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Effect of diclofenac on the pharmacokinetics of ciprofloxacin in quail

Y.Z. Alabdaly

Department of Physiology, Biochemistry and Pharmacology College of Veterinary Medicine, University of Mosul, Mosul, Iraq

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Correspondence:
Y.Z. Alabdaly
yalabdali@yahoo.com

Abstract

This study investigated the Pharmacokinetics of ciprofloxacin alone or with diclofenac sodium in adult Japanese quails. The quails divided into two groups, the first group was dosed intraperitoneally with 50 mg/kg of ciprofloxacin, the second group was injected by 50 mg/kg of ciprofloxacin intraperitoneally then directly injected intraperitoneally by diclofenac sodium at a dosage of 5 mg/kg. Plasma concentrations of ciprofloxacin were determined by the spectrophotometer at wavelength 290 nm. Co-admiration of ciprofloxacin with diclofenac lead to appearing ciprofloxacin in plasma at 12.02, 6.4, 5.3, 3.30, 1.36, 0.60 µg/ml in the periods of 0.25, 0.50, 1, 2, 4 and 8 hours post-injection. A significantly increased in the concentration of ciprofloxacin at times of 0.25, 0.50, 1, and 2 hours post-injection and appeared at a concentration of 6.96, 3.09, 2.2, and 0.72 µg/ml. The pharmacokinetics of ciprofloxacin when given with diclofenac sodium was represented by 91% decrease in elimination constant rate, 53% decrease in elimination half-life t1/2, 64% decrease in volume of distribution to steady-state, 22% decrease in clearance, 28% increase area under curve, 41% decrease in area under moment curve, 53% decrease in mean residence time and 37% increase in maximum plasma concentration. Our study concludes that co-administration of ciprofloxacin with diclofenac sodium lead to alteration in some pharmacokinetic data of ciprofloxacin like effect on the plasma concentration and volume of distribution and clearance. This effect must be considered when therapy by ciprofloxacin with diclofenac, the co-administration of diclofenac with ciprofloxacin decrease the elimination of ciprofloxacin.

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Introduction

Ciprofloxacin belongs to Fluoroquinolones its molecular formula is $C_{17}H_{18}FN_3O_3$, it's an antibiotic with a broad spectrum, the mechanism of its action is inhibiting DNA gyrase and a type II topoisomerasen (1). Diclofenac is a non-steroidal anti-inflammatory drug. The toxicokinetic in quail has belonged to metabolic capacity with $t1_{/2}$ and mean residence time MRT above 8 hours with apparent signs of toxicities (2-4). Study of pharmacokinetics for enrofloxacin and ciprofloxacin in cow and steers showed the plasma elimination half-life for two drugs were longer in steers lactating cow than in cow (5). Bioavailability of ciprofloxacin when orally given is within a percentage of 70-80%, complete absorption of ciprofloxacin is generally not achieved following oral administration with no substantial loss by first-pass metabolism (6). Bioavailability of ciprofloxacin after oral administration is not altering by drug-food interactions although prolong the time required to reach maximum plasma concentration (t max) and thus affect the area under the concentration-time curve (7). Because it is little binding to plasma proteins and good penetration in various fluids and tissues of the body. It has high distribution, except the central nervous system (CNS) (8,9). Ciprofloxacin is different from other drugs in degree of metabolism and elimination in the liver or by renal excretion, that in the metabolism of ciprofloxacin decrease antimicrobial activity by glucuronide conjugation at the 3-

carboxylic group. The piperazine ring increased metabolism, and these results reduced antimicrobial activity (10). Ciprofloxacin is excreted by kidney through glomerular filtration and renal tubular secretion, although elimination occurs by other routes like liver especially in case of renal impairment, in this case dose, adjustment is required for that case (8). In the study of pharmacokinetic data of ciprofloxacin and enrofloxacin for different animals species recorded no difference between the clearance and volume of distribution (11). In the comparative study between marbofloxacin and ciprofloxacin during the steady-state period, found the interstitial fluid and plasma-unbound concentrations were similar for two drugs despite differences in lipophilicity and pharmacokinetic parameters of the two drugs (12). Enrofloxacin is high lipophilicity and protein binding than marbofloxacin and ciprofloxacin (13).

