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Pharmacokinetics of Norfloxacin in Control Healthy and *E. coli* Infected Lactating Goats

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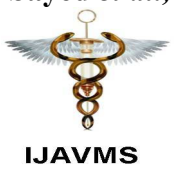
Abstract

The pharmacokinetics of norfloxacin was studied following repeated intramuscular injections in normal and experimentally infected goats. The serum concentrations of norfloxacin following repeated intramuscular injections of 10 mg/kg.b.wt. once daily for five consecutive days, peaked 4 hours after each intramuscular dose with lower significant values recorded in experimentally infected goats than in normal ones. Urine and milk concentrations of norfloxacin were decreased significantly in infected than in normal goats following repeated intramuscular injections. Following a single intravenous injection of norfloxacin in normal goats, serum concentration-time curve was best described by a two compartments open model with elimination half life ($t_{0.5(\beta)}$=5.96 h), volume of distribution (V_d=0.42 L/kg) and total clearance of the drug (CL_{tot}=0.18 ml/kg/min). The mean systemic bioavailability of norfloxacin following intramuscular injection in normal goats was 70.04%. The extent of serum protein binding of norfloxacin in goats was 14.07%. Following intramuscular injection of 10 mg/kg.b.wt of norfloxacin for 5 consecutive days, norfloxacin showed a cumulative behaviour in serum, urine and milk of goats. Results of this study indicated that norfloxacin was useful for treatment of urinary tract infections and mastitis in goats.

Key words: Pharmacokinetics, Goats, Bioavailability, Norfloxacin, Milk.

Pharmacokinetic abbreviations:



Introduction

Norfloxacin is synthetic antimicrobial agent of the fluroquinolones class. Like other fluoroquinolones, norfloxacin acts principally by inhibition of DNA gyrase, an enzyme required for the proper supercoiling of bacterial chromosomes [1]. Norfloxacin is active mainly against Gram-negative pathogens such as *Escherichia coli, Klebsiella spp., Pseudomonas spp*., *Salmonella spp*., and *Campylobacter spp* [2]. However Gram-positive pathogens such as *Staphylococcus aureus, Streptococcus feacalis and Actinobacillus spp*. were susceptible to this drug as well. It has a wide spectrum of activity and rapidly bactericidal at low concentration, often at a minimum inhibitory concentration (MIC) of less than 0.1 µg/ml [3]. The antimicrobial spectrum of norfloxacin makes this drug attractive in veterinary therapy [4,5,6]. Clinical pharmacology of norfloxacin was studied in man, chicken, dog, swine and sheep [1,7,8,9,4]. Little literature were found concerning the pharmacokinetics of norfloxacin in goats. Thus, the aim of present work was undertaken to study the pharmacokinetic parameters of norfloxacin after intravenous and intramuscular administration in normal and experimentally *Escherichia coli* infected goats. Also the bioavailability of norfloxacin was calculated after intramuscular injection in normal goats.

Material and Methods

Drug:

Norfloxacin was obtained as pure powder from Sigma Pharmaceutical Industries Company, industrial zone, Quissina, Menoufia, Egypt. Nicotinic acid was obtained as pure powder from El-Gomhoria Company, Cairo, Egypt. Norfloxacin is a new water soluble synthetic antimicrobial agent of the fluoroqinolone class and is an adduct (1:1) of norfloxacin and nicotinic acid.

Experimental animals:

Twelve lactating goats, eight clinically normal lactating baladi and four experimentally *Escherichia coli* infected lactating goats were used in this investigation. The body weight and age of the tested goats ranged from 20-26 kg.b.wt. and from 2 to 3 years old (for normal goats) and from 22 – 29 kg.b.wt. and from 2.5 to 3.5 years old (for experimentally *Escherichia coli* infected goats). They were housed in hygienic stable fed on barseem, drawa and concentrate and water was provided *ad-libitum*.

