PHARMACOKINETICS AND TISSUE RESIDUES OF NORFLOXACIN IN NORMAL AND EXPERIMENTALLY *E.COLI* INFECTED BROILER CHICKEN.

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A B S T R A C T

The pharmacokinetics of norfloxacin was studied following single intravenous, oral administration in normal chicken and repeated oral administrations of norfloxacin in normal and experimentally *E.coli* infected broiler chicken. The pharmacokinetic parameters following a single intravenous injection of 10 mg/kg b.wt., revealed that norfloxacin obeyed a two compartments open model, distribution half-life ($t_{0.5(\alpha)}$) was 0.149±0.001 h, volume of distribution (V_{dss}) was 2223.17±65.62 ml/kg, elimination half-life ($t_{0.5(\beta)}$) was 4.71±0.06 h and total body clearance (CL_{tot}) was 1.72±0.02 ml/kg/min. Following oral administration, norfloxacin was rapidly and efficiently absorbed through gastrointestinal tract of chicken as the absorption half-life ($t_{0.5(ab)}$: 0.57±0.01 h). Maximum serum concentration (C_{max}) was 3.87±0.04 µg/ml, reached its maximum time (t_{max}) at about 2.09±0.03 h, elimination half-life ($t_{0.5(el)}$) was 5.72±0.05 h and total body clearance (CL_{tot}) was 4.02±0.06 ml/kg/min indicating the tendency of chicken to eliminate norfloxacin in slow rate. Oral bioavailability was 66.89±1.95 % indicating moderate absorption of norfloxacin after oral administration from oral site. The *in- vitro* protein binding was 10.37±0.22 %. Serum concentrations of norfloxacin following repeated oral administration of 10 mg/kg BW once daily for five consecutive days, peaked 2 hours after each oral dose with lower significant values recorded in experimentally infected chicken than in normal ones. Tissues residues of norfloxacin in slaughtered normal and experimentally *E.coli* infected chicken could not be detected by microbiological assay in all tested tissues except in lung, liver, and kidneys in chicken at 48 hours post last administration, so the chicken must not be slaughtered before 3 days of stopping of drug administration.

Key words: Norfloxacin, Pharmacokinetics, Tissue residues, Chicken.

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1. INTRODUCTION

Norfloxacin is a synthetic antibacterial belonging to the flouroquinolones class and is usually prescribed for the treatment of urinary tract infections. Flouroquinolones are gaining popularity as important antibacterial agents in veterinary practice because of their broad antimicrobial activity (Park *et al*., 1998). Quinolones are active against gram negative and gram-positive bacteria *in vitro* (Wolfson and Hooper, 1985), as well as trimethoprim/sulfonamide resistant microbes (Preheim *et al*., 1987). In addition, these antimicrobials are also active against Mycoplasma (Brown, 1996). Moreover, no plasmid resistance has been demonstrated and flouroquinolones have a favorable margin of safety (Bahri and Blouin, 1991). The pharmacokinetics of norfloxacin in laboratory animals (Gilfillan *et al*., 1984), dogs (Walker *et al*., 1989; Brown *et al*., 1990), chicken (Anadon *et al*., 1992), pig (Anadon *et al*., 1995), donkeys (Lavy *et al*., 1995), calves (Gips and Soback, 1984), sheep (Gonzalez *et al*.,

1997), cow (Shem-Tov *et al*., 1998), horse (Park and Yun, 2003), rabbits (Pavithra *et al*., 2009) and goats (El-Sayed *et al*., 2011) was studied.

The aim of this study is to investigate the pharmacokinetic profile of norfloxacin (10 mg/kg b.wt.) following single intravenous, oral administration in normal chicken and repeated oral administrations in normal and experimentally *E.coli* infected broiler chicken. Also, tissue residues following repeated oral administrations in normal and experimentally *E.coli* infected broiler chicken was evaluated.

2. MATERIALS AND METHODS

2.1. Drug :

Norfloxacin was obtained as an oral solution from ATCO Pharma for pharmaceutical industries under a trade name (Atonor®). Each ml contains 300 mg of norfloxacin base.

2.2. Experimental chicken:

Forty eight clinically normal Cobb chicken of four weeks of age weighting about 1100 to 1300 gm. Each chosen randomly from Gharbia poultry farm to be used in this investigation. Chicken were fed on a balanced ration free from antibiotics for two weeks to withdraw any antibiotic residues. Before drug administration, the weight of chicken ranged between 1650 to 1850 gm for each.

Grouping of chicken :

Group (1): Six normal chicken were intravenously administrated into the wing vein with a single dose of 10 mg/kg body weight. These chicken were left for 15 days to ensure complete elimination of tested drug from their bodies and then given the same dose by oral administration, to determine the oral bioavailability.

