Bioavailability of Ciprofloxacin and Fleroxacin: Results of a Preliminary Investigation in Healthy Adult Nigerian Male Volunteers

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The absolute bioavailability (BA) of ciprofloxacin and fleroxacin were evaluated in 19 adult Nigerian male volunteers. Subjects meeting the selection criteria were randomized to receive treatment either with fleroxacin (200 mg-i.v. and 200 mg oral dose) or ciprofloxacin (200 mg-i.v. and 250 mg oral dose). The i.v./oral or oral/i.v. switch was made after a one week washout period. Blood and urine samples were collected at pre-determined time intervals over a 72 h period for analysis of drug levels.

Following intravenous administration the maximum serum concentration ($C_{\max}$) was 2.7 ± 1.06 mg/l for ciprofloxacin and 0.99 ± 0.41 mg/l for fleroxacin; the area under the blood level curve (AUC) was 8.82 ± 3.19 mg·h/l with ciprofloxacin and 8.52 ± 3.83 mg·h/l with fleroxacin. Following oral administration the $C_{\max}$ was 1.52 ± 0.94 mg/l with ciprofloxacin and 0.57 ± 0.08 mg/l with fleroxacin; the AUC was 9.87 ± 4.10 and 7.55 ± 1.42 mg·h/l, respectively. The absolute BA following oral administration was found to be 0.79 ± 0.47 for ciprofloxacin and 1.01 ± 0.78 for fleroxacin. When these BA results were corrected for renal clearance (Cl_r) and elimination half-life ($t_{1/2}$) the values were reduced to 0.37 ± 0.17 and 0.31 ± 0.18 , respectively, for ciprofloxacin and 0.53 ± 0.23 and 0.99 ± 0.38 , respectively, for fleroxacin. Only 38% with ciprofloxacin and 59% with fleroxacin, of the administered dose, was excreted unchanged following oral administration.

More work, however, needs to be done on ciprofloxacin to support and/or confirm the above findings. Fleroxacin, on the one hand, exhibited a different trend from that observed in the literature with respect to $C_{\max}$ and AUC where the values observed in this study were 3—4 fold lower than expected following identical doses, whilst on the other hand the observed BA profile in this study was consistent with literature trends.

Key words quinolone; bioavailability; Nigerian

Fluoroquinolones were introduced into the Nigerian market about 10—12 years ago and are represented by ciprofloxacin, ofloxacin, norfloxacin and (more recently) pefloxacin. They are currently enjoying wide acceptance and usage as they have been reported to be effective in the management of certain infections, which resist other known antibiotics. It is, however, observed that the bioavailability (BA) profiles of these drugs in Nigerian subjects have not been adequately established.

Ciprofloxacin is the most widely used quinolone in Nigeria. In studies conducted elsewhere,¹⁾ $C_{\max}$ for ciprofloxacin was found to be 2 mg/l following a single oral dose of 250 mg, and the absolute BA was about 60%. About 30% of unchanged drug was said to be recovered from urine within 24 h. Absorption after oral administration was found to be rapid and satisfactorily described by a zero order process, and $t_{\max}$ ranged between 1—2 h.

Fleroxacin is a newer fluoroquinolone with potent antibacterial activity against various pathogens covering a gram-positive and a gram-negative bacteria spectrum.²⁾ Fleroxacin differs from ciprofloxacin by virtue of its chemical structure (*N*-4-methylation at the piperazine side chain), and its pharmacokinetic profile (particularly the long $t_{1/2}$, which in combination with other pharmacological parameters allows for a once daily dosage regimen). The absolute bioavailability for fleroxacin was reported to be 96%³⁾ and high plasma levels ($C_{\max}$ = 4.5 mg/l) were achieved after a single oral dose of 400 mg.

The main purpose of this study was to establish the ab-

solute bioavailability profile of ciprofloxacin in Nigerian subjects and compare it with that of fleroxacin in view of their different chemical structure and the imminent introduction of fleroxacin into the Nigerian market.

METHODS

Study Design The study was approved by the ethics committee of the University College Hospital (UCH) Ibadan. Volunteers were subjected to physical, laboratory and clinical screening 10 d prior to study start. Signed informed consent was obtained from all volunteers. Patients who met the selection criteria were included in the study. Complete medical history, physical examination, vital signs, haemogram and blood chemistry profile were obtained for each patient at baseline (just prior to treatment) and at the end of treatment. Subjects were randomized to receive treatment with either fleroxacin (i.v. or oral) or ciprofloxacin (i.v. or oral). Blood samples were collected from each volunteer at pre-determined time intervals over a 72 h period. After a 7 d wash-out period, subjects were switched to the cross over regimen (i.v. or oral) and the sampling procedure was repeated.