Experimental design:

The goats were divided into 3 groups:

Group (1): It included 4 normal post-partum lactating goats. Each goat was injected intravenously into the left jugular vein with 10 mg norfloxacin per kilogram body weight [10]. These goats were left for 15 days after the intravenous injection to ensure complete excretion of norfloxacin from bodies of goats. Then each goat was injected intramuscularly into the gluteus medius muscle with 10 mg norfloxacin per kilogram body weight to calculate the bioavailability of norfloxacin after intramuscular injections.

Group (2): It included 4 post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 10 mg norfloxacin per kilogram body weight, once daily for five consecutive days.

Group (3): It included 4 experimentally *Escherichia coli* infected post-partum lactating goats. Twenty four hours peptone water culture of enteropathogen *Escherichia coli* O_{111} were cultured on nutrient agar plates for 24 hours, then suspension of culture were collected by sterile saline. By opacity tube, the required concentration of 10^9 micro-organisms/ml was obtained. Four milliliters of required concentration (10^9 micro-organisms/ml) were injected subcutaneously in the neck region of goats (Two milliliters in each side). The clinical symptoms of bacteraemia as fever and diarrhea appeared after 48 hours of injection with *Escherichia coli* suspension,then each goat was injected intramuscularly into the gluteus medius muscle with 10 mg norfloxacin per kilogram body weight once daily for five consecutive days.

Collection of samples:

Blood samples:

Blood samples were collected from right jugular vein following a single intravenous and intramuscular injection of norfloxacin in normal goats. (Group 1) at 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours of administration. Blood samples following the second, third, fourth and fifth intramuscular doses in (Groups 2&3) were collected at 0.5, 1, 2, 4, 8, 12 and 24 hours post injection. Serum samples were separated by centrifugation and stored at –20°C until norfloxacin assay.

Urine samples:

Urine samples were taken by using sterile rubber balloon catheter (Folatex No. 41.585.12). Goats were catheterized and bladder was evacuated before each experiment. Following injection of norfloxacin urine samples were taken after 0.25 , 0.50 , 1 , 2 , 4 , 8 , 12 and 24 hours.Urine sample was measured using graduated cylinder and its PH was determined using PH meter (WPA, England). Samples were stored at - 20°C until assay for norfloxacin. After

the end of each experiment, the urinary bladder was irrigated with 15 milliliters potassium permanganate solution 1: 5000 as antiseptic agent.

Milk samples:

The udder was completely evacuated before drug administration and milk samples were collected by hand stripping from both teats. Following repeated intramuscular injections of norfloxacin in normal and experimentally *Escherichia coli* infected goats, milk samples were taken after 0.50, 1, 2, 4, 8, and 12 and 24 hours of administrations, Milk samples from goats of all groups were centrifuged. The skimed milk was collected and stored at – 20°C until assay for norfloxacin.

Analytical procedures

Norfloxacin was determined in biological fluids by modification of the agar-plate diffusion method using *Escherichia coli* ATCC 25922 as assay organism and Muller-Hinton agar media [11]. The protein binding percent of norfloxacin was assayed in normal goat serum according to the method explained by [12]. This estimation was based on the fact that free unbound part of norfloxacin only capable to diffuse through agar. The pharmacokinetic parameters were calculated according to [13.14.15]. All statistical analysis was carried out according to [16].

Results

Following a single intravenous injection of 10 mg norfloxacin/kg b.wt. in normal goats, norfloxacin could be detected therapeutically for 24 hours post intravenous injection. The serum concentration – time curve of norfloxacin following intravenous injection showed that the drug obayed a two compartments open model. The disposition kinetics of norfloxacin following a single intravenous and intramuscular injections were recorded in tables (1&2) and showed in figure (1).

Intramuscular injection of 10 mg norfloxacin / kg.b.wt once daily for five consecutive days in normal and *Escherichia coli* infected goats revealed a lower significant serum norfloxacin concentration at all time sampling in *Escherichia coli* infected goats than in normal goats.The pharmacokinetic parameters of norfloxacin after repeated intramuscular injections in normal goats were compared to those in *Escherichia coli* infected goats (Table 3).

