}) is an indication of diffusion of the drug in the body tissues (Gilman *et al*., 1980). The Vd_{ss} was greater than unity (> one L kg^{-1}) indicating higher distribution of the drug in the extra vascular tissues than in the serum, this result was supported by Baggot (1978) and Baggot (1983).

The lower percent of *in-vitro* protein binding of cephradine in serum (mean 10.03 %) may explain the high diffusion of cephradine in tissues of chicken and high value of volume of distribution. The total body clearance (Cl_B) 2.35 L kg^{-1} h^{-1} was lower than that reported in human (14.9 L kg^{-1} h^{-1}) when injected (1000 mg) (Rattie *et al*., 1976), but higher than that reported in equine (0.404 L kg^{-1} h^{-1}) when injected 25 mg kg^{-1} (Henry *et al*., 1992). These differences may be due to the high apparent volume of cephradine distribution in chicken and also due to species variation and the given dose.

Following IM injection of cephradine, it was rapidly absorbed with a shorter absorption half-life ($t_{0.5(ab)}$) 0.154 h than that reported in normal goats (0.64 h) by El-Sayed *et al*. (1994). The systemic bioavailability after IM, SC and oral administration of 59.386, 84.50 and 97.97 % indicated lower absorption of the drug from the site of IM and SC routes than of the oral route. Following repeated oral administration the drug was found to be concentrated in liver, kidney, spleen, lung, and intestine and not detected in muscles. This finding is close to that reported for cephradine in rat by Klimova (1979). In this study the drug concentrations of cephradine in the serum were lower than the MIC of the tested organisms. Cruichshank *et al*., (1975) considered that a bacterium may be sensitive to antibiotic if the MIC is not more than 0.25-0.5 its average concentration in blood.

It could be concluded that the withdrawal time of cephradine from tissue of chicken is 2 days following the last dose. *Proteus mirabilis* was sensitive to cephradine but *E. coli* O78 *and pseudomonas aeroginosa* were resistant. Cephradine produces no adverse effect on the liver but has mild kidney toxicity.

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المسار الحركي وفارماكوديناة السيفرادين في الدجاج

تم دراسة المسار الحركي للسيفرادين (٥٠ مجم/كجم من وزن الجسم) في الدجاج. كما تم تعيين معدل الاستفادة الحيوية من العقار وتعيين نسبة إتحاده ببروتينات المصل وتركيزه بعد الحقن المتكرر في المصل والأنسجة ودراسة تأثيره على نشاط بعض إنزيمات الكبد وتركيز حمض البوليك فى المصل. وتم دراسة وتأثير العقار على بعض الميكروبات داخل المعمل. وقد أظهرت الدراسة انه بعد الحقن الوريدي للسيفرادين قد سلك منحنى التركيز بالدم مقابل الزمن مسلك ثنائي الحجرات وفترة نصف عمر التوزيع ((t0.5(α)) 0.120 ساعة وفترة نصف عمر الإخراج ((t0.5(β)) 1.047 ساعة. وقد كان حجم توزيع العقار عى الأنسجة كبيرا (Vdss) ٢.١٨٧ لتر/ كجم. ووجد أن معدل طرح سيفرادين (ClB) هو ٢.٣٥٠ لتر/كجم/ساعة. أما بعد الحقن العضلي و تحت الجلد وعن طريق الفم فقد كان أقصى تركيز للدواء (Cmax) ٨.٨٦٣ و ٨.٧٧٣ و ٥.٧٩ ميكروجرام / مللي على التوالي وبعد زمن (tmax) ٠.١٢٩ و ٠.٢٩١ و ١.٣٨ ساعة من الحقن على التوالي. وقد كانت فترة نصف عمر الامتصاص ((t0.5(ab)) ٠.١٥٤ و ٠.٣٦٤ و ٠.٦٥ ساعة وفترة نصف عمر الإخراج ((t0.5(el)) ٠.٨٥٩ و ٢.٦٥٢ و ١.٧٤ ساعة على التوالي. ووجد أن الدواء لا يحدث تغيير في نشاط بعض إنزيمات الكبد (ALT and AST). إتضح من الاختبار المعملي أن ميكروب البروتيس ميرابيلس حساس للسيفرادين بينما ميكروبات القولون الأشريكى (الأشيرشياكولى) والزائفة الزنجارية كانت أكثر مقاومة للدواء