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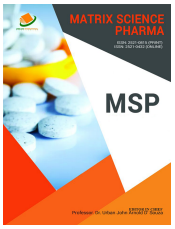

RENAL CLEARANCE AND URINARY EXCRETION OF MOXIFLOXACIN IN HEALTHY MALE VOLUNTEERS

Asia Farid*, Tanweer Khaliq, Hafiz Alam Sher, Atifa Mushtaq, Abdullah Abid

Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture Faisalabad, Faisalabad, Pakistan
****Corresponding Author Email: asiafaridsa@gmail.com***

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ABSTRACT

Moxifloxacin is a 4th generation fluoroquinolone. Study was planned on renal clearance and urinary excretion of moxifloxacin on healthy male volunteers by applying sensitive, rapid and accurate HPLC-UC analytical method. For this study 8 healthy male subjects similar in all physical conditions were selected. Moxifloxacin (Avelox® 400 mg) was administered orally under fasting conditions. First sample of urine and blood was collected before administration of moxifloxacin and other samples of blood were taken at 0.5, 1.5, 2.5, 3.5 hr and urine samples were withdrawn at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hr. The pH of the samples was measured by pH meter. Blood and urine samples were analyzed with HPLC for drug determination. Endogenous creatinine was measured by reagent kit method. The plasma concentration of endogenous creatinine and drug were 12.61 ± 0.85 µg/mL and 1.678 ± 0.062 µg/mL. The renal clearance of endogenous creatinine ranges from 1.17 to 3.18 ml/min/kg with an average ± SE value of 2.67 ± 0.24 mL/min/Kg. Renal clearance of moxifloxacin was 0.476 ± 0.04 mL/min/Kg ranged between 0.27 – 0.609 mL/min/Kg. Urinary excretion of moxifloxacin calculated as cumulative percent dose excreted 20.48 ± 0.88. A positive relationship was found between diuresis and renal clearance of drug indicated that besides glomerular filtration passive diffusion is also involved at kidney tubular level.

KEYWORDS

Moxifloxacin, fluoroquinolone, Blood, Endogenous creatinine, glomerular filtration, kidney tubular.

1. INTRODUCTION

The fluoroquinolones are a rapidly growing family of synthetic antibiotics that has proved to be helpful in cure of number of ailments. Moxifloxacin is an important fluoroquinolone with broad spectrum of antibacterial activity being used to treat variety of infection in human being and animals. Moxifloxacin is readily absorbed and thoroughly distributed in body after oral dose. Moxifloxacin is not bio transformed by cytochrome P450 system rather it is metabolized by microsomal enzymes [1]. In clinical studies moxifloxacin has shown 88 – 97% success rate and 90 - 97% eradication rates of bacteria. No dose adjustment has been required in patients with renal impairment or mild to moderate hepatic dysfunction. Moxifloxacin is safe and effective antibiotic and very helpful in treatment of community acquired pneumonia and acute bacterial exacerbation of chronic bronchitis [2].

Asian population is living under a varying degree of geographical and environmental settings that could affect their lives in different ways. The knowledge related to health, disease, nutritional conditions, environmental and genetic factors effecting health states of man, is acquired from literature of the western countries, which are different from those of the Asian countries. Previous studies have indicated that drug disposition kinetics, renal clearance and urinary excretion should be determined in the environment and species where the drug is to be employed clinically [3,4]. The study of urinary excretion of a dug after administration of drug provides important information regarding distribution, absorption and excretion parameter of drug from body. Measurement of renal clearances is important in clinical practice. Determination of renal clearance is important to assess kidney function, response to treatment, progression of kidney disease and to assess the dialysis requirement [5].

There are many methods for the evaluation of moxifloxacin in human body fluids. These methods are reverse-phase HPLC/fluorescence, high-performance liquid chromatography (HPLC), capillary electrophoresis voltammetry. HPLC has been used commonly for the quantitative analysis of quinolones in animal tissues and body fluids [6]. The present study was conducted to increase the understanding of the contribution of factors such as demographics variability in the renal clearance and urinary excretion of this drug in indigenous conditions.