To date, pharmacokinetic parameters have only been studied for ciprofloxacin and its interaction with another drug in pharmacological doses. Thus, we conducted to study the effect of diclofenac on the pharmacokinetics of high dose ciprofloxacin in quail.

Materials and methods

Animals

Adult male Japanese quail weighing 200-290 gram, aged 40 days. Animals were raised in cages under uniform conditions in room temperature, water, and food in the animal house of the College of Veterinary Medicine, Mosul University.

Drugs and chemicals used

Pure ciprofloxacin hydrochloride powder and pure diclofenac sodium powder (drug nenava industry) were used. The original drug acetonitrile from TEDA Company, England. Ninety-six males of quail divided into two groups were used in the study; each group consists of 48 birds, which is randomly divided. The first group, treated intraperitoneally i.p by ciprofloxacin 50 mg/kg body weight, the second group treated by ciprofloxacin 50 mg/kg i.p and then directly injected by diclofenac sodium 5 mg/kg i.p (14). Blood sampling collected with anticoagulant heparin from TEDA Company by cutting jocular vein of each bird in the periods of 0.25, 0.50, 1, 2, 4 and 8 hours (birds for each group). All blood samples were centrifuged at 3000 cycles/minute for 15 min and then the plasma was separated. The obtained plasma samples were stored at -20 ° C. The method depends on spectrophotometric ciprofloxacin estimation (15).

Preparation of standard solutions

A stock standard solution 1mg/ml of ciprofloxacin hydrochloride. Working standard solutions 100, 10 and 1 µg / mL were prepared by serial dilution of the stock standard solution with distilled water. The standard solutions were protected from light and were used on the same day. Linear regression analysis of the calibration data was performed using the linear equation y = MX + c (Figure 1).

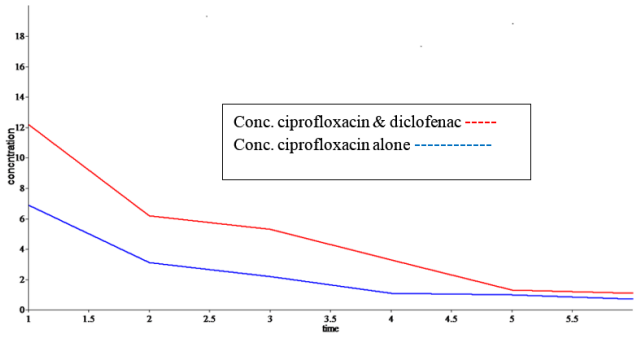

Figure 1: Semi-logarithmic plasma concentration-time profiles of concentration of ciprofloxacin in plasma of quail treated with and without diclofenac.

Sample preparation

Plasma blank in a 5-ml Eppendorf tubes, 2 mL of acetonitrile was added to 1 mL of plasma. The mixture was mixed up for 30 s with a mechanical shaker and centrifuged for 5 min at 10000g. A 2.5 ml volume of clear supernatant was transferred into a qewvite to measure the ciprofloxacin plasma concentration by UV spectrophotometer at wave length 290 nm. The data of ciprofloxacin concentration was used for the Pharmacokinetic analysis program.

Pharmacokinetic analysis

The analysis was carried out using specialized software non-compartmental Windows-based computer program (16). The parameter was elimination constant rate (k), Elimination half-life t1 / 2, the volume of distribution to steady-state (Vss), Clearance, the area under curve AUC 0-, AUMC, MRT, and maximum plasma concentration (C max).

Static analysis

Result analysis by two-way analysis of variance then result was applied to least significant difference by SPSS program of the level of significant $P<0.05$.

Results

Pharmacokinetic data

Plasma concentration of single dose of ciprofloxacin 50 mg/kg i.p, when co-administered with diclofenac 5 mg / kg i.p were 12.0, 6.4, 5.3, 3.3, 1.3 and 1.1 µg / kg after time of 0.25, 0.50, 1, 2, 4 and 8 hour (Table 1). While ciprofloxacin plasma concentration when treated animals with single dose of ciprofloxacin 50 mg / kg i.p., were 6.9, 3.09, 2.2, 1.07, 1.14, and 0.71 after time of 0.25, 0.50, 1, 2, 4 and 8 hour.

