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Effect of Diabetes on the Pharmacokinetic Profile of Fluoroquinolones

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Abstract

Fluoroquinolones are broad spectrum antibiotics used clinically to treat bacterial infectious diseases. They are among the commonly and widely prescribed antibiotics. Reports have linked the use of fluoroquinolones to significant dysglycemia. This work was designed to investigate the pharmacokinetic profile of ciprofloxacin, levofloxacin and moxifloxacin in diabetic rats. **Methods.** Streptozotocin-induced diabetic rats were treated orally with the fluoroquinolones for 7 days, Blood samples were collected from the retro orbital plexus for the estimation of serum concentration, area under the curve, mean retention time, half lives, volume of distribution and other pharmacokinetic indices. **Results:** The result revealed increase in the values of maximum serum concentration (Cmax), area under the curve (AUC), area under the moment curve (AUMC), mean resident time (MRT), half life ($t_{1/2}$), volume of distribution (Vd) and decreased clearance rate (Cl) compared with the values in non diabetic rats. The effects were more on moxifloxacin and least on ciprofloxacin. **Conclusion:** Diabetes state significantly ($p < 0.05$) elevated the pharmacokinetic indices of fluoroquinolones.

Keywords: Diabetes mellitus, fluoroquinolones, pharmacokinetics, rats

1. Introduction

Quinolones have been of considerable scientific and clinical interest since their discovery in the early 1960s. They potentially offer many of the attributes of ideal antibiotic combining high potency, broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution, indicating concentration in tissues and a potentially low incidence of side-effects (Ball, 2000). They were developed for activity against gram negative, gram positive, *chlamydiae* and *mycoplasmas,* and are effective against some penicillin non susceptible or multi drug resistant *P. neumococci* and some methicillin resistant *Staphylococcus aureus* (MRSA). They are commonly used to treat pneumonia and urinary tract infections. Their action is believed to be due to the inhibition of the replication and transcription of bacterial DNA which consequently results in cell death (Cozzarelli & Dalhoff 1980, Schmidt et al 1998)

Fluoroquinolones have been associated with increased risk of blood sugar abnormalities in diabetic patients (Sherine et al 2009). Stephen (2014) attributed much of the increase in the incidence of type-2 diabetes in the United States of America from 1990 to the use of fluoroquinolones. Diabetics on oral fluoroquinolones have been shown to have greater risk of severe dysglycemia, and that hypoglycemic risk varied according to the type of fluoroquinolone, with mexifloxacin been the most common culprit (Hsu-wen et al 2013). Reports have also linked the use of gatifloxacin (Mohr et al, 2005, LaPlante et al 2008) and levofloxacin (Friedrich and Dougherty 2004, Singh and Jacob 2008, Kelesidis & Canseco 2009) to significant dysglycemia. This action was described as "a class effect" as it varied among fluoroquinolones with odds of hypoglycemia and hyperglycemia greater with gatifloxacin and levofloxacin but not ciprofloxacin (Aspinall et al 2009, Sherine et al 2009).

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Diabetes mellitus is a prevalent disorder due to the body's inability to produce and/or make use of insulin. Diabetic patients are prone to use more drugs, including antibiotics compared to non diabetics of comparative age. Information on the influence of diabetics on the pharmacokinetics of drugs are limited, and this has made dosage adjustments in diabetic patients somehow difficult. However, pathophysiological alterations in diabetes have been shown to have the potential to affect the absorption (Welling et al 1982, Adithan et al 2007), distribution, metabolism (Madacsy et al 1975, Wang et al 2003), and excretion (Garcia et al 1997) of various drugs.

In this study, we investigated the effect of diabetes on the pharmacokinetic profile of three fluoroquinolones

2. Methods

2.1 Drugs

Pure samples of ciprofloxacin (Pauco Pharmaceutical Industry Nig. Ltd), levofloxacin and moxifloxacin (Mercury Healthcare PVT. Ltd, Mumbai, India) were used in this study.