Discussion

In the preset investigation, intravenous injection of 10 mg norfloxacin / kg.b.wt. In normal goats, 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, broiler chicken, pigs, donkeys, rabbits and horses [8,17,9,18,19,20].

Following a single intramuscular injection of 10 mg norfloxacin/kg.b.wt, the drug reached its maximum serum concentrations after 4 hours of injection. Norfloxacin could be detected in serum in a therapeutic level (0.92 µg/ml) at 24 hours. The mean peak serum concentrations of norfloxacin (C_{max}) was achived at maximum time (t_{max} = 4.01 h). The reported (t_{max}) was nearly similar to that reported in dogs 5 h by [21] and differed with those recorded in human (1.5 h) and in chicken (0.6 h) [22,17]. These variations might be attributed to anatomical differences between species, healthy status and the dose administered in each case [23].

The bioavailability of norfloxacin in normal goats was 70.04 %. This value referred to a better absorption of norfloxacin from its site of intramuscular administration. This value was nearly similar to those recorded for norfloxacin in lambs 73.51 %, danofloxacin in goats 65.70 % and pefloxacin in lactating goats 70.63 %, [24,25,26]. On other hand this value was higher than the bioavailabilities recorded for norfloxacin in dogs 35-46 %, donkeys 31.5 % and in rabbits 45 % [8,18,19].

The obtained blood levels of norfloxacin in *Escherichia coli* infected goats were significally lower than those in normal goats following repeated intramuscular administrations. These lower blood concentrations in infected goats might be attributed to the higher penetrating power of norfloxacin to the diseased tissues [27].

The relative higher serum concentrations of norfloxacin after the last dose compared to the first doses indicated the accumulation of norfloxacin in blood during multiple dosing at 24 hours intervals for five consecutive days. These observations agreed with data reported by [28] who found that progressive daily increase in the mean serum concentration following the intramuscular injection of ciprofloxacin in lactating goats in a daily dose of 5 mg/kg.b.wt. for five consecutive days.

The mean peak urine concentrations of norfloxacin were reached 2 hours after each intramuscular injection and 1 hour following single intravenous injection. The lower urine norfloxacin concentrations in Escherichia coli infected goats than in normal goats might be attributed to the accumulation of the drug in the inflammed tissues [27]. The high concentrations

of norfloxacin in the urine, made it suitable for treatment of urinary tract infections in goats. This obtained result in this study was similar with those obtained by [29] who suggested that norfloxacin was effective in the treatment of severe prostatitis and pyelonephritis in human.

Norfloxacin clearance / creatinine clearance ratio was less than 1 and this was an indication for its renal elimination by glomerular filtration. These obtained results were inconsistent with that reported by [9] who found that most of norfloxacin administered to swine was excreted through the kidney by passive filtration through the glomeruli and active excretion via the tubules.

The highest concentrations of norfloxacin in milk were recorded 4 hours after intramuscular injections. These concentrations were significantly decreased in *Escherichia coli* infected goats than in normal goats. This might be attributed to accumulation of the drug in the inflammed tissues [27]. The mechanism of blood–milk passage of norfloxacin could be explained on the basis of the non-ionic passive diffusion principle. Milk concentrations of norfloxacin exceeded the concurrent serum concentrations at 8, 12 and 24 hours after each intramuscular injection in goats. Because of the presence of a carboxylic acid and one or more basic amine-functional groups, norfloxacin, like several other fluoroquinolones, is amphoteric in nature and considered zwitterionic however between the pka of the acidic and basic functional groups, between pH 6 and 8, these compounds are sufficiently lipid-soluble to be able to penetrate tissues [30]. From the obtained results, high milk concentrations of norfloxacin in lactating goats suggested that norfloxacin could be used for treatment of mastitis caused by sensitive organisms in lactating goats as it excreted in milk.