Group (2): Six normal chicken were orally administrated 10 mg/kg b.wt., once daily for five consecutive days, to determine the blood concentrations and pharmacokinetics of the drug.

Group (3): Six experimentally *E.coli* infected chicken were orally administrated 10 mg/kg b.wt., once daily for five consecutive days, to determine the blood concentrations and pharmacokinetics of the drug.

Group (4): Fifteen normal chicken were orally administrated 10 mg/kg b.wt., once daily for five consecutive days, to determine the blood and tissue residues.

Group (5): Fifteen experimentally *E.coli* infected chicken were orally administrated 10 mg/kg b.wt., once daily for five consecutive days, to determine the blood and tissue residues.

2.3. Samples:

2.3.1. Blood samples:

About half milliliter of blood was taken from the right wing vein, following administration of the drug. Blood samples were collected at 5, 10, 15, 30 minutes, 1, 2, 4, 8, 12, 24 hours after single intravenous and single oral administration. Blood samples following repeated oral administrations in normal chicken and experimentally infected chicken for 5 consecutive days were taken daily at 15, 30 minutes, 1, 2, 4, 8, 12, 24 hours. All blood samples were collected in sterilized centrifuged tubes and allowed to clot. Serum was separated by centrifugation at 3000 r.p.m for 10 minutes. Sera were kept frozen until assayed.

2.3.2. Tissue samples:

After the end of fifth day of repeated oral administration of norfloxacin, three chicken were slaughtered from group (4) and group (5) at 24, 48, 72, 96, 120 hours. From each slaughtered chicken, lung, heart, liver, kidneys, skin with fat, breast muscles and thigh muscles were taken for drug assay.

Analytical procedures:
Norfloxacin in both collected blood and tissue samples were assayed using microbiological assay method using *E.coli* (ATCC 25922) as a test organism for norfloxacin (Arret *et al*., 1971).
The data were expressed as (Mean ± SE) and analyzed using SPSS (16) software (SPSS Inc., Chicago, USA) and differences between the averages were examined by Duncan's multiple-range test. Mean values within a row with different superscript letters are significantly different ($P< 0{\cdot}05$).

3. RESULTS

Following a single intravenous injection of 10 mg/kg b.wt. of norfloxacin in normal chicken, norfloxacin could be detected therapeutically for 24 hours. The serum concentration – time curve of norfloxacin following intravenous injection showed that the drug obeyed a two compartments open model. The disposition kinetics of norfloxacin following a single intravenous and oral administration were recorded in table (1) and showed in figure (1). Oral administration of 10 mg/kg.b.wt every 24 hours for five doses in normal and *E.coli* infected chicken revealed a lower significant serum norfloxacin concentration at all-time sampling in *E.coli* infected chicken than in normal ones. The pharmacokinetic parameters of norfloxacin after repeated oral administration in normal chicken were compared to those in *E.coli* as shown in table (2). Tissues residues of norfloxacin in slaughtered normal and *E.coli* infected chicken could not be detected by microbiological assay in all tested tissues except in lung, liver, and kidneys in chicken at 48 hours post last administration.