2. MATERIALS AND METHODOLOGY

2.1 Chemicals

A commercial preparation of Moxifloxacin, tablets Avelox®, 400 mg (Bayer HealthCare, Pakistan) was used in the present study. Heparin sodium salt (B. Braun Melsungen AG, Germany), Moxifloxacin standard was 97.99 % pure, Ethylene Diamine Tetraacetic Acid (EDTA), Acetonitrile (RCI LABSCAN LIMITED, THAILAND), Methanol (FISHER SCIENTIFIC LIMITED, UK), Deionized water, Dichloromethane Sodium chloride, Phosphate buffer. All the solvents were of analytical grade.

2.2 Instrumentation and chromatography

Chromatography was performed with a High-Performance Liquid Chromatograph (Sykam, S-1122) and analyses were determined using UV detector (Sykam, S-3210). A stainless-steel column packed with YMC pack A-312 (BDS-C18 with 250 x 4.6mm dimensions and 5µm particle size) was used. The output of the detector was monitored with computer software (Peak Simple Chromatography Data System, Buck Scientific Inc., East Norwalk). Analytical Balance (Sartorius, Germany). Centrifugation Machine (MSE Micro Centaur, Sanyo UK). Sonication apparatus (Oqawa seiki Co, Japan). Sample Injector Sykam S5111 Valve Bracket.

2.3 Stock solutions and standards

Moxifloxacin was made up as 1 mg / ml stock solutions in methanol and distilled water (1:10 by volume). The calibration curve of moxifloxacin in plasma was prepared by making the standard dilutions (10-100 µg/ml) from the moxifloxacin stock solution (1 mg/ml) prepared in drug-free (controlled) plasma. The calibration curves of moxifloxacin in controlled urine was prepared by making the standard dilutions (320, 160, 80, 40 and 20 µg/mL)

from the stock solutions (1 mg/ml) of moxifloxacin prepared in drug-free controlled. Aliquots of these working standard solutions were stored at -20 °C. This range was based on the concentration of moxifloxacin in human plasma after oral administration of 400 mg dose. These solutions were filtered through Whatman membrane filters of 0.45 mm pore size (25 mm filter) and 20 µL was injected into HPLC for analysis. Calibration graph was prepared by using peak area verses concentrations of working solutions.

2.4 Study design

Eight healthy male volunteers were recruited to participate in this study. The average age was 25years (range25-27) and the average weight was70 kg range (68-74 kg). The study protocol was approved by the ethical committee at University of Agriculture Faisalabad. The nature of the study was explained to the volunteers and a written consent was obtained from each volunteer. All the volunteers had normal kidney and liver functions and were free from any chronic disease such as hypertension, diabetes, hypotension or liver abnormalities. First sample of urine and blood was collected before administration of moxifloxacin and other samples of blood were taken at 0.5, 1.5, 2.5, 3.5 hr and urine samples were withdrawn at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hr.

2.5 Plasma Sample Preparation

Plasma was prepared from heparinized whole blood samples collected from the volunteers 250µL of the plasma samples were taken and transferred to 2 ml polyethylene vial in which 1 ml of acetonitrile and acetic acid were already added. The samples were centrifuged at 4000 rpm for 1 min. The aqueous layer was discarded, and the organic phase was transferred to 2 ml glass vials. The solvent was evaporated to dryness at 40 °C under stream of nitrogen. The residue was re-dissolved in 250 µL of mobile phase, of which 20 µL was taken and injected in chromatographic column for moxifloxacin analysis.

2.6 Urine Sample Preparation

Frozen urine was allowed to thaw at room temperature. Dichloromethane (5 ml), sodium chloride (0.25 g) and 0.5 M phosphate buffer (pH 8.0) (500 µl) were added to 1.0 ml of urine in a screw capped tube. After shaking with a vortex mixer for 10 min and centrifugation at 4000 rpm for 15 min, the aqueous layer was discarded. The remaining organic phase was transferred into a new glass tube and evaporated with a vacuum evaporator at 40°C. The residue was reconstituted with 200 µL of the mobile phase and 20 µ1 were injected into the HPLC apparatus.

2.7 Preparation of mobile phase

The mobile phase was consisted of Acetonitrile, double distilled water and Methanol. The water for mobile phase was prepared by double glass distillation. The ratio of methanol, acetonitrile and water was 45:30:25. After mixing the solvents, mobile phase was passed through filtration assembly, having the filter paper size of 0.45 µm Whatman (Schleicher & Schuell 12.5 mm. Then, the filtered mobile phase was sonicated for 15 minutes to remove any air bubbles.