2.2 Animals and test organism

Swiss male albino rats (150 – 160 g) were obtained from the Animal House of the Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka. The animals were housed in standard laboratory conditions of 12/12 h light/day cycle, room temperature (36 co), and 40 – 60 % relative humidity. They were fed with rodent feed (Guinea Feeds Nigeria Ltd), and had free access to food and water *ad libitum*. Animal experiments were conducted in line with NIH guide for care and use of laboratory animals (Pub No: 85-23 Revised 1985), and approved by Nnamdi Azikiwe University Ethical Committee on the use of laboratory animals. Mueller Hinton agar and the strains of *Escherichia coli* were used for the study. The strains of *Escherichia coli* were clinical isolates obtained from the Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Nigeria.

2.3 Induction of diabetes

Forty eight (48) Swiss male albino rats were fasted overnight and fasting blood glucose determined thereafter. They were given single intraperitoneal injection of streptozotocin (70 mg/kg). Fasting blood glucose was determined 72 h post induction using One Touch UltraMini Glucometer (LifeScan, GmbH, Swizerland). Rats with blood glucose concentration of 200 mg/dl and above were considered diabetic and selected for the study.

2.4 Experimental design

The animal were grouped into 8 groups of 6 rats per group (24 diabetic and 24 non diabetic) and treated as follows:

1A: Diabetic control 5% Tween 20 (5 ml/kg)
1B: Non-diabetic control 5% Tween 20 (5 ml/kg)

2A: Diabetic treated ciprofloxacin (80 mg/kg)
2B: Non-diabetic treated ciprofloxacin (80 mg/kg)

3A: Diabetic treated levofloxacin (40 mg/kg)
3B: Non-diabetic treated levofloxacin (40 mg/kg)

4A: Diabetic treated moxifloxacin (36 mg/kg)
4B: Non-diabetic treated moxifloxacin (36 mg/kg)

The doses of the drugs were based on previously established therapeutic doses (Erden et al., 2001; Rodriguez & Marinez, 2008, Shenoy et al., 2011), and all drug administrations were by the oral route, and given once daily for seven days.

2.5 Determination of fluoroquinolones pharmacokinetics

Plasma concentrations of ciprofloxacin, levofloxacin and moxifloxacin of diabetic and non- diabetic rats were determined utilizing their ability to inhibit susceptible strain of *Escherichia coli*..

After drug administration, 500 µl of blood were collected from each animal through retro orbital plexus at 0.5, 1, 2, 4, 6, 8, 10 and 12 h. The blood samples were allowed to clot for 30 min and then centrifuged at 3000 rpm for 10 min for serum collection. The supernatant (serum) was collected for bioassay and stored at -20ºC.

2.5.1 Preparation of the media

The media was prepared by dispensing 48 g/l of the agar powder into distilled water, homogenized and sterilized at 121°C for 15 min using autoclave.

2.5.2 Determination of drug concentration – IZD relationship

The concentration – IZD plot for the fluoroquinolones were determined using diffusion microbiological assay technique (Okore, 2009). The drugs (ciprofloxacin, levofloxacin and moxifloxacin) were separately dissolved in 50% dimethyl sulfoxide (DMSO) to give concentrations of 10, 5, 2.5, 1.25, 0.625, 0.3125 µg/ml. Standardized *Escherichia coli* culture was seeded into 20 ml of the sterile molten agar mixed evenly and allowed to solidify in the petri dish. Wells were bored on the seeded agar plate for the inoculation of the drug concentrations using 7mm diameter sterile cork borer. A volume of 0.1ml each of the serial dilutions of the fluoroquinolones were dispensed into the agar wells using micropipette and allowed for pre-diffusion for about 20 min. The resultant preparations were incubated at 37 °C for 24 hr and the inhibition zone diameter were determined and the mean of the duplicate taken. Plots of inhibition zone diameter (IZD) against concentrations of each fluoroquinolones were drawn to serve as standard plot for determination of unknown serum drug concentrations. 10 µg/l of the serum collected at the different time interval was also dispensed in agar plate in duplicates. The resultant inhibitions were measured which was used to extrapolate the unknown concentrations of the drug in the serum from the standard plot.