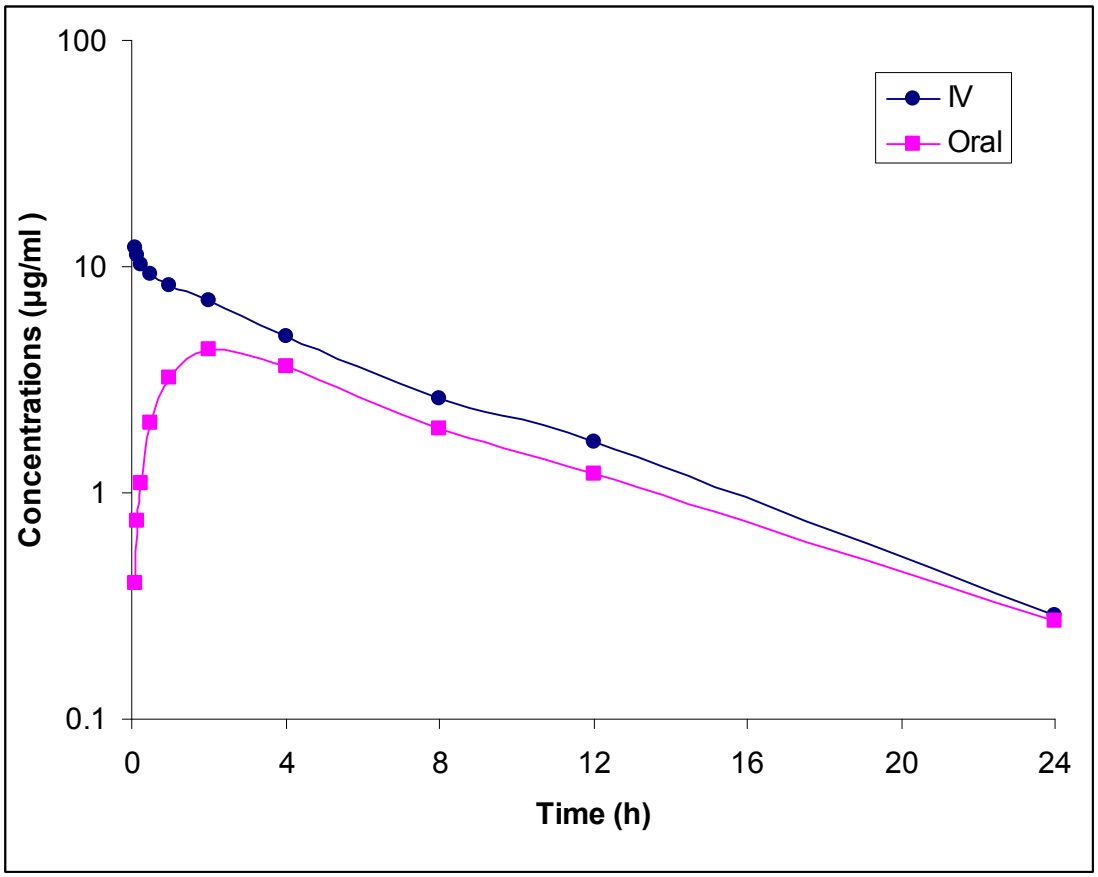
Table (1): Pharmacokinetic parameters of norfloxacin in chicken following single intravenous and oral administration of 10 mg/kg b.wt. (n=6)

Parameter	Unit	Intravenous ($\bar{X}$ ± S.E.)	Oral ($\bar{X}$ ± S.E.)
C^o	μg ml^{-1}	14.86 ± 0.28	—
α (k_{ab})	h^{-1}	4.65 ± 0.03	1.21 ± 0.02
β (k_{el})	h^{-1}	0.15 ± 0.002	0.12 ± 0.001
$t_{0.5\alpha}$ ($t_{0.5ab}$)	h	0.15 ± 0.001	0.57 ± 0.01
$t_{0.5\beta}$ ($t_{0.5el}$)	h	5.72 ± 0.05	4.71 ± 0.06
AUC	μg $ml^{-1}h^{-1}$	5.77 ± 0.07	3.86 ± 0.10
Vd_{ss}	l kg^{-1}	2.22 ± 0.07	—
Cl	ml $kg^{-1}m^{-1}$	1.72 ± 0.02	4.02 ± 0.06
C_{max}	μg ml^{-1}	—	3.87 ± 0.04
t_{max}	h	—	2.09 ± 0.03
F	%	—	66.89 ± 1.95

Table (2): Pharmacokinetic parameters of norfloxacin in normal (N) and experimentally *E.coli* infected chicken (E) during repeated oral administration of 10 mg/kg b.wt., once daily for five consecutive days (n=6).