2.8 Creatinine analysis

The creatinine concentration in plasma and urine samples was determined by using spectrophotometer (spectronic212, Bausch & Lomb, Germany) according to method of Bonsnes and Taussky (1945) by Jaffe-reaction after treating creatinine reagent kit.

3. RESULTS

The renal clearance of creatinine and moxifloxacin and urinary excretion of moxifloxacin was investigated in eight healthy males after the per-oral dose (OD) of 400 mg tablets. Blood and urine samples were collected at predetermined intervals of time for the measurement of diuresis (rate of urine flow), renal clearance of creatinine and moxifloxacin. Following result show Mean ± S.E values of the above-mentioned variables.

3.1 Renal clearance

The results of renal clearance are summarized in the table1. The Mean ± SE value of diuresis in male was 0.046 ± 0.0015 mL/min/kg. Value ranged from 0.043 to 0.05 mL/min./kg. The concentration of endogenous creatinine in plasma ranged from 10.2 – 17.2 µg/mL with a Mean ± SE value 12.61 ± 0.85 µg/mL. The values of creatinine concentration in urine varied form 777.35 µg/mL to 1637.5 µg/mL with a Mean ± SE value of 1130 ± 96.09 µg/mL. The Mean ± SE value of renal clearance of endogenous creatinine found to be 2.67 ± 0.24 mL/min/kg. The Mean ± SE value of plasma moxifloxacin concentration in the blood sample was found to be 1.68 ± 0.05 µg/mL ranged from 1.55 – 1.89 µg/ml. Mean ± SE moxifloxacin concentration in urine sample was found to be 27.18 ± 2.45 µg/mL. The value ranged from 20.14 – 43.0 µg/mL. The Mean ± SE value of renal clearance of moxifloxacin was found to be 0.476 ± 0.04 mL/min/kg. Its value ranged from 0.27 – 0.609 mL/min/kg. The Mean ± S.E value of ratio was 0.203 ± 0.045 range (0.092 - 0.503).

Table 1: Average data of renal clearance of endogenous creatinine and moxifloxacin in 8 healthy male volunteers after oral administration of moxifloxacin 400 mg

Sr. No	Body Wt Kg	Diuresis ml/min /kg	pH		Creat. Conc µg/ml		Creat Cl ml/ min/kg	Drug Conc µg/ml		Renal Clearance of drug µg/ml	Cl Ratio Cl drug/ Cl cr
			Blood	Urine	Plasma	Urine		Plasma	Urine		
1	68	0.048	7.46	6.13	17.2	777.3	1.17	1.89	43.0	0.591	0.503
2	70	0.05	7.49	7.0	12.95	1637	2.953	1.74	20.14	0.270	0.092
3	73	0.045	7.44	6.05	13.63	1187	3.18	1.59	23.56	0.540	0.170
4	71	0.043	7.45	6.78	10.05	997.2	3.073	1.55	29.42	0.588	0.191
5	69	0.046	7.47	6.68	11.23	1019	2.671	1.80	24.66	0.403	0.151
6	72	0.045	7.44	5.90	10.2	889.3	2.361	1.64	24.1	0.398	0.169
7	74	0.047	7.50	5.58	14.18	1212.	2.837	1.46	26.80	0.609	0.215
8	70	0.045	7.46	6.10	11.45	1325	3.163	1.71	25.73	0.411	0.130
Mean± SE	**70.9 ±0.72**	**0.046 ±0.0015**	**7.46 ±0.007**	**6.28 ±0.17**	**12.61 ±0.85**	**1130.7 ±96.09**	**2.67 ±0.24**	**1.68 ±0.05**	**27.18±2.45**	**0.476±0.04**	**0.203 ±0.045**

3.2 Correlation between Diuresis, pH of Urine VS Clearance Ratio

There is significant (<0.05) positive correlation (r=0.1356) between rate of urine flow and moxifloxacin renal clearance as shown in Figure 1. There is a non-significant and positive correlation (r=0.2830) between pH of urine and moxifloxacin clearance as shown in Figure 2.