Nineteen healthy adult Nigerian male volunteers, taken from the student and staff population of the UCH Ibadan, were enrolled into the study. There were two treatment schedules, A and B:

Treatment A: A single dose of either 200 mg (oral) tablets or 200 mg/100 ml (i.v.) infusion of Fleroxacin.

Treatment B: A single dose of either 250 mg (oral) tablets or

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200 mg/100 ml (i.v.) infusion of Ciprofloxacin.

Each subject received a dispensing coded envelope containing two tablets of study medication or a number coded i.v. preparation. The tablets were taken on an empty stomach together with 200 ml of portable water. The i.v. preparation was administered as a slow i.v. infusion lasting approximately 60 min. No subject was allowed to consume alcohol or caffeine containing beverages during the 12 h period preceding and throughout the study period.

Analysis of Biological Samples The HPLC method described by Heizmann *et al.*⁴⁾ was used for the determination of ciprofloxacin, fleroxacin and its metabolites in serum and urine. Serum samples were de-proteinized with acetonitrile, and after evaporation and reconstitution of the supernatant, samples were analyzed on a reversed phase column. The HPLC was equipped with a fluorescence detector. The limit of detection of fleroxacin and ciprofloxacin in serum was 20 µg/l and 10 µg/l, respectively. Urine samples were diluted with the mobile phase and an aliquot was then injected directly onto the column. The limits of quantification were 0.6 mg/l and 2 mg/l, respectively, for fleroxacin and ciprofloxacin. Pipemidic acid was used as internal standard for determination of the drugs in both urine and serum specimens because the proposed internal standard (AM735, from Roche) interfered with fleroxacin peaks.

Data Analysis The pharmacokinetic profiles of both drugs were evaluated by means of PC-Nonlin® version 4.2 (SCI software, CM Metzler and DL Weiner, 1992). Both compartmental and non-compartmental analyses were employed in the evaluation of the pharmacokinetic parameters.

The parameters were estimated by fitting the respective models with different weighting schemes and estimation methods (iterations). The model of best fit was that with the most minimized weighted sum of squares and standard error; the *F*-test was also employed in the determination of the output of best fit.

The area under the blood level curve (*AUC*) was determined after i.v. and oral administration and the BA was calculated as:

$$F = (AUC_{\text{oral}} \cdot \text{Dose}_{\text{i.v.}}) / (AUC_{\text{i.v.}} \cdot \text{Dose}_{\text{oral}})$$

In order to minimize the effect of intra-individual variation following the two dosing intervals involved, *F* was further corrected for half-life (*F'*) and renal clearance (*F''*); for this the following equations were applied:

$$F' = [AUC_{\text{oral}} \cdot \text{Dose}_{\text{i.v.}} \cdot (t_{1/2})_{\text{i.v.}}] / [AUC_{\text{i.v.}} \cdot \text{Dose}_{\text{oral}} \cdot (t_{1/2})_{\text{oral}}]$$

$$F'' = [AUC_{\text{oral}} \cdot \text{Dose}_{\text{i.v.}} \cdot (Cl_r)_{\text{oral}}] / [AUC_{\text{i.v.}} \cdot \text{Dose}_{\text{oral}} \cdot (Cl_r)_{\text{i.v.}}]$$

The *C*_{max} and time to attain this value (*T*_{max}), mean residence time (*MRT*), mean absorption time (*MAT*) were also determined where appropriate, as were some relevant pharmacokinetic parameters such as distribution rate constant (*α*), the elimination rate constant (*β*) and the exit rate constant (*K*₁₀). The estimated parameters were further subjected to within and between groups parametric comparison using MS-Excel statistical tools (descriptive and summary statistics, and *t*-test).

A confidence level of 95% (alpha=0.05) was chosen for all statistical tests.

Table 1. Demography

	Ciprofloxacin	Fleroxacin
No. of subjects	10	9
Weight (kg) [mean±S.D.]	67.8±8.1	63.6±6.5
Range	56—88	30—73
Age (yr) [mean±S.D.]	23.3±1.7	24.0±2.5
Range	22—26	20—30

Table 2. Results of Analysis of Blood Level Data Following i.v. Administration

Parameter	Unit	Treatment	
		Ciprofloxacin	Fleroxacin
<i>n</i>		10	9
<i>T</i> _{max}	h	0.81±0.19	0.92±0.22
<i>C</i> _{max}	mg/l	2.70±1.06	0.99±0.41
<i>AUC</i>	mg·h/l	8.82±3.19	8.52±3.83
<i>MRT</i>	h	6.82±5.05	20.46±8.75

Table 3. Results of Analysis of Blood Level Data Following Oral Administration

Parameter	Unit	Treatment	
		Ciprofloxacin	Fleroxacin
<i>n</i>		10	9
<i>T</i> _{max}	h	1.48±0.45	1.56±1.13
<i>C</i> _{max}	mg/l	1.52±0.94	0.57±0.08
<i>AUC</i>	mg·h/l	9.87±4.10	7.55±1.42
<i>F</i>		0.79±0.47	1.01±0.78
<i>MAT</i>	h	10.68±4.98	21.87±10.46
<i>K</i> _a	h ⁻¹	0.61±0.1	0.05±0.02

RESULTS .

