Pharmacokinetics, Urinary Excretion and Milk Penetration of Marbofloxacin in Lactating Buffaloes

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Abstract: The pharmacokinetics aspects of marbofloxacin were studied in healthy lactating buffaloes after single intravenous (IV) and single intramuscular (IM) injections at a dose of 2 mg/kgb.wt. Drug concentration in blood, milk and urine were determined by microbiological assay. After IV injection, marbofloxacin serum concentration–time curves were characteristic of a two-compartment open model. The distribution and elimination half-lives ($T_{0.5\alpha}$, $T_{0.5\beta}$) were 0.31 and 4.74 h respectively. Following IM injection, peak serum concentration (C_{max}) of 1.49 µg ml^{-1} was attained at 1.36 h. The absorption and elimination half-lives ($T_{0.5ab}$, $T_{0.5el}$) were 0.43 and 3.27 h respectively. The systemic bioavailability of the IM administration (F %) was 99.39%. Following IV and IM administration, the drug penetration into the milk was rapid and extensive with marbofloxacin concentration exceeding those of serum. It was eliminated from the milk by slower rate than that of the serum and the drug was not detected in milk 24h after treatment. Marbofloxacin was detected in the urine in a high concentration than that of serum and reach high level in urine 1 h after administration then decline until 24 h. So marbofloxacinis suitable and effective for injection to buffaloes by a dose of 2 mg/kg every 12 h for treatment of mastitis and urinary tract infection caused by sensitive organism.

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1. Introduction

Fluoroquinolones antibacterial are increasingly being employed in veterinary medicine for treatment of mild to severe bacterial infection (Bakken, 2004). Marbofloxacin is an antimicrobial fluoroquinolone, carbxylic acid derivative recently introduced for use in veterinary medicine (Brown, 1996)**,** high plasma concentration initially is important as the drug act by concentration dependent mechanism. It has extended spectrum of activity which include mainly Gram-negative pathogen and some of Gram-positive and mycoplasma species (Meunier et al., 2004). Marbofloxacin is approved for treatment of respiratory, urinary, dermatological disease and gastrointestinal infectious disease. Similar to other fluoroquinolone, marbofloxacin is a bactericidal antibacterial its mechanism of action is as inhibitor of DNA gyrase is an essential cell enzyme necessary for the supercoiling of DNA, which allows bacterial DNA to fit within the bacterial cell and leads to rapid bacterial cell death (Chu and Fernandes, 1991). In the past therapeutic recommendation of the drug applied to single ruminant species as there is no difference were recognized, but a different pharmacokinetics behavior described along the ruminant species (Elsheikh, 1997). It is important to know the pharmacokinetics of the drugs in each species, in order to minimize dosage errors, which leads to therapeutic failures, toxic effect or bacterial resistance. The pharmacokinetics of the fluoroquinolones drugs includes marbofloxacin may be changed in lactating animals (Soback et al., 1994). The pharmacokinetics of marbofloxacin were evaluated in many species such pregnant or lactating sows (Petracca et al., 1993) and preruminant and ruminant cattle (Thomas et al., 1994a,b). The aim of this study was to determine the pharmacokinetics parameters and the penetration from blood to the urine and milk in lactating buffaloes following single IV and IM injections.

2. Materials and Methods

2.1. Drugs and Chemicals

Marbofloxacin is a novel Fluoroquinolones, available as a 10% solution for injection for cattle and buffaloes under the trade name of Marbocyl®, obtained from (Laboratoire veto quinol, lure, France), and Mueller-Hinton agar was purchased from Mast Group Ltd., Merseyside, UK.

2.2. Experimental animals.

Experiment was conducted on five clinically normal lactating buffaloes weighing (300-400Kg). Buffaloes located at farm of faculty of veterinary medicine, Benha University, Egypt. They were housed in hygienic stable fed antibacterial free ration, fed on barseem, draw and concentrate and water was provided ad-libitum. During acclimatization (at least three weeks before starting the experiment to ensure the complete withdrawal of any residual drugs) and

subsequent treatment periods, their health status was checked by daily observations and no clinical signs diseases were seen. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Benha University, Egypt.