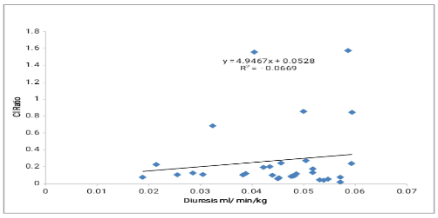

Figure 1: Relationship between pH of urine and renal clearance of moxifloxacin

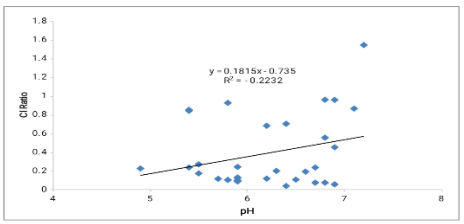

Figure 2: Relationship between diuresis and Renal clearance of moxifloxacin

3.3 Urinary Concentration

The results of urinary excretion of moxifloxacin are expressed in terms of amount excreted in mg and cumulative percentage dose excreted. Dose (mg) of moxifloxacin excreted in urine has been graphically presented in Figure 3. The mean ± SE value for mg of dose excreted in urine at 1hr was 4.28 ± 0.77 mg. At 2 hr mean ± SE value was 3.58± 0.64 mg. Mean ± SE values at 3 and 4 hr were 7.33 ± 0.55 and 5.56 ± 0.81 mg respectively. At 6 and 8 hr the value of mean ± SE for dose excreted in mg were7.50 ± 0.76 and 2.23 ± 0.47. Mean ± SE values were 8.96 ± 0.29 mg (range 7.36 – 10.14 mg) at 10 hr, 20.69 ± 1.85 at 12 hr, and 9.68 ± 1.44 at 24 hr. At 36 hr and 48 hr the value of mean ± SE were 4.16 ± 0.29 mg and 6.304 ± 0.65 mg (2.55 – 8.47) respectively. The cumulative percent does of moxifloxacin excreted at 12, 24, 36 and 48 hr post medication of moxifloxacin 400 mg oral administration in urine male volunteers is presented in Table 2. Mean ± SE values was 15.4 ± 0.61 (range 13.64 –18.22) at 12 hr, 17.86 ± 0.70 (range 16.05 – 21.10) at 24 hr, 18.90 ± 0.76 (range 0.26 – 3.10) at 36 hr. At 48 hr the value of mean ± SE was 20.48 ± 0.88% (ranged from 17.61 – 24.71) respectively.

Table 2: Cumulative percent dose excreted in urine after oral administration of moxifloxacin 400 mg in eight volunteers

Sr. No	Time hr			
	12	24	36	48
1	18.22	21.10	22.59	24.71
2	16.18	16.43	17.44	19.16
3	13.64	16.49	17.32	19.05
4	17.63	20.74	21.89	23.84
5	15.1	18.1	19.08	20.32
6	14.16	17.08	18.05	19.57
7	14.6	16.05	16.97	17.61
8	14.01	16.91	17.88	19.55
Mean ± SE	**15.4 ±0.61**	**17.86 ±0.70**	**18.90 ±0.76**	**20.48 ±0.88**

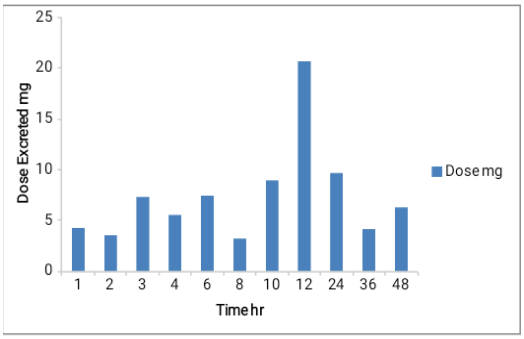

Figure 3: Mean dose (mg) of moxifloxacin excreted urine after oral administration of moxifloxacin 400 mg in male volunteers