2.6 Statistical analysis

All data obtained were expressed as mean ± SEM. Mean differences were compared using one way analysis of variance (ANOVA) followed by Dunnet's post-hoc test. P-values < 0.05 were considered significant.

3. Results

The pharmacokinetic parameters of the fluoroquinolones in both diabetic and non diabetic albino rats are shown in Table 1. The plasma concentration graphs used for the estimation of the pharmacokinetic parameters using WinNonlin Pharmacokinetic Program (Pharsight Corporation, Mountain View California) are shown in figures 1, 2 and 3.

Ciprofloxacin maximal concentration (Cmax) was significantly enhanced in the diabetic state from 2.83 ± 0.33 to 6.26 ± 0.00 µg/ml, and this occurred at a maximum time interval of 0.5 ± 0.00 hr compared to maximum time interval of 0.69 ± 0.06 hr in non diabetics. The area under curve (AUC) and area under the moment curve (AUMC) of ciprofloxacin in diabetic rats increased significantly ($p<0.05$) from 1.16 ±0.43 to 15.97 ± 6.29 and from 0.71 ± 0.25 to 39.78 ± 27.83 respectively. The mean resident time (MRT) was increased from 0.56 ± 0.06 in non diabetic rats to 1.99 ± 0.73 in the diabetic rats. A non observed half life ($t_{½}$) in non diabetic rat and a half life ($t_{½}$) of 1.72 ± 0.98 in the diabetic rats were recorded. In the non diabetic rats the volume of distribution (Vd) and Clearance (Cl) were not obtainable, however values of 15.12 ± 2.86 and 8 .04 ± 3.43 were obtained in diabetic rats.

For levofloxacin, the maximal concentration (Cmax) of the diabetic rats (7.61 ± 2.67) and that of the non diabetic rats (7.11 ± 0.99) were not significantly ($p > 0.05$) different, and they occurred at the same time interval. The area under curve (AUC) and the area under the moment curve (AUMC) of the diabetic rats significantly ($p < 0.05$) increased from 3.88 ± 0.26 to 23.00 ± 1.73 and 1.68 ± 0.14 to 62.53 ± 2.16 respectively. The mean resident time (MRT) and half life ($t_{½}$) were significantly increased ($p<0.05$) in the diabetic rats. The clearance of levofloxacin in diabetic rats was significantly decreased, whereas the volume of distribution (Vd) was increased (Table 1).

Diabetes state non-significantly ($p > 0.05$) increased the maximum concentration (Cmax) of moxifloxacin in the serum (Table 1), and this occurred at a maximum time interval of 0.05 ± 0.00 (Figure 3). The area under curve (AUC) and the area under the moment curve (AUMC) of the diabetic rats were also significantly ($p<0.05$) increased. The mean resident time (MRT) and the half life ($t_{½}$) were significantly increased ($p<0.05$) in the diabetic rats. The clearance (Cl) of moxifloxacin in the diabetic state was significantly ($p < 0.05$) reduced, whereas the volume of distribution (Vd) was increased in the diabetic rats.

Table 1: Effect of Diabetes on Pharmacokinetic Parameters of Fluoroquinolones

Treatment	Dose(µg/ml)	tmax (h)	Cmax (µg/ml)	AUC	AUMC	MRT	$t_{1/2}$	Vd	Cl
Ciprofloxacin	80								
Normoglycermic		0.69 ± 0.06	2.83± 0.33	1.61± 0.43	0.71± 0.25	0.56± 0.06	-	-	-
Diabetic		0.50 ± 0.00	6.26± 0.00*	15.97 ±6.29*	39.78± 27.85*	1.99± 0.73*	1.72± 0.98	15.12± 2.86	8.04± 3.43
Levofloxacin	40								
Normoglycemic		0.50 ± 0.00	7.11± 0.99	3.86± 0.26	1.68± 0.14	0.50± 0.02	0.40± 0.05	5.90± 0.77	10.27± 0.71
Diabetic		0.50 ± 0.50	7.61± 2.67	23.00± 1.73*	62.53± 2.16*	2.74± 0.12*	5.44± 1.12*	6.80± 1.16	0.88± 0.04*
Moxifloxacin	36								
Normoglycemic		0.25 ± 0.00	17.44± 0.32	28.54 ± 3.87	20.55± 5.31	0.84± 0.11	1.47± 0.31	1.87± 0.11	1.00± 0.21
Diabetic		0.50 ± 0.00	17.83± 0.22	92.58 ±1.02*	282.10± 2.31*	3.05± 0.02*	47.94± 6.08*	2.14± 0.03	0.03± 0.00*