2.3. Experimental Design

Post-partum lactating buffaloes were individually weighed before drug administration and doses were calculated precisely. Marbofloxacin was injected intravenously into the left jugular vein with 2 mg/kg b.wt (Shem-Tov et al., 1997)**.** These animals were left for 15 days after the IV injection to ensure complete excretion of marbofloxacin from bodies of buffaloes, then each buffalo was injected intramuscularly into lower third region of the neck with the same dose.The aim of a single IM injection was to calculate the bioavailability of marbofloxacin in normal buffaloes. Blood samples (10 ml) were collected from right jugular vein immediately prior to medication (time = 0) and then at 0.08, 0.17, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after treatment, serum was separated after centrifugation at 3,000 g for 15 minutes. The serum was decanted, labeled, and frozen at -20°C until the assays were performed. The urine samples were taken by using sterile catheter. The buffaloes were catheterized and bladder was evacuated before each experiment. Following injection of marbofloxacin (single IV and IM injection), urine samples were taken after 0.25, 0.50, 1, 2, 4, 8, 12 and 24 hours of administration. All urine samples were stored at -20°C until assay of marbofloxacin. Urine samples after single IV injection were diluted with phosphate buffer (1:5). After the end of each experiment, the urinary bladder was irrigated with 15 ml potassium permanganate solution 1:5000 as antiseptic agent.

The udder was completely evacuated before drug administration and milk samples were collected by hand stripping from both teats. Following injection of marbofloxacin (single IV and IM) in normal buffaloes milk samples were taken after 0.50, 1, 2, 4, 8, 12 and 24 hours.The udder of each buffaloes was completely evacuated before taken milk samples.

2.4. Analytical Method

The concentration of marbofloxacin in serum, milk and urine samples was estimated by a standard microbiological assay using *Escherichia coli* ATCC 10536 as test microorganism (Bennett et al., 1966). This method estimated the level of drug having antibacterial activity, without differentiating between the parent drug and its active metabolites. The application of microbiological assay for measuring marbofloxacin concentration is suitable (Albarellos et al., 2005). Standard curves were constructed using antibacterial free serum, milk and urine collected from buffaloes. The wells were filled with 100 µL of either the test samples or marbofloxacin standards. The plates were kept at room temperature for 2 h before being incubated at 37°C for 18 h. Zones of inhibition were measured using micrometers, and the marbofloxacin concentrations in the test samples were calculated from the standard curves. The calibration curves of serum were prepared with different concentrations between 0.025 and 50 µg/ml using blank buffalo serum, milk and urine. The limit of quantification (LOQ) was 0.025 µg/ml of marbofloxacin in supplemented buffalo serum and urine but limit of quantification (LOQ) was 0.05 µg/ml using blank buffalo milk under our experimental conditions, the linearity of the method was from 0.05 to 50 µg/ml of marbofloxacin in buffalo serum, urine and milk.

2.5. Pharmacokinetic Analysis

Serum concentrations of marbofloxacin after IV and IM injections were subjected to a compartmental analysis. The analysis was done with the help of a computerized program WinNonlin 4.1 (Pharsight, Mountain View CA, USA) was used to analyze the concentration-time curves for each individual buffalo after the administration of marbofloxacin. Following IV administration, the serum concentration vs time data of marbofloxacin in buffaloes were fitted to a two-compartment open model system according to the following bi-exponential equation (Baggot, 1978):

$C_p = Ae^{-\alpha t} + Be^{-\beta t}$

where C_p is the concentration of drug in the plasma at time t, A and B are the zero-time drug intercepts of the distribution and elimination phase expressed as µg/ml, α and β are the distribution and elimination rate constants expressed in units of reciprocal time (h^{-1}), and e is the natural logarithm base.

For the IV 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). The volume of distribution at steady state (V_{dss}), the total body clearance (Cl) and mean residence time (MRT) were computed according to standard equations (Gibaldi and perrier, 1982). Following IM injection, serum concentration data in buffaloes were analyzed by compartmental and non-compartmental methods based on the statistical moment theory (Gibaldi and perrier, 1982). The area under the concentration time curve (AUC), and area under the first moment curve (AUMC), was calculated by the method of trapezoids. Mean residence time (MRT) was calculated as MRT =AUMC/AUC and the systemic clearance as Cl= Dose/AUC. The absolute bioavailability was calculated as $F = AUC_{IM}/AUC_{IV} \times 100$. The pharmacokinetic parameters were reported as mean± SE.