4. DISCUSSION

There is no single mechanism to describe renal handling of endogenous and exogenous substances. The multiple mechanisms of glomerular filtration, active or passive back diffusion and active secretion, alone or in combination, are involved in the renal handling of these substances. It was studied that fluoroquinolones (FQs) exist as charged molecules in blood and urine making their absorption, distribution, and elimination likely to be affected by active transport mechanisms. Due to their zwitter ionic nature, fluoroquinolones are likely to interfere with cation transporters and organic anion within the solute carrier (SLC) superfamily. The ATP binding cassette (ABC) transporters also may interact with them [7]. The main functions of kidney are urine formation and water conservation, and this is the major channel of water excretion as compared to intestine, skin and lungs. As the glomerular filtrate flow through the tubules, over 99% of its water and varying amount of its solute are normally are absorbed into the vascular system and small amounts of some substances are secreted into the tubules. The remaining tubular water and dissolved substances become urine [8]. The average ± SD for rate urine flow in this study is 0.046 ± 0.0007 ml/min/Kg. This value is comparable to mean ± SE value for diuresis 0.018 ± 0.0056 ml/min/Kg, ranged from 0.011 to 0.05 ml/min/Kg [9]. The volume and composition of body fluid is mainly regulated kidneys through an adjustment in composition and volume of urine voided which profoundly influenced by environmental temperature. As in summer evaporation via sweating causes reduced urine flow during summer, while lower temperature of winter increases the urine flow in winter. It has been observed in mammal including humans propose that variation in serum creatinine (SC) and estimated glomerular filtration rate (eGFR) may take place during summer [10].

Renal clearance of endogenous creatinine is used as an index of glomerular filtration rate (GFR). In present study renal clearance of endogenous creatinine ranges from 1.17 to 3.18 ml/min/Kg with an average ± SE value of 2.67 ± 0.24 ml/min/Kg which are comparable to mean ± SE value 0.519 ± 0.068 ranged from 0.379 to 0.911ml/min/Kg reported in an earlier study [9]. Such differences have already been found not only in human being but also in other species under indigenous showing GFR (creatinine clearance) values that are higher than the values given in literature. The reason might be environmental influences on genetics [11]. The mean ± SE value of renal clearance of moxifloxacin in present study was 0.476 ± 0.043 ml/min Kg, ranged between 0.27-0.609 ml/min/Kg (26.37 ml/min). It was comparable to the mean value of renal clearance of moxifloxacin that was 1.3-3 L/hr (35.83 ml/min) reported in an earlier study [12]. The clearance equals the GFR if there is no net tubular secretion or reabsorption. The clearance of substance exceeds the GFR if there is net tubular secretion and is less than the GFR if there is net tubular reabsorption [13]. The mean ± SE value for clearance ratio between clearance of drug and creatinine clearance was 0.2025 ± 0.045. This value indicates reabsorption (back diffusion) of moxifloxacin. Renal clearance of moxifloxacin 40-51 ml/min/1.73 m^2 (2.4 to 3.0 L/hr) has shown approximately 52% partial tubular reabsorption of the drug [14]. The results of dieresis in relation to clearance were plotted in Figure 1. There is a significant positive correlation between the two parameters. The positive correlation between diuresis and clearance indicated that besides glomerular filtration, passive diffusion of drug is at kidney tubular level. Drugs bound to serum proteins remain in the circulation; only unbound drug is contained in the glomerular filtrate. Un-ionized forms of drugs and their metabolites tend to be reabsorbed readily from tubular fluids [3,8]. The urine pH and the clearance ratio have been plotted in Figure 2. From the figure it is seen that there is trend of positive correlation although the correlation is non-significant. Renal excretion accounts for most drug elimination that are predominately ionized at physiological pH and for polar drugs, drug metabolites with low lipid solubility [8].

The cumulative percentage of moxifloxacin excreted in urine male volunteers is presented in Table 2. After 48 hr of oral administration of moxifloxacin, mean ± SE values 20.48 ± 0.88 percent of total dose was excreted in urine. The urinary excretion of the unchanged moxifloxacin accounts for only 19-22% of the given dose after 48 hr of oral administration [15]. 20% of administered dose is excreted in urine [16]. In 48 hr the mean urinary excretion of the drug was 15.1% [17]. Over 24 hr, 15% of drug was recovered in urine when administer by either route [18]. Only 20% of administered the drug was excreted by the kidney as unchanged parent drug [19]. The difference in the urinary excretion under local condition is due to environment and genetics [20].

5. CONCLUSION

The present study demonstrated considerable variation in the renal clearance of moxifloxacin in healthy male volunteers with similar studies conducted under different environmental conditions. This study indicates that renal clearance of moxifloxacin is affected by genome, temperature, life style and environmental conditions in population in local population. The results of urinary excretion of moxifloxacin were almost similar as indicated in literature, so this data shows that urinary excretion of moxifloxacin is not affected by genome temperature life style and environmental conditions in population in local population.

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