The in-vitro studies on protein binding of norfloxacin to goat's serum was 14.07%. This indicates that the drug is slightly bound to serum protein. The protein binding percent in this study was consistent with those reported in goats for ciprofloxacin (14.2%) and danofloxacin (13.55%) [28,25].

Conclusion: Therapeutic level of norfloxacin in serum of normal and *Escherichia coli* infected goats for 24 hours following intravenous and repeated intramuscular administrations and exceeded the MIC_{90} for most of Gram positive and negative bacteria, recommended once daily dosage. The highest concentrations of norfloxacin in urine and milk indicated that norfloxacin was useful for treatment of urinary tract infections and mastitis in goats. Better absorption of norfloxacin from its site of intramuscular injections.

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Pharmacokinetic abbreviations:

A & B : Zero time plasma drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml).

α & β : Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h-1).

AUC : Total area under the serum drug concentration versus time curve from t = 0 to t = α after administration of a single dose.

C° : Drug concentration in the serum at zero time immediately after a single intravenous injection (µg / ml).

C_{max} **:** Maximum serum concentration of drug in blood after extra vascular administration (µg / ml).

$C\text{-}_{max}$ **:** Maximal serum concentration at steady - state during a multiple dose regimen (µ/ml).

$C\text{-}_{min}$**:** Minimal serum concentration at steady - state during a multiple dose regimen (µg/ml) .

Cl_{tot} **:** The total clearance of a drug , which represents the sum of all Clearance processes in the body (ml/kg /min).

K_{ab} **:** Apparent first order absorption rate constant (h-1).

K_{el} **:** First - order elimination rate constant for disappearance of drug

From central compartment (h-1).

K_{12} : First - order transfer rate constant for drug distribution from Central to peripheral compartment (h-1).

K_{21} : First order transfer rate constant for drug distribution from Peripheral to central compartment (h-1).

K_{13} : First order elimination rate constnt for dispperance of drug from the central compartment (h^{-1}).

$t_{0.5}$: The absorption half- life (h).

$t_{0.5(\alpha)}$: Distribution half - life (h).

$t_{0.50(\beta)}$: Elimination half - life (h).

t_{max} : The time at which the maximum concentration of drug was reached after extra vascular administration (h) .

$V1_c$: The apparent volume of central compartment (ml/kg).

$V_{d(B)}$: The apparent volume of distribution Which calculated by extrapolation method (ml/kg).

$V_{d(area)}$:

The apparent volume of distribution which was calculated by The area method (ml/kg).

V_{dss} :

The apparent volume of distribution which was calculated by Steady - state method (ml/kg).

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Tables

Table (1): Pharmacokinetic parameters of norfloxacin in normal goats following a single intravenous injection of 10 mg/kg.b.wt. (n = 4).

Parameter	Unit	$\bar{X}$ (X±S.E.)
C^{o}	µg/ml	38.15 ± 045
A	µg/ml	24.59 ±0.32
α	h^{-1}	0.29 ±0.01
$t_{0.5(\alpha)}$	h	2.38 ± 0.09
V^{1}_{c}	ml/kg	333.64 ±25.98
V_{dss}	ml/kg	423.60 ± 39.64
$V_{d(\beta)}$	ml/kg	701.36 ± 21.40
$V_{d(area)}$	ml/kg	483.28 ± 33.63
K_{12}	h^{-1}	0.043 ± 0.002
K_{21}	h^{-1}	0.181 ± 0.002
B	µg/ml	13.56 ± 0.25
B	h^{-1}	0.122 ± 0.002
$t_{0.5(\beta)}$	h	5.69 ±0.08
K_{13}	h^{-1}	0.199 ± 0.01
Cl_{tot}	ml/kg/min	0.184 ±0.004

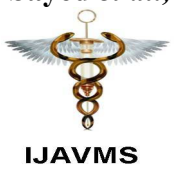

Table (2): Pharmacokinetic parameters of norfloxacin in normal goats following a single intramuscular injection of 10 mg /kg.b.wt. (n = 4).