Day		1st day		2nd day		3rd day		4th day		5th day	
Parameter	Unit	N	E	N	E	N	E	N	E	N	E
		($\bar{X}$ ± SE)	($\bar{X}$ ± SE)	($\bar{X}$ ±SE)	($\bar{X}$ ± SE)	($\bar{X}$ ±SE)	($\bar{X}$ ± SE)	($\bar{X}$ ± SE)	($\bar{X}$ ± SE)	($\bar{X}$ ± SE)	($\bar{X}$ ± SE)
A	µg/ml	5.78 ± 0.11^{f}	4.66 ± 0.08^{g}	8.77 ± 0.06^{b}	6.73 ± 0.23^{e}	8.11 ± 0.02^{c}	7.72 ± 0.10^{d}	7.06 ± 0.06^{e}	8.31 ± 0.16^{c}	8.19 ± 0.04^{c}	9.90 ± 0.17^{a}
K_{ab}	h^{-1}	1.21 ± 0.02^{f}	1.33 ± 0.01^{de}	1.08 ± 0.01^{h}	1.36 ± 0.01^{cd}	1.53 ± 0.02^{b}	1.37 ± 0.01^{c}	1.30 ± 0.01^{e}	1.85 ± 0.02^{a}	1.10 ± 0.01^{h}	1.16 ± 0.003^{g}
$t_{0.5ab}$	H	0.56 ± 0.01^{c}	0.53 ± 0.002^{d}	0.64 ± 0.003^{a}	0.51 ± 0.003^{e}	0.46 ± 0.01^{f}	0.50 ± 0.003^{e}	0.53 ± 0.01^{d}	0.37 ± 0.005^{g}	0.63 ± 0.01^{a}	0.60 ± 0.002^{b}
C^{-}_{max}	µg/ml	4.01 ± 0.09^{h}	3.56 ± 0.05^{h}	4.67 ± 0.10^{g}	4.78 ± 0.04^{g}	7.00 ± 0.52^{f}	6.61 ± 0.06^{f}	8.76 ± 0.21^{c}	7.73 ± 0.04^{e}	11.77 ± 0.05^{a}	9.98 ± 0.09^{b}
C^{-}_{min}	µg/ml	0.31 ± 0.01^{f}	0.27 ± 0.02^{f}	0.39 ± 0.01^{e}	0.41 ± 0.01^{e}	0.71 ± 0.02^{c}	0.56 ± 0.02^{d}	0.89 ± 0.02^{b}	0.69 ± 0.01^{c}	1.20 ± 0.02^{a}	0.90 ± 0.02^{b}
C_{max}	µg/ml	4.09 ± 0.06^{i}	3.27 ± 0.03^{j}	4.96 ± 0.19^{g}	4.58 ± 0.04^{h}	7.53 ± 0.06^{d}	5.70 ± 0.09^{f}	7.90 ± 0.05^{c}	6.16 ± 0.05^{e}	9.79 ± 0.10^{a}	8.65 ± 0.02^{b}
t_{max}	H	2.06 ± 0.04^{c}	2.06 ± 0.04^{c}	2.67 ± 0.01^{a}	2.08 ± 0.02^{c}	2.09 ± 0.01^{c}	2.09 ± 0.03^{c}	2.09 ± 0.04^{c}	1.73 ± 0.03^{d}	2.38 ± 0.02^{b}	2.34 ± 0.03^{b}
B	µg/ml	4.67 ± 0.08^{i}	3.89 ± 0.04^{j}	7.34 ± 0.03^{e}	5.39 ± 0.02^{h}	8.97 ± 0.06^{d}	6.72 ± 0.05^{g}	9.80 ± 0.06^{c}	6.90 ± 0.08^{f}	12.47 ± 0.05^{a}	11.08 ± 0.09^{b}
K_{el}	h^{-1}	0.123 ± 0.002^{a}	0.117 ± 0.002^{bc}	0.122 ± 0.001^{ab}	0.110 ± 0.001^{d}	0.079 ± 0.001^{e}	0.116 ± 0.001^{c}	0.110 ± 0.003^{d}	0.116 ± 0.002^{c}	0.106 ± 0.002^{d}	0.118^{a} ± 0.002^{ab}
$t_{0.5\beta}$	H	5.57 ± 0.14^{e}	5.95 ± 0.08^{d}	5.75 ± 0.06^{de}	6.32 ± 0.06^{bc}	8.72 ± 0.09^{a}	6.04 ± 0.09^{cd}	6.32 ± 0.16^{bc}	5.99 ± 0.13^{d}	6.54 ± 0.10^{b}	5.90 ± 0.11^{d}
CL_{tot}	ml/kg /min	3.94 ± 0.11^{b}	4.78 ± 0.02^{a}	2.79 ± 0.02^{d}	3.19 ± 0.03^{c}	1.48 ± 0.03^{e}	2.76 ± 0.04^{d}	1.79 ± 0.04^{f}	2.59 ± 0.01^{e}	1.47 ± 0.03^{e}	1.74 ± 0.03^{f}

$^{a, b, c, d, e, f, g, h, i}$ Mean values having different letters in column differ significantly (P<0.05).