Table 1: Plasma concentration of ciprofloxacin in animals treated with and without diclofenac

Groups	Time /hour					
	0.25	0.50	1	2	4	8
Ciprofloxacin 50 mg/kg	6.9±0.4	3.1±0.2	2.2±0.05	1.1±0.1	1.0±0.08	0.7±0.1
Ciprofloxacin 50 mg/kg + diclofenac 5 mg/kg	*12.2±0.5	*6.4±0.3	*5.3±0.5	*3.3±0.2	1.3±0.3	1.1±0.4

The value represents group of 6 animals. *value is significantly different from group of Ciprofloxacin 50 mg/kg.

This result reflected on pharmacokinetic parameters for group of ciprofloxacin with diclofenac by Elimination constant rate (k) = 0.69 hr-1, Elimination half-life t 1/2 = 4.25 hr., Volume of distribution to steady state (Vss) =10.63 L/kg, Clearance = 2.01 L/h/kg, area under concentration extrapolated to time infinity = 24.88 µg/hr / ml., area under moment concentration AUMC = 131.5 µg / hr-1 / ml, Mean Resident Time MRT = 5.22 hr., and highest plasma concentration (C) 12.2 µg / ml (Table 2). The changes in pharmacokinetic data when comparing between the two groups of ciprofloxacin with and without diclofenac sodium were represented as percentage of 91% decrease in elimination constant rate (k), 53% decrease in elimination half-life t1 / 2, 64% decrease in volume of distribution to steady-state (Vss), 22% decrease in clearance, 28% increase area under curve AUC 0-, 41% decrease in AUMC, 53% decrease in MRT and 37% increase in maximum plasma concentration (Table 2).

Table 2: Pharmacokinetic parameters of ciprofloxacin in animals treated with diclofenac and without it

Pharmacokinetic parameters	Ciprofloxacin 50mg/kg	Ciprofloxacin50mg/kg with diclofenac 5mg/kg	%changes from two groups
CL L/h/kg Clearance	2.57	2.01	22% ↓
MRT hr Mean residence time	11.38	5.29	53% ↓
Vss L/kg Volumes of Distribution	29.21	10.63	64% ↓
Terminal K- Elimination constant rate	7.7	0.69	91% ↓
Terminal t1\2 hr.	8.97	4.25	53% ↓
T max hr. Maximum time	1.00	1.00	0
C max µg/mL Maximum concentration	6.96	12.02	73% ↑
AUC extrapolated to time infinity µg. h/mL	19.48	24.88	28% ↑
Presented extrapolated AUC µg. h/mL	47.03	24.05	49% ↓
AUMC Area Under Moment Curve	221.74	131.58	41%↓
Percent extrapolated AUMC	38.51	27.50	29% ↓

Discussion

There are different aspects of drug interaction at the pharmacokinetics and pharmacodynamics levels (17). In the present study, the pharmacokinetic parameters following intravenous administration of ciprofloxacin in quail were very similar to those reported previously conducted in humans and animals (18-21). but there is no study on this type of interaction in quail birds, therefore we have conducted this study. However, the pharmacokinetic analysis showed that the concomitant administration of diclofenac and ciprofloxacin decreased in ciprofloxacin clearance that agreement with (22). That effect may back to increasing renal tubular reabsorption and reduced renal clearance that maybe belong to alkaline in pH number for the ciprofloxacin and diclofenac sodium that causes competition between ciprofloxacin and diclofenac that result consistent with the study (23) that showed NSAIDs can cause drug-drug interactions specially in excretion. Also (18) recorded that oral co-administration of ciprofloxacin with diclofenac elevated ciprofloxacin AUC and Cmax, and decreased ciprofloxacin tmax and total body clearance, in addition to affect the intrinsic hepatic clearance.