Parameters	Unit	$\bar{X}$ (X±S.E.)
A	µg/ml	21.01±0.56
K_{ab}	h^{-1}	0.43±0.02
$T_{0.5(ab)}$	h	1.61±0.07
$t_{max\ (obs)}$	h	4.01±0.11
$C_{max\ (obs)}$	µg/ml	11.33±0.43
C^{-}_{max}	µg/ml	12.35±0.33
C^{-}_{min}	µg/ml	0.98±0.05
B	µg/ml	18.34±0.42
K_{el}	h^{-1}	0.143±0.01
$t_{0.5(\beta)}$	h	4.89±0.27
Cl_{tot}	ml/kg/min	1.29±0.07

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Table (3): Pharmacokinetic parameters of norfloxain in normal (N) and experimentally *Escherichia coli* infected goats (E) during repeated intramuscular injections of 10 mg/kg..b.wt. once daily for fire consecutive days (n=4).

Parameter	Unit	1st day		2nd day		3rd day		4th day		5th day	
		_ N (X±S.E)	_ E (X±S.E)	_ N (X±S.E)	_ E (X±S.E)	_ N (X±S.E)	_ E (X±S.E)	_ N (X±S.E)	_ E (X±S.E)	_ N (X±S.E)	_ E (X±S.E)
A	µg/ml	21.50 ±0.28	15.05*** ±0.38	`23.36 ±0.35	15.09*** ±0.77	28.06 ±0.48	16.40*** ±0.89	34.54 ±0.49	26.89*** ±0.69	32.21 ±0.82	28.16** ±0.70
K_{ab}	h^{-1}	0.43 ±0.003	0.42 ±0.01	0.47 ±0.35	0.57 ±0.03	0.44 ±0.01	0.56*** ±0.01	0.43 ±0.01	0.43 ±0.01	0.73 ±0.03	0.70 ±0.05
$t_{0.5(ab)}$	h	1.66 ±0.12	1.67 ±0.04	1.48 ±0.04	1.23 ±0.06	1.41 ±0.14	1.24 ±0.02	1.60 ±0.06	1.63 ±0.06	0.96 ±0.03	0.97 ±0.07
$t_{max\ (cal)}$	h	4.16 ±0.13	3.99 ±0.07	4.12 ±0.02	3.91* ±0.06	4.53 ±0.03	4.01*** ±0.05	4.91 ±0.09	4.08*** ±0.06	4.16 ±0.19	3.67 ±0.20
C_{max}	µg/ml	11.47 ±0.13	8.12*** ±0.24	14.69 ±0.51	8.27*** ±0.13	21.03 ±0.69	12.82*** ±0.98	23.98 ±0.84	16.12*** ±0.26	30.30 ±1.32	21.11*** ±0.44
C^{-}_{max}	µg/ml	11.83 ±0.32	8.97** 0.44±	17.94 ±0.18	9.66*** ±0.45	23.33 ±0.35	14.23*** ±0.53	26.37 ±0.34	19.71*** 0.71±	35.95 ±0.82	25.21*** 0.71±
C^{-}_{min}	µg/ml	0.89	0.60**	1.71	1.70	2.99	2.40*	5.92	2.77***	7.17	5.22**