4. DISCUSSION

In the present investigation, intravenous injection of 10 mg/kg b.wt. of norfloxacin in normal chicken, showed that the drug disposition best fitted a two-compartments- open model, a compartment of plasma and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for norfloxacin in dogs (Brown *et al*., 1990), broiler chicken (Anadon *et al*., 1992), donkeys (Lavy *et al*., 1995), rabbits (Park *et al*., 1995) and horses (Park and Yun, 2003). Norfloxacin was eliminated in current study following a single intravenous injection with elimination half-life ($t_{0.5(el)}$) = 4.71±0.06 h. This observation agreed with the data reported after intravenous injection of norfloxacin(5.44 h) in horses (Park and Yun, 2003). On contrast this value was longer than those recorded in other species as (3.56 h) in dogs (Brown *et al*., 1990), (2.1 h) in swine (Shem-Tov *et al*., 1994), (3.65 h) in pigs (Anadon *et al*., 1995), (3.51 h) in donkeys (Lavy *et al*., 1995) and (3.93 h) in rabbits (Park *et al*., 1998). On the other hand, it was shorter than (8 h) in chicken (Anadon *et al*., 1992) and (7.42 h) in pigs (Chang *et al*., 2007). Such differences are relatively common and frequently related to inter-species variation, assay methods used, the time between blood samplings, and / or the health status and age of the animals (Haddad *et al*., 1985). The Vd_{ss} for norfloxacin was 2.22 l/kg, suggesting good penetration through biological membranes and tissue distribution after intravenous administration in broiler chicken. The obtained value was longer to that recorded for marbofloxacin (1.41 l/kg) in turkeys (Haritova *et al*., 2006a), marbofloxacin (0.57 l/kg) in muscovy ducks (Goudah and Hasabelnaby, 2011) and shorter than danofloxacin and enrofloxacin (6.59, 3.57 l/kg) in turkeys (Haritova *et al*., 2006b; Dimitrova *et al*., 2007), respectively. The total body clearance (CL_{tot}) was 0.10 l/h/kg, this value was close to other fluoroquinolones as marbofloxacin (0.23 l/h/kg) in muscovy ducks (Yuan *et al*., 2011), but shorter than danofloxacin (0.59 l/h/kg) in turkeys (Haritova *et al*., 2006).

Following oral administration, norfloxacin was rapidly and efficiently absorbed through gastrointestinal tract of broiler chicken as the absorption half-life ($t_{0.5(ab)}$) was 0.57±0.01 h. The obtained value was longer than marbofloxacin (0.36 h) in muscovy ducks (Yuan *et al*., 2011) and shorter than difloxacin (1.74 h) in chickens (Anadon *et al*., 2011). The elimination half-life ($t_{0.5(el)}$) was 5.72±0.05 h. This value was nearly similar to marbofloxacin (4.61 h) in muscovy ducks (Yuan *et al*., 2011) and shorter than those for norfloxacin, marbofloxacin, danofloxacin and enrofloxacin (9.07, 9.74, 7.73, 6.92 h, respectively) in turkeys (Laczay *et al*., 1998; Haritova *et al*., 2006a; Haritova *et al*., 2006b; Dimitova *et al*., 2007). Maximal plasma concentration (C_{max}) was 3.87±0.04 µg/ml achived at (t_{max}) 2.09±0.03 h. These values were similar to difloxacin (4.34 µg/ml) in chickens (Ding *et al*., 2008). The (C_{max}) obtained in present study was higher than those reported in healthy broiler chicken (1.96 µg/ml), turkeys (0.95 µg/ml) and geese (1.58 µg/ml) given norfloxacin at a dose level of 10 mg/kg BW (Laczay *et al*., 1998).

The bioavailability of norfloxacin in normal broiler chicken was 66.89±1.95 %. This value referred to a better absorption of norfloxacin from gastrointestinal tract. This value was nearly similar to those recorded for norfloxacin (73.51 %) in lambs (Gonzalez *et al*., 1997), danofloxacin (65.70 %) in goats (Atef *et al*., 2001) and pefloxacin (70.63 %) in lactating goats (Abd El-Aty and Goudah, 2002). On other hand, this value was higher than the bioavailabilities recorded for norfloxacin (35-46 %) in dogs (Brown *et al*., 1990), (31.5 %) donkeys (Lavy *et al*., 1995) and (45 %) in rabbits (Park *et al*., 1998). Also these values were lower than the bioavailability recorded for ciprofloxacin (95.92 %) in lactating goats (El-Banna and Abo-El-Sooud, 1998). *In vitro* plasma protein binding showed that, norfloxacin displayed a low level of binding to plasma proteins (10.37±0.22 %) to broiler chicken plasma. The results of *in vitro* protein binding may differ substantially depending on the methodology and experimental conditions (Zlotos *et al*., 1998). This value was lower than those reported values of 27% for danofloxacin in turkey (Haritova *et al*., 2006b) and 23.52% for levofloxacin in quails (Aboubakr, 2012).

The obtained blood levels of norfloxacin in *Escherichia coli* infected broiler chicken were significally lower than those in normal chicken following repeated oral administrations. These lower blood concentrations in infected chicken might be attributed to the higher penetrating power of norfloxacin to the diseased tissues (Baggot, 1980). The relative higher plasma concentrations of norfloxacin after the last dose compared to the first doses indicating the accumulation of norfloxacin in blood during multiple dosing at 24 hours intervals for five consecutive days. These observations agreed with the progressive daily increase in the mean serum concentrations following the intramuscular injection of ciprofloxacin in lactating goats in a daily dose of 5 mg/kg body weight for five consecutive days (El-Banna and Abo-El-Sooud, 1998).