3. Results

Clinical examination of all buffaloes before and after each trial did not reveal any abnormalities. No local or adverse reactions to marbofloxacin occurred after IV and IM administrations. The mean serum concentration-time profiles of marbofloxacin following single IV and IM administrations of 2 mg/kg bwt in healthy buffaloes were presented graphically in Figure 1. Pharmacokinetics parameters estimated from the curve fitting following IV and IM administrations were shown in Tables 1 and 2. The drug antimicrobial activity was less than 0.1 µg/ml well maintained at least for 12 h after IV and IM injection. Drug bioavailability after IM route was 99.39% for buffaloes. Urine and milk concentrations (µg ml^{-1}) of marbofloxacin in lactating buffalo following IV and IM administration of 2 mg/kg b.wt. were shown in Table 3. Marbofloxacin was rapidly penetrated from blood into milk and urine after IV and IM treatment. Drug concentration in the milk is higher than of the serum at 2 h and the drug equivalent activity well be maintained in the milk till 24 h; marofloxacin was eliminated from the milk by slower rate than that of the serum. Marbofloacin was rapidly eliminated from the blood into urine and detected in the urine by a concentration higher than that of serum and reach high level in urine 1 h after administration then decline until reach 24 h remain higher than MIC for the bacterial infection to the urinary bladder≥0.1µg/ml.

Table (1): Pharmacokinetic parameters of marbofloxacin in buffaloes following a single IV injection of 2 mg/kg.b.wt in buffaloes (n=5).

Parameters	Unit	(X±S.E)
C^o	µg ml^{-1}	2.83±0.21
A	µg ml^{-1}	1.41 ±0.23
B	µg ml^{-1}	1.41 ±0.24
α	h^{-1}	2.63 ±0.92
B	h^{-1}	0.15±0.02
$T_{0.5\alpha}$	h	0.31 ±0.18
$T_{0.5\beta}$	h	4.74 ±0.93
AUC	µg ml^{-1} h^{-1}	10.51 ±0.44
AUMC	µg ml^{-1} h^{-2}	63.09±6.95
MRT	h	5.98±0.41
CL	L kg^{-1} h^{-1}	0.19 ±0.01
Vd^{ss}	L kg^{-1}	1.14 ±0.03

C° 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 after IV injection , respectively; $\mathbf{T_{0.5(\alpha)}}$ distribution half-life after IV injection; $\mathbf{T_{0.5(\beta)}}$ elimination half-life after IV administration; **AUC**; area under serum concentration-time curve; **AUMC** area under moment curve; **MRT** mean residence time; $\mathbf{Vd_{ss}}$ volume of distribution at steady state; **Cl** total body clearance.

Table (2): Pharmacokinetic parameters of marbofloxacin in buffaloes following a single IM injection of 2 mg/kg b.wt in buffaloes previously given the same dose by a single IV injection (n=5).

Parameters	Unit	X±S.E
A	µg ml^{-1}	2.03±0.22
B	µg ml^{-1}	2.31±0.13
K_{ab}	h^{-1}	1.60±0.08
K_{el}	h^{-1}	0.21±0.01
$T_{0.5(ab)}$	h	0.43±0.05
$T_{0.5(el)}$	h	3.27±0.22
AUC	µg ml^{-1} h^{-1}	10.43±0.24
AUMC	µg ml^{-1} h^{-2}	55.09±1.48
MRT	h	5.27±0.22
C_{max}	µg ml^{-1}	1.49±0.06
T_{max}	h	1.36±0.10
F	%	99.39±4.45
C_{max}/MIC	Ratio	93.65±1.69
AUC/MIC	Ratio	655.53±8.03

$\mathbf{k_{ab}}$; $\mathbf{K_{el}}$ absorbtion and elimination rate constant after IM administration; $\mathbf{T_{0.5(ab)}}$ absorbtion half life after IM administration; $\mathbf{T_{0.5(el)}}$ elimination half life after IM administration; $\mathbf{C_{max}}$ maximum serum concentration; $\mathbf{T_{max}}$ time to peak serum concentration; **F** fraction of drug absorbed systemically after IM injection; $\mathbf{C_{max}/MIC}$ maximum serum concentration/minimum inhibitory concentration ratio; **AUC/MIC** area under the plasma concentration–time curve/MIC ratio.