		±0.05	±0.03	±0.10	±0.04	±0.17	±.0.11	±0.11	±0.13	±0.43	±0.22
B	µg/ml	18.18 ±0.41	12.32*** ±0.35	20.05 ±0.28	12.59*** ±0.34	29.89 ±0.62	18.23*** ±0.99	33.69 ±0.45	26.51* ±2.48	38.29 ±0.58	29.35*** ±0.56
K_{el}	h-1	0.144 ±0.01	.0.13 ±0.004	0.12 ±0.005	0.09** ±0.004	0.11 ±0.005	0.09* ±0.004	.0.09 ±0.005	0.09 ±0.004	0.08 ±0.003	0.08 ±0.01
$t_{0.5\,(\beta)}$	h	4.85 ±0.25	5.35 ±0.17	5.69 ±0.23	7.75** ±0.35	6.20 ±0.27	8.16** ±0.40	7.99 ±0.42	7.79 ±0.36	8.97 ±0.31	8.37 ±0.50
Cl_{tot}	ml/kg/min	1.30 ±0.04	1.69** ±0.07	0.84 ±0.03	1.25*** ±0.04	0.68 ±0.07	1.13* ±0.13	0.42 ±0.02	0.60** ±0.03	0.36 ±0.02	0.53*** ±0.02

* P< 0.05 ** P<0.01 *** P<0.001

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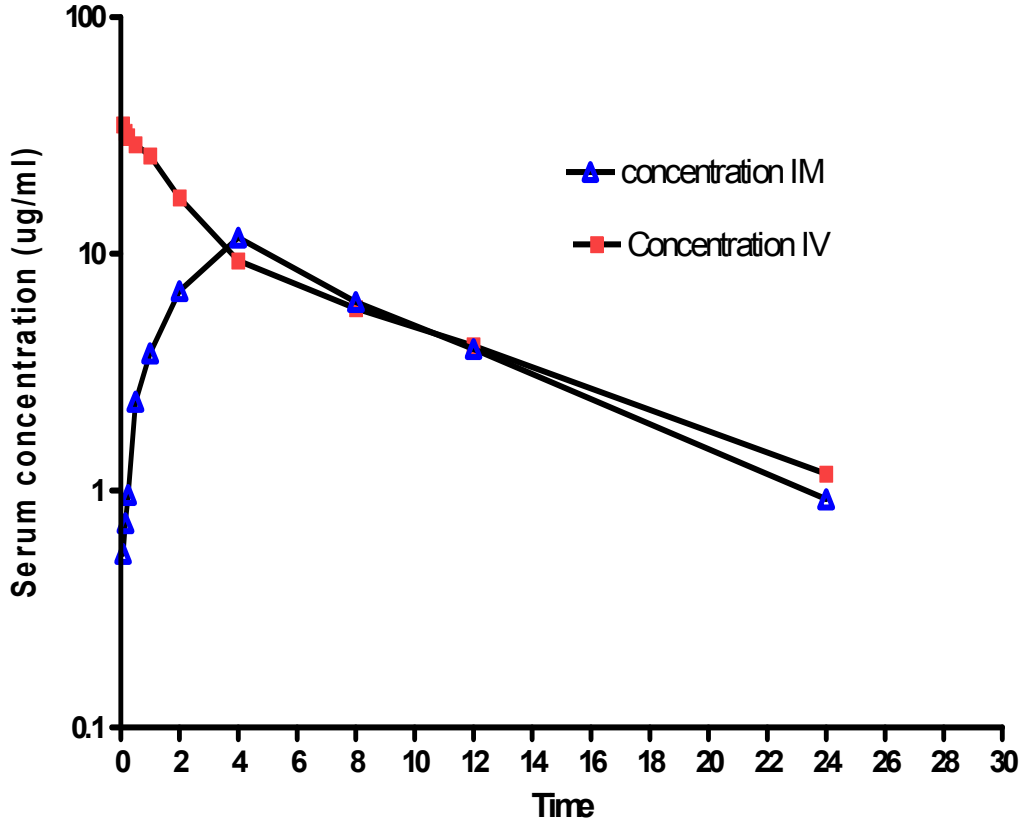

Figure (1): Semilogarithmic graph depicting the time course of norfloxacin in serum of normal goats following a single intravenous and intramuscular injection of 10 mg/kg.b.wt. (n=4).