The decrease in Vd and body clearance may have been due to a decrease in intrinsic hepatic clearance and blood flow or a decrease in renal clearance, as has been observed with co-administration of intravenous ciprofloxacin with orally administered probenecid (21). Increased bioavailability of ciprofloxacin has also been reported with co-administration of ciprofloxacin with probenecid. Similar modifications in ciprofloxacin pharmacokinetic characteristics augmented AUC and Cmax and body clearance were also reported with phenazone co-administered by dogs (18).

Significant modifications in important pharmacokinetic parameters of ciprofloxacin noted when diclofenac is administered simultaneously indicates that diclofenac can modify ciprofloxacin absorption / metabolism / elimination. Ciprofloxacin has also decreased overall clearing of the body. These findings suggest that as a result of concomitant diclofenac administration the tissues distribution of the drug

are significantly decreased volume of distribution are lead to increase concentration in the blood coupled with a decrease in drug concentration in tissue (24,25). We need more studies to detect the effect of drug interaction with other non-steroidal anti-inflammatory drugs on another aspect.

Conclusions

The key results of this study are that the bioavailability of ciprofloxacin increases with the administration of diclofenac and co-management must be taken with further precautions.

Acknowledgement

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Conflict of interest

There is no conflict of interest.

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تأثير الديكلوفيناك على الحركية الدوائية للسيبروفلوكساسين في السمان

يمامة زهير العبدلي

فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

بحثت هذه الدراسة الحركية الدوائية للسيبروفلوكساسين لوحده أو مع ديكلوفيناك الصوديوم في السمان الياباني البالغ. قسمت حيوانات السمان إلى مجموعتين، المجموعة الأولى حقنت داخل الخلب بجرعة

٥٠ مجم / كجم من سيبروفلوكساسين. أما المجموعة الثانية فحقنت بجرعة ٥٠ مجم / كجم من السيبروفلوكساسين ثم حقنت مباشرة بالديكلوفيناك صوديوم بجرعة ٥ مجم / كجم داخل الخلب. حدد تركيز السيبروفلوكساسين في البلازما بواسطة جهاز المطياف الضوئي عند الطول الموجي ٢٩٠ نانومتر. تسببت المعاملة المشتركة بلسيبروفلوكساسين مع الديكلوفيناك إلى ظهور السيبروفلوكساسين في البلازما عند التراكيز التالية ١٢,٠٢ و ٦,٤ و ٥,٣ و ٣,٣٠ و ١,٣٦ و ٠,٦٠ ميكروغرام / مل في الأوقات ٠,٢٥ و ٠,٥٠ و ١ و ٢ و ٤ و ٨ ساعة بعد الحقن. سجلت زيادة معنوية في تركيز السيبروفلوكساسين في الأوقات ٠,٢٥ و ٠,٥٠ و ١ و ٢ ساعة بعد الحقن وظهرت بتركيز ٦,٩٦ و ٣,٠٩ و ٢,٢ و ٠,٧٢ ميكروغرام / مل. تمثلت الحركية الدوائية للسيبروفلوكساسين عند إعطائه مع ديكلوفيناك الصوديوم بانخفاض في معدل ثابت الإطراح بنسبة ٩١٪ وانخفاض بنسبة ٥٣٪ في نصف عمر الإطراح مع انخفاض بنسبة ٦٤٪ في حجم التوزيع إلى الحالة الثابتة مترافقا مع انخفاض بنسبة ٢٢٪ في التصفية وزيادة بنسبة ٢٨٪ في المنطقة تحت المنحنى وانخفاض بنسبة ٤١٪ في المنطقة الواقعة تحت المنحني مع انخفاض بنسبة ٥٣٪ في متوسط وقت الإقامة، وزيادة بنسبة ٣٧٪ في أقصى تركيز للبلازما. خلصت الدراسة الحالية إلى أن الإعطاء المشترك للسيبروفلوكساسين مع الديكلوفيناك صوديوم يؤدي إلى تغيير في بعض بيانات الحركية الدوائية للسيبروفلوكساسين منها التأثير على تركيز البلازما وحجم التوزيع والتصفية. يجب أخذ هذا التأثير في نظر الاعتبار عند العلاج بالسيبروفلوكساسين مع الديكلوفيناك.