Following repeated oral administration of 10 mg/kg b.wt. of norfloxacin once daily in normal and experimentally infected chicken for five consecutive days, the drug could not be detected by microbiological assay in all tested tissues except in lung, liver, and kidneys at 48 hours post last administration. In particular the high clearance of norfloxacin indicated the reduced possibility of finding residues of antimicrobial in broiler chicken a few days after treatment and necessity of shorter withdrawal time for this antimicrobial i.e. three days. The obtained results was shorter than that recorded after oral administration of moxifloxacin at 5 mg/kg

for 5 days, a pre-slaughter withdrawal time of more than 7 days is needed to ensure that the drug is eliminated from the tissues(Goudah, 2009).

It could be concluded that oral administration of norfloxacin at 10 mg/kg b.wt. may be highly efficacious against susceptible bacteria in broiler chicken. Chicken must not be slaughtered before 3 days of stopping norfloxacin administration.

5. **REFERENCES**

Abd EL-Aty, A.M., goudah, A. 2002. Some pharmacokinetic parameters of pefloxacin in lactating goats. Vet. Res. Commun. 26: 553-561.

Aboubakr, M. 2012. Pharmacokinetics of levofloxacin in Japanese quails (Coturnix japonica) following intravenous and oral administration. Br. Poult. Sci. 53: 784-789.

Anadon, A., Larranaga, M., velex, C., Diaz, M.J., Bringas, p. 1992. Pharmacokinetic of norfloxacin and its desethyl and oxometabolites in broiler chickens. Am. J. vet. Res. 53: 2084-2089.

Anadon, A., Martinez-Larranaga, M.R., Diaz, M.J., Fernandez, R., Martinez, M.A., Fernandez, M.C. 1995. Pharmacokinetics and tissue residues of norfloxacin and its N-desethyl-and oxo-metabolites in healthy pigs. J. Vet. Pharmacol.Therp. 18: 220-225.

Anadón, A., Suárez, F.H., Martínez, M.A., Castellano, V., Martínez, M., Ares, I., Ramos, E., Gamboa, F., Martínez-Larrañaga, M.R. 2011. Plasma disposition and tissue depletion of difloxacin and its metabolite sarafloxacin in the food producing animals, chickens for fattening. Food. Chem. Toxicol. 49: 441-449.

Arret, B., Johnson, D.P., Kirshbaum, A. 1971. Outline of details for microbiological assays of antibiotics: second revision. J. Pharm. Sci. 60: 1689-1694.

Atef, M., EL-Gendi, A.Y., Aziza, M.M., Abd El-Aty, A.M. 2001. Some pharmaco-kinetic data for danofloxacin in healthy goats. Vet. Res. Commun. 25: 367-377.

Baggot, J.D. 1980. Distribution of antimicrobial agents in normal and diseased animals. J. A. V. M. A. 19: 1085-1090.

Bahri, E.L., Blouin, A. 1991. Fluroquinolones: a new family of antimicrobials. Com. Cont. Edu. Prac. Vet. 13: 1429-1433.

Brown, S.A., Cooper, J., gouze, J.J., Gerco, D.S., weise, D.W., Buck, J.M. 1990. Pharmacokinetics of norfloxacin in dogs after single intravenous and single and multiple oral administration of the drug. Am. J. Vet. Res. 51: 1065-1070.

Brown, S.A. 1996. Fluoroquinolones in animal health. J. Vet. Pharmacol. Ther. 19: 1-14.

Chang, Z.Q., Oh, B.C., Kim, J.C., Jeong, K.S., Lee, M.H., Yun, H.I., Hwang, M.H., Park, S.C. 2007. Clinical pharmacokinetics of norfloxac in-glycine acetate after intravenous and oral administration in pigs. J. Vet. Sci. 8: 353-356.

Dimitrova, D.J., Lashev, L.D., Yanev, S.G., Pandova, B. 2007. Pharmacokinetics of enrofloxacin in turkeys. Res. Vet. Sci. 82: 392-397.

Ding, H.Z., Yang, G.X., Huang, X.H., Chen, Z.L., Zeng, Z.L. 2008. Pharmacokinetics of difloxacin in pigs and broilers following intravenous, intramuscular, and oral single-dose applications. J. Vet. Pharmacol. Ther. 31: 200-204.

