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Pharmacokinetics of Enrofloxacin in Broiler Chicks

Ishraga G. Ibrahim[1] and Yarsan[2], E.
Central Veterinary Research Laboratories Centre, Animal Resources Research Corporation, P.O. Box 8067, (Al Amarat), Khartoum, Sudan. (2) Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey.

ملخص البحث

إرتكزت هذه الدراسه على فحص حركيات دواء الأنروفلكساسين في كتاكيت الدجاج اللاحم عمر عشرة أيام . جرع الدواء بمقدار 10مجم/كجم يوميا و لمدة 5 ايام. أخذت عينات من الدم قبل وبعد 0.25, 0.5, 1 , 12,8,4,2، 24 ساعة من تجريع الدواء. تم تحديد تركيز الدواء والمواد المتأيضة منه في بلازما الدم بإستعمال فحص الانتشارالميكروبي فى الهلام بمقارنة نشاط الدواء ضد الاشريكيه القولونيهِ ACC25922 في التركيز القياسى. اوضحت النتائج أن منحنى تراكيز الدواء مع مرور الوقت يمكن وصفه بنموذج لحجرتين مفتوحتين. وقد كان النصف العمري لإخراج الدواء, ومتوسط بقاء الدواء فى البلازما 2.06 و 33.91 ساعة على التوالى. تم إمتصاص الدواء ببطء نسبياً وقد استغرق 1.5 ساعة للوصول لأقصى تركيز فى البلازما و مقداره 3.91 مجم/لتر. أثبتت الدراسة أن للدواء تركيز ممتد فى المنطقه تحت المنحنى مما يعنى أن الدواء يبقى لفترة طويلة فى جسم الكتاكيت . خلصت الدراسة إلى أن تجريع 10مجم /كجم بالفم كل 24 ساعه ولمدة 5 أيام مناسبه لعلاج الإصابات البكتيريه للكتاكيت اللاحمه.

Summary

The pharmacokinetics of enrofloxacin was investigated in 10-day-old broiler chicks. Enrofloxacin was orally administered at a dose of 10 mg /kg body weight daily for 5 days. Blood samples were taken for 5 days prior to and after 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hrs following, drug administration. Using microbiological agar gel diffusion analysis, plasma concentration of the enrofloxacin and its metabolites were determined by correlating the composite of antimicrobial activity of enrofloxacin and its metabolites with the actual concentration. After drug administration, the plasma concentration- time curve was characterized by two compartment open model. The elimination half-life and the mean residence time of enrofloxacin for plasma were 2.06 and 33.91 hrs, respectively. Enrofloxacin was absorbed slowly with time to reach its maximal plasma concentration of 3.91 mg/l after 1.5 hr. Enrofloxacin presented an extensive AUC indicating that the drug remains longer than other quinolones in the body. The study concluded that a dose of 10 mg/kg given orally at 24 h interval for five successive days to broiler chicks is suitable for control of bacterial infection in broiler chicks.

Introduction

Enrofloxacin is a synthetic bactericidal agent of the fluoroquinolones group developed specifically for veterinary use (Altreuther, 1987). It is active against a wide range of Gram-negative aerobes, a number of Gram-positive bacteria, *Mycoplasma* and some rickettsial organisms. It is active at low concentrations, appropriate to other classes of antimicrobial drugs (Brown, 1996; Langston *et al*, 1996). The bactericidal activity of enrofloxacin is mediated by affecting bacterial DNA-gyrase (Brander *et al*, 1994). The pharmacokinetics behaviour of enrofloxacin has been studied in several animal species including poultry (Anadon *et al*, 1995; Bugyei *et al*, 1999), sheep (Mengozzy *et al*, 1996; Elsheikh *et al*, 2002), horses (Giguere *et al*, 1996; Langston *et al*, 1996; Kaartinen *et al*, 1997) and pigs (Anadon *et al*,1999). In all cases, enrofloxacin had good absorption and bioavailability after oral administration.