*p < 0.05; n=6

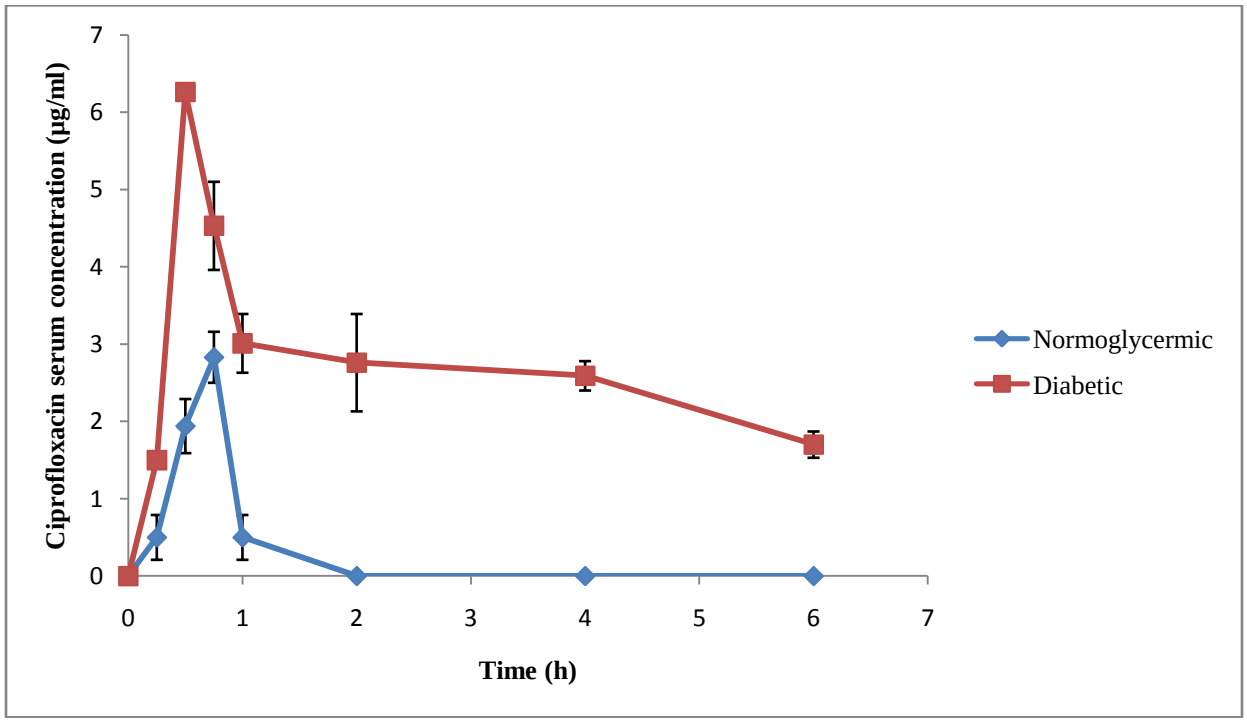

Figure 1. Effect of Diabetes on Serum Concentration of Ciprofloxacin

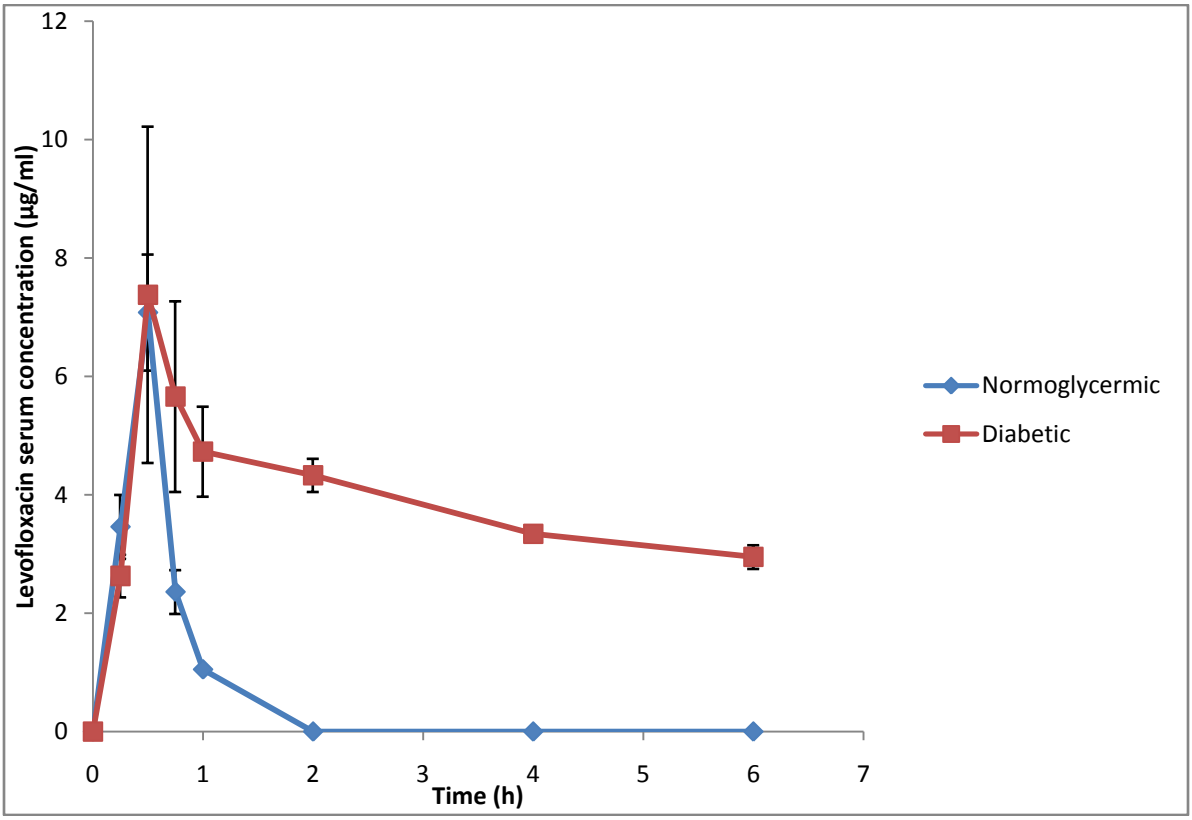

Figure 2. Effect of Diabetes on Serum Concentration of Levofloxacin

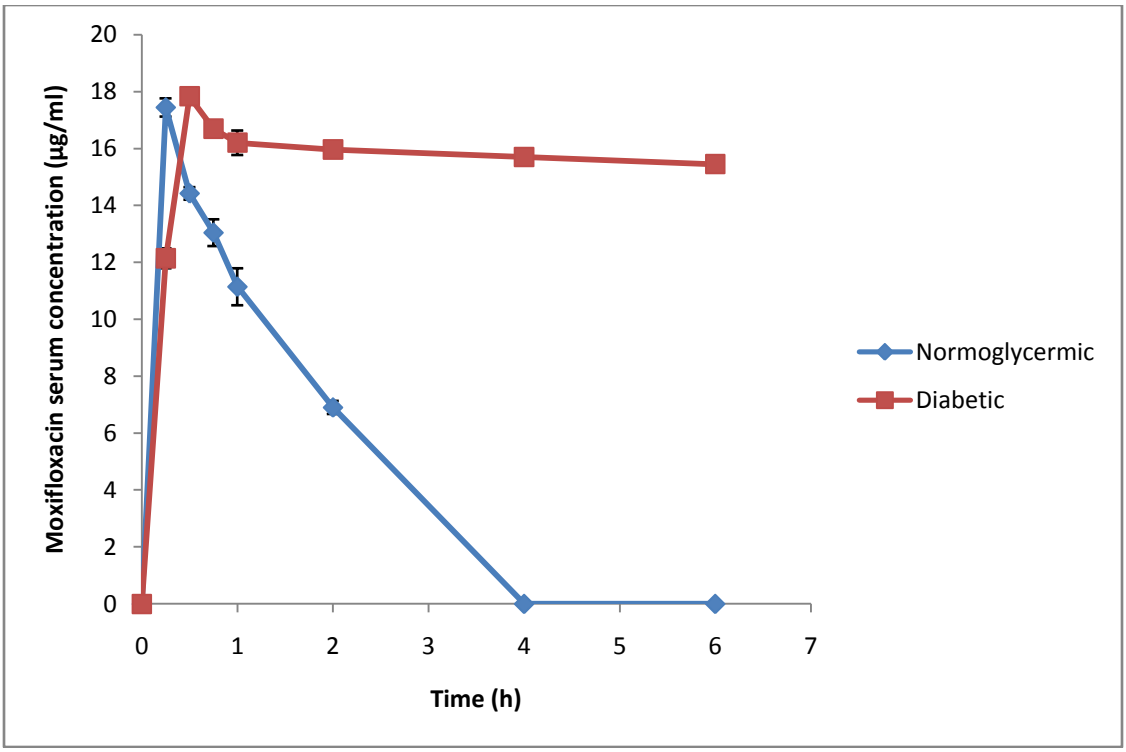

Figure 3. Effect of Diabetes on Serum Concentration of Moxifloxacin

4. Discussion

Significant increase in the maximum concentrations (Cmax), area under the curve (AUC) and area under the moment curve (AUMC) are indicative of enhanced absorption and bioavailability of drugs (Jambhekar & Breen, 2009). Since the drug concentrations are always decreasing after oral administration, the maximum concentration (Cmax) and the time to attain it (tmax) are dependent on the extent and rate of absorption and disposition profile of the drug. The results of this investigation revealed that diabetes state enhanced the extent of ciprofloxacin, levofloxacin and moxifloxacin absorption as evidenced by the increase in their area under the curve (AUC), maximum concentration (Cmax), and the area under the moment curve (AUMC). These parameters give