EL-Banna, H.A., Abo-El-sooud, K. 1998. Disposition kinetics of ciprofloxacin in lactating goats. Dtsch. Tierarztl. Wochenschr. 105: 35.38.

El-Sayed, M., El-Komy, A., Aboubakr, M. 2011. Pharmacokinetics of Norfloxacin in control healthy and E.

coli infected lactating goats. IJAVMS. 5: 123-137.

Gilfillan, E.C., Pelak, B.A., Bland, J.A., Malatesta, P.F., Gadebusch, H.H. 1984. Pharmacokinetic studies of norfloxacin in laboratory animals. Chemotherapy. 30: 288-296.

Gips, M., Soback, S. 1996. Norfloxacin nicotinate pharmacokineti cs in unweaned and weaned calves. J. Vet. Pharmacol. Ther. 19: 130-134.

Gonzalez, F., Rodriguez, C., Nieto, J., De-Vicente, M.L., San Andres, M.D., San Andres, M.I. 1997. Age-related differences in norfloxacin pharmacokinetic behaviour following intravenous and oral administration in sheep. Vet. Q. 19: 145-150.

Goudah, A. 2009. Pharmacokinetics and tissue residues of moxifloxacin in broiler chickens. Br. Poult. Sci. 50: 251-258.

Goudah, A., Hasabelnaby, S. 2011. The disposition of marbofloxacin after single dose intravenous, intramuscular and oral administration to Muscovy ducks. J. Vet. Pharmacol. Ther. 34: 197-201.

Haddad, N.S., Pedersoli, W.M., Ravis, W.R., Fazeli, M.H., Carson, R.L. 1985. Combined pharmacokinetics of gentamicin in pony mares after a single intravenous and intramuscular administration. Am. J. Vet. Res. 46: 2004-2007.

Haritova, A.M., Rusenova, N.V., Parvanov, P.R., Lashev, L.D., Fink-Gremmels, J. 2006a. Integration of pharmacokinetic and pharmacodynamic indices of marbofloxacin in turkeys. Antimicrob. Agents. Chemother. 50: 3779-3785.

Haritova, A.M., Rusenova, N.V., Parvanov, P.R., Lashev, L.D., Fink-Gremmels, J. 2006b. Pharmacokinetic-pharmacodynamic modelling of danofloxacin in turkeys. Vet. Res. Commun. 30: 775-789.

Laczay, P., Semjén, G., Nagy, G., Lehel, J. 1998. Comparative studies on the pharmacokinetics of norfloxacin in chickens, turkeys and geese after a single oral administration. J. Vet. Pharmacol. Ther. 21: 161-164.

Lavy, B., Ziv, G., Glickmon, A. 1995. Intravenous disposition kinetics, oral and intramvscular bioavailability and urinary excretion of norfloxacin nicotinate in donkeys. J. Vet. Pharmocol. Therap. 18: 101-107.

Park, S.C., Yun, H.I. 2003. Clinical pharmacokinetics of norfloxacin-glycine acetate after intravenous and intramuscular administration to horses. Res. Vet. Sci. 7: 79-83.

Park, S.C., Yun, H.I., Oh, T.K. 1998. Comparative pharmacokiretic profiles of two norfloxacin formulation after oral administration in rabbits. J.Vet. Med. Sci. 60: 661-663.

Pavithra, B.H., Prakash, N., Jayakumar, K. 2009. Modification of pharmacokinetics of norfloxacin following oral administration of curcumin in rabbits. J. Vet. Sci. 10: 293-297.

Preheim, L., Cuevas, T., Roccaforte, J., Mellencamp, M., Bittner, M. 1987. Oral use of ciprofloxacin in the treatment of elderly patients with complicated urinary tract infections due to trimethoprim/ sulfamethoxazole-resistant bacteria. Am. J. Med. 82: 295–297.

Shem –Tov, M., Rav-Hon, O., Ziv, G., lavi, E., Glickman, A., Soran, A. 1998. Pharmacokinetics and penetration of danofloxocin from the blood into the milk of cows. J. Vet. Pharmacol. Therap. 21: 209-213.

Shem-Tov, M., Ziv, G., Gips, M. 1994. Tissue distribution and binding to plasma proteins of norfloxacin nicotinate after intramuscular administration in pigs. Zentralbl. Veterinarmed. B. 41: 257-263.

Walker, R.D., Stein, G.E., Budsberg, S.C., MacDonald, K.H. 1989. Serum and tissue fluid norfloxacin concentrations after oral administration of the drug to

healthydogs. Am. J. Vet. Res. 50:154-157.