The antimicrobial properties of enrofloxacin indicate that it might have advantages for use in poultry (Anadon *et al*, 1995). Meager information is available on disposition, metabolism and safety of enrofloxacin use in young chickens. This study was carried out to determine plasma disposition of orally administered enrofloxacin to broiler chicks.

Materials and Methods

Twenty 1-day-old broiler chicks (Ross-38) were used. On arrival, all birds were kept in cages under controlled temperature and light; an acclimatization period of ten days was allowed before starting the drug administration.

Antibiotic-free feed and water were supplied *ad libitum*. To avoid absorption variability due to possible enrofloxacin-feed interaction, the birds were starved from feed for 4 hrs before dosing. Water was withdrawn 1 hr prior to drug administration to minimize variation in stomach empting or degree of enrofloxacin dilution (Sumano *et al*, 2003).

Each chick received, based on its individual weight, a single dose of 10 mg/kg enrofloxacin, directly into the crop, using a thin plastic tube attached to a syringe. Approximately 0.5 ml whole blood sample was collected in heparinized tubes from the wing vein of each chick daily prior to and at 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hrs after drug administration for 5 days. Plasma was separated after centrifugation and stored at -20^{o}C in eppendorf tubes until analyzed.

Microbiological assay:

The concentration of enrofloxacin in the plasma was determined according to Ellerbrock (1991) method by Agar Gel Diffusion Microbiological Assay using *Escherichia coli* ATCC 25922. The diameters of bacterial inhibition zones were measured and converted to enrofloxacin concentration equivalents by the use of standard curve calibrated by adding known amounts of pure enrofloxacin to blank chick's plasma. Each test sample or standard was assayed in triplicate and the mean of the three observations was determined; the limit of quantitation of the assay was 0.025 mg/10ml.

Pharmacokinetic Variables Analysis:

The plasma drug concentration time- data for each individual chick were fitted to two-compartment open model for kinetic analysis technique using the computer programme PACKAL (Wanger, 1979). The plasma concentration and the pharmacokinetic variables of enrofloxacin are expressed as mean ±SD (+ range).

Results

The mean peak plasma drug concentration of enrofloxacin that was obtained after a single oral administration of 10mg/kg is shown in Fig.1. The plasma concentration time-curve indicated a biphasic decrease and data of good fit to two- compartment open model was obtained. The variables for the pharmacokinetic data are presented in Table 1.

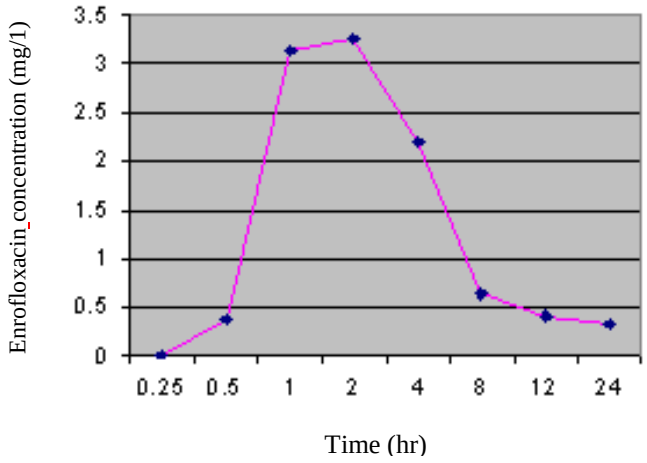

Fig. 1. Plasma concentration of enrofloxacin in chicks after a single oral administration at a dose of 10 mg/kg b.wt to 1-day-old broiler chicks.

Relatively, enrofloxacin was slowly absorbed in broiler oral administration of 10 mg/kg (t½a=28.14). The maximun peak plasma concentration was 3.91 µg/ml and the time to reach it was 1.5 hr. Table 1 shows that the constant elimination rate (B hr) was 0.36 (±0.09) hr and the area

under the plasma concentration-time curve was 21.74 (±1.52) mg/ml/hr. On the other hand, enrofloxacin showed fast elimination phase (t½ß= 2.06 ± 0.61).