a measure of the amount of drug in systemic circulation (Jambhekar & Breen, 2009). These results collaborated with the findings of Nduka et al, (2013), who reported similar observation on the influence of Ginger (*Zingiber Officinale*) extract on the pharmacokinetic profile of pefloxacin. Adequate absorption of ciprofloxacin has been reported in patients with diabetic gastroparesis (Marangos et al 1995).

The higher values of the area under curve (AUC), the area under the moment curve (AUMC) and maximum concentration (Cmax) are usually indicative of enhanced systemic availability of drugs and possible suppression of cytochrome enzyme responsible for the metabolism of drugs which might have caused the significant increase in the mean resident time (MRT) and half life ($t_{½}$) with corresponding decrease in clearance in the diabetic rats. Studies have shown that diabetes is associated with reduced CYP 3A4 activity and expression in humans (Dostalek et al 2011, 2012), and this will ultimately result in the increase in MRT and $t_{1/2}$ as evidenced in this study. On the other hand, shorter half life is indicative of possible induction of metabolizing enzymes.

A decrease in the volume of distribution is usually indicative of increased protein binding while an increase in the volume of distribution is an indicative of decreased protein binding of drugs. It has been reported that albumin, along with hemoglobin can be glycated in the presence of increased concentration of glucose (Baraka-Vidot et al 2012). Albumin purified from diabetic patients or glycated in vitro has been reported to significantly impair the binding capacity of highly albumin binding drugs (Baraka-Vidot et al 2012). The increase in the volume of distribution of the three fluoroquinolones in the diabetic rats may suggest an alteration in the protein binding ability of the drugs.

5. Conclusion

In comparison to non diabetic rats, this study revealed that diabetic state enhanced the serum maximum concentration, half lives, mean retention time and other pharmacokinetic parameters of fluoroquinolones. This calls for caution in the administration of fluoroquinolones to diabetic patients

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