Wolfson, J.S., Hooper, D.C. 1985. The fluroquinolones: structures, mechanism of action and resistance and spectra of activity in vitro. Antimicrob. Agents. Chemother. 28: 581-586.

Yuan, L.G., Wan, R., Sun, L.H., Zhu, L.X., Luo, X.Y., Sun, J., Fang, B.H., Liu, Y.H. 2011. Pharmacokinetics of marbofloxacin in Muscovy ducks (Cairina moschata). J. Vet. Pharmacol. Ther. 34: 82-85.

Zlotos, G., Bucker, A., Kinzig-Schippers, M., Sorgel, F., Holzgrabe, U. 1998. Plasma protein binding of gyrase inhibitors. J. Pharmaceut. Sci. 87: 215-220.

حركية ومتبقيات الأنسجة للنورفلوكساسين في الدجاج السليم والمصاب تجريبيا

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الملخص العربي

أجريت هذه الدراسة على عدد 48 من دجاج التسمين (27 سليمة و21 مصابة بميكروب القولون العصوي) وقد تم تقسيم الدجاج إلى 5 مجموعات وذلك لدراسة حركية 10مج/ كجم من وزن الجسم من عقار النورفلوكساسين عند إعطائة مرة واحدة عن طريق الوريد أو عن طريق الفم وعند تناوله بالفم مرة واحدة يوميا لمدة خمسة أيام متتالية ، كم تم قياس معدل خروج الدواء و معدل الأتاحة و بقايا الدواء فى انسجة الدجاج السليم وكذلك المصاب. كما تم أيضا قياس نسبه إتحاد عقار النورفلوكساسين مع بروتينات الدم معمليا. وقد وجد أنه عند حقن النورفلوكساسين فى الوريد مرة واحدة بجرعة 10مج/ كجم من وزن الجسم فى الدجاج السليم أمكن قياس تركيز الدواء فى مصل الدجاج لمدة 24 ساعة بعد الحقن. حيث وصل تركيز النورفلوكساسين فى نهاية ال 24 ساعة إلى 0,29 ±0.09 ميكرو جرام/ مللى. وقد وجد أنه بعد تناول عقار النورفلوكساسين بالفم مرة واحدة بجرعة10مجم/ كجم من وزن الجسم وصل أعلي تركيز للدواء فى الدم بعد ساعتين وهو 3.87 ± 0.04 ميكروجرام / مللى ويستمر وجود الدواء فى الدم حتى 24 ساعة من تناوله ليصل تركيزه 0.28 ± 0.01 ميكرو جرام / مللى. وكان معدل الأتاحة للدجاج السليم بعد تناول عقار النورفلوكساسين بالفم هى 66,89 ± 1.95% وهذه النسبة تعبر عن امتصاص متوسط لعقار النورفلوكساسين بعد تناوله بالفم. وقد وجد معملياً أن نسبة إتحاد النورفلوكساسين مع بروتينات الدم كانت 10,37 ± 0.22 %. وقد لوحظ أنه بعد تناول النورفلوكساسين بالفم مرة واحدة يومياً لمدة خمسة أيام متتالية بجرعة 10 مج/ كجم من وزن الجسم فى الدجاج السيلم وكذلك الدجاج المعدى بميكروب القولون العصوي أن هناك زيادة معنوية فى تركيز الدواء فى مصل الدجاج الدجاج السليم عن تركيزه فى مصل الدجاج المصاب. وبدراسة الجوانب الفارماكوكينتيكية لعقار النورفلوكساسين بعد إعطائه مرة واحدة لمدة خمسة أيام متتالية عن طريق الفم بجرعة 10 مجم / كجم من وزن الجسم وذلك فى الدجاج السليم والدجاج المعدى بميكروب القولون العصوي لوحظ أن معدل الأمتصاص يزداد فى الدجاج المصاب عن الدجاج السليم. كما وجد أن فترة نصف العمر لإفراز الدواء ($t_{0.5\beta}$) تزداد فى الدجاج المصاب عن الدجاج السليم و لوحظ أن عقار النورفلوكساسين يتم اخراجه من الجسم (CL_{tot}) بمعدلات عالية فى الدجاج المصاب عن الدجاج السليم. وعند دراسة بقايا النورفلوكساسين فى انسجة الدجاج السليم وكذلك الدجاج المصاب بعد ايقاف التجريع وجد أن عقار النورفلوكساسين لم يمكن قياسه بطريقة المعايرة الميكروبيه فى جميع الأنسجة التى تم فحصها ما عدا الرئه والكبد والكلى وذلك عند 48 ساعة من اخر جرعة.

(مجلة بنها للعلوم الطبية البيطرية: عدد 26(1):10-18, مارس 2014)