Table1: Pharmacokinetic parameters after the disposition of enrofloxacin and its metabolite in 1-day-old broiler chicks following (a single oral dose) of 10 mg/kg b.wt.

Parameter	**Mean±SD (range)**
AUC mg/ml/hr (0-24)	21.74±1.52 (19.97-23.68)
k_a hr^{-1}	(0.03±0.006) (0.02-0.03)
ß hr^{-1}	0.36±0.09 (0.25-0.46)
T½a hr^{-1}	28.2±0.14 (19.0-38.2)
T½α hr^{-1}	0.21±0.15 (0.07-0.37)
MAT (h)	2.41±0.63 (2.03-3.50)
t½ß (h)	2.06±0.61 (1.50-2.82)
MRT (h)	33.91±6.32 (26.79-38.87)
C_{max} (µg/ml)	3.91±0.60 (3.27-4.71)
T_{max} (h)	1.50±0.85 (1.00-2.00)

Data are expressed as mean±SD+ range; AUC= area under curve from 0-24h; ka= first order absorbtion rate constant; ß= hybrid rate constant for terminal elimination phase; α hybrid rate constant for distribution; MAT= mean absorption time; t½ß= half life at ß phase; MRT= mean resident time; C_{max}=maximum concentration in plasma; T_{max}=time needed to reach C_{max}.

Discussion

An attempt was made, in the present study, to characterize the pharmacokinetic parameters of enrofloxacin in 1-day-old broiler chicks after a single oral administration of a dose of 10 mg/kg b.wt. Enrofloxacin has been shown to be partially biotransformed to pharmacologically active metabolite, ciprofloxacin, in several animal species (Kaatinen *et al*, 1997; Anadon *et al*, 1999). The microbilogical assay didn't distinguish between enrofloxacin and its active metabolite, ciprofloxacin, and so the total antimicrobial activity was measured (Heinen, 2002). Oral administration of enrofloxacin to broiler chicks in a single dose of 10 mg/kg resulted in peak plasma drug concentration (C max) of 3.91µg/ml at 1.5 hours; the same dose produced peak plasma concentration of 1.2 µg/ml at 1.5 hr in mature chicken (Sumano *et al*, 2003). In addition, a Cmax of 2.44 µg/ml was reported in chickens given an oral dose 10 mg/Kg/ bw of enrofloxacin (Anadon *et al*, 1995).

Enrofloxacin presents an extensive AUC indicating that the drug remains in the body longer than other quinolones. Similar results for enrofloxacin and ciprofloxacin were reported by Aramayona *et al* (1996) in neonatal rabbit.

In the current study, when given orally, enrofloxacin was slowly absorbed from the gastrointestinal tract of broiler chicks (t½a =28,14 ± 6,39). This value is higher than those reported

by Anadon *et al* (1995) in adult chickens. The difference may be due to difference in bird's age. Moreover, chicks eliminate enrofloxacin rapidly (t½ß= 2,06±0.61); this finding is similar to that reported in African Grey Parrot (Flammer *et al*, 1991) and less than that in chickens (Anadon *et al*, 1995).

Our study revealed a rapid initial distribution phase (T½α0.21±0.15). The estimated MRT was 33.91±6.32; this value differs greatly from that reported by Anadon *et al* (1995). In addition, the estimated value of t½ß (2.06±0.61) for enrofloxacin in the broiler chicks of this study is less than that of Knoll *et al* (1999) and more than that of Sumano *et al* (2003).

In conclusion, our results indicate that enrofloxacin is well absorbed and widely distributed after oral administration to 1-day-old broiler chicks. On the basis of the present results, a single dose of 10 mg/kg given orally to one-day-old broiler chicks is appropriate for control of bacterial infection in this breed of broiler chicks.

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