Table 3. Mean ± SEM of urine and milk concentrations (µg ml^{-1}) of marbofloxacin in lactating buffaloes following IV and IM administration of 2 mg/kg b.wt.) (n=5).

Time (h)	Mean ± SEM			
	IV		IM	
	Milk	Urine	Milk	Urine
0.5	0.41±0.01	21.16±0.14	0.25±0.01	9.22±0.08
1	0.72±0.01	24.06±0.21	0.30±0.01	12.34±0.15
2	1.60±0.03	18.8±0.15	0.41±0.01	10.32±0.17
4	1.15±0.01	15.42±0.16	0.70±0.03	6.70±0.15
8	0.62±0.01	5.68±0.14	0.50±0.02	3.16±0.13
12	0.40±0.13	2.40±0.13	0.22±0.01	1.22±0.06
24	0.15±0.01	0.15±0.01	0.08±0.01	0.13±0.01

4. Discussion

The present investigation revealed that the elimination half-life of marbofloxacin in healthy buffaloes following IV injection was 4.74 h. This observation agreed with the data reported for marbofloxacin in calves (4.6 h; Ismail and El-Kattan, 2007), longer than that reported in calves (1.61 h; Dumka and Srivastava, 2007) and shorter than that

reported in rabbits (7.5 h; Destache et al., 2001)and donkey (9.24 h; Gonzalez et al., 2007). The apparent volume of distribution was 1.14 L/kg, suggesting good penetration through biological membranes and tissue distribution after IV injection. This value was similar to those values reported for marbofloxacin in lactating ewes (1.3L/kg; Fernandez-Varon et al., 2006) and levofloxacin in quails (1.27 L/kg; Aboubakr, 2012), higher than that reported in lactating goats (0.73 L/kg: Goudah and Abo El-Sooud, 2009) and lower than that reported for danofloxacin in ducks (5.41 L/kg; Goudah and Mouneir,2009). This difference might be attributed to anatomical difference between animals and method of detection of antibiotics. The total body clearance of marbofloxacin following IV injection was 0.19L/kg/h; these results agreed with the data reported for levofloxacin in stallion (0.21 L/kg/h; Goudahet al., 2008). The high value of AUC (10.51 µg/ml/h) reflects that a vast area of the body is covered by drug concentration.

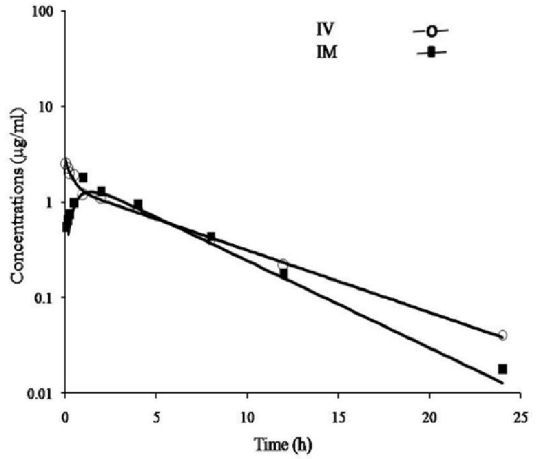

Figure 1. Semi-Logarithmic graph depicting the time-concentration of marbofloxacin in serum of buffaloes after a single IV (○) and IM (■) administration of 2 mg/kg b.wt. (n=5).

Following IM injection, marbofloxacin was rapidly absorbed as the absorption half-life (0.43 h). The obtained value was similar to levofloxacin in lactating goats (0.54 h; Goudah and Abo-El-Sooud, 2009) and marbofloxacin in ducks (0.34 h; Goudah and Hasabelnaby, 2011). The elimination half-life was 3.27 h; this observation was similar to levofloxacin in lactating goats (3.64 h; Goudah and Abo-El-Sooud, 2009), shorter than the data reported for marbofloxacin in ducks (4.61 h; Yuan et al., 2011) and longer than that for moxifloxacin in chickens (1.69 h; Goudah, 2009). Maximal plasma concentration was 1.49 µg/ml achieved at 1.36 h. These values were similar to those for marbofloxacin in ducks (1.13 µg/ml at 1.41 h; Yuan et al., 2011) and lower than those for pefloxacin in chicken (3.78 µg/ml at 3.33 h; Pant et al., 2005). Bioavailability is the fraction of a drug administered by any nonvascular route that gains access to the systemic circulation. Following IM injection, the systemic bioavailability of marbofloxacin in healthy buffaloes was 99.39% which is almost the same with was similar to the values reported by Waxman et al., 2001, who recorded the bioavailability of marbofloxacin in lactating goats were (100.74%).

The *in-vitro* studies on protein binding of marbofloxacin to buffalo serum Was 13.63%. 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%; El-Banna and Abo El-Sooud, 1998) and danofloxacin (13.55%; Atef et al., 2001).

Based on many *in vitro* and *in vivo* studies performed in humans and animals, it has been established that for concentration dependent antibacterial agents, such as fluoroquinolones, the AUC/MIC ratio is the most important factor in predicting efficacy, with the rate of clinical cure being greater than 80%, when this ratio is higher than 100–125 (Forrest et al., 1993; Lode et al., 1998). A second predictor of efficacy for concentration dependent antibiotic is the ratio/MIC, considering that values above 8–10 would lead to better clinical results and to avoidance of bacterial resistance emergence (Dudley, 1991; Madaras-Kelly et al., 1996; Walker, 2000). Marbofloxacin pharmacokinetic/pharmacodynamics integration revealed significantly higher values for C_{max}/MIC and AUC/MIC ratios in healthy buffalo, indicating the excellent pharmacokinetic characteristics of the drug. So marbofloxacin given by IM injection was effective against bacterial strain isolates with MIC≤0.016 µg/ml. The MIC_{90} of 0.016 µg/ml was reported as minimum therapeutic concentration (MIC_{90}) for marbofloxacin against most bacteria (Schneider et al., 2004). Following IM administration in healthy buffaloes, C_{max} /MIC ratio of 93.65 and AUC/MIC ratio of 655, indicates potential clinical and bacteriological efficacy of marbofloxacin in buffaloes.

Mastitis is a major disease affect in production of buffaloes, it is generally accepted that xenobiotic cross the blood milk barrier in the udder by non-ionic passive diffusion is influenced by the physicochemical properties of the drug (Atkinson and Begg, 1990). Because of the presence of a carboxylic acid and one or more basic amine-groups, Marbofloxacin like several fluoroquanilone is amphoteric. However, between the PK_a of the acidic and the basic functional groups (between PH 6 and 8), these compound are sufficiently lipid soluble which able to penetrate tissues (Brown, 1996). The milk is considered as

peripheral body compartment. Extensive penetration of marbofloxacin from blood to milk and considerable amount of drug can be found in the milk (Atkinson and Begg, 1990). The accumulation of marbofloxacin in milk resemble to other quinolones as enrofloxacin in cows (kaartinen et al., 1995) and marbofloxacin in lactating ewes (Shem-Tov et al., 1997). Moxifloxacin penetration from blood to milk was quick for both routes of administration and high milk/plasma ratios indicated a wide penetration of moxifloxacin into the milk (Fernandez-Varon et al., 2006). From the obtained results, high milk concentrations of marbofloxacin in lactating buffaloes suggested that marbofloxacin could be used for treatment of mastitis caused by sensitive organisms.

In the present study, the urine concentrations of marbofloxacin were greater than the concurrent serum concentrations following IV and IM injections. This result similar to that recorded after administration of norfloxacin in pigs (Shem-Tov et al., 1994) and levofloxacin in lactating goats (Goudah and Abo-El-Sooud, 2009). The high concentration of marbofloxacin in urine of buffaloes is an indication for renal elimination and is considered the main route of elimination of drug.

5. Conclusion

These data allow the conclusion that marbofloxacin administered IV and IM to buffaloes at a dose rate of 2 mg/kg bwt could be useful in treatment bacterial infection mainly causes mastitis and urinary tract infection.

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