The demographic data of the study population is presented on Table 1. A total of 19 adult healthy male volunteers with an age range of 20—30 yr participated in the study. Following oral administration the input rate constant for ciprofloxacin was best described by a zero order rate process whilst that of fleroxacin was first order.

The summaries of results following evaluation of the blood level data are presented in Tables 2 and 3 and Figs. 1 and 2. The uncorrected absolute BA was found to be 0.79±0.47 for ciprofloxacin and 1.01±0.78 for fleroxacin; Table 4 shows the effect of renal clearance (*Cl*_r) and *t*_{1/2} correction on the absolute BA of the test drugs.

The urinary excretion profiles for both drugs following i.v. and oral administration are presented in Table 5 and graphically in Figs. 3 and 4. The results show that 70% and 71% of unchanged drug was excreted in urine for ciprofloxacin and fleroxacin respectively, following i.v. administration. However, following oral administration only 34% and 48%, respectively, of the administered dose was excreted unchanged in urine. The result of the paired *t*-test parametric comparison of i.v. versus oral profile for the test drugs is presented in Table 6. For ciprofloxacin, there was a significant difference between the i.v. and oral profile for all the parameters evalu-

ated, with the exception of AUC and the terminal elimination rate constant (β), whilst for fleroxacin significant differences were observed only with K_{10} , alpha half-life and C_{max} .

DISCUSSION

The mean absolute BA (uncorrected) of 0.79 found for ciprofloxacin in this study is in line with reported values in the literature which range from 0.65–0.85.⁵⁾ When the BA results obtained were corrected for Cl_r and elimination half-life ($t_{1/2}$) the values were reduced to 0.37 and 0.31, respectively, for ciprofloxacin and 0.53 and 0.99, respectively, for fleroxacin (Table 4). It could be observed that this reduction was substantial for ciprofloxacin and less for fleroxacin fol-

Fig. 1. Fleroxacin: Log-Serum Concentration vs. Time Curve Following Intravenous and Oral Administration

Fig. 2. Ciprofloxacin: Log-Serum Concentration vs. Time Curve Following Intravenous and Oral Administration

Fig. 3. Ciprofloxacin: Cumulative Amount of Unchanged (X_u) Drug Excreted in Urine with Time

Fig. 4. Fleroxacin: Cumulative Amount of Unchanged (X_u) Drug Excreted in Urine with Time

Table 4. Bioavailability Data for the Test Drugs and Effect of Correction for Cl_r and $t_{1/2}$

Data type	F (mean $\pm$ S.D.)	
	Ciprofloxacin	Fleroxacin
Compartmental analysis	0.79 ± 0.48	1.10 ± 0.81
Corrected for Cl_r	0.37 ± 0.17	0.53 ± 0.23
Corrected for $t_{1/2}$	0.31 ± 0.18	0.99 ± 0.38
Model independent analysis	0.79 ± 0.47	1.01 ± 0.78
Corrected for Cl_r	0.37 ± 0.17	0.56 ± 0.64
Corrected for $t_{1/2}$	0.49 ± 0.25	1.0 ± 0.30

Table 5. Some Important Urinary Excretion Parameters 72 h after Administration of Test Drugs

Parameter	Ciprofloxacin		Fleroxacin	
	i.v.	Oral	i.v.	Oral
Fraction excreted unchanged (f_u)	0.7	0.34	0.71	0.48
<i>N</i> -oxide metabolite (f_{m1})	—	—	0.037	—
<i>N</i> -desethyl metabolite (f_{m2})	—	—	0.04	—
Cl_r	15.8 ± 5.6	10.6 ± 6.4	24.0 ± 20.76	12.8 ± 4.9

Table 6. Paired *t*-Test Parametric Comparison of i.v. vs. Oral Profile for Ciprofloxacin and Fleroxacin

Parameter	Ciprofloxacin			Fleroxacin		
	Mean		<i>p</i>	Mean		<i>p</i>
	i.v.	Oral		i.v.	Oral	
α (h^{-1})	17.93	1.1	0.0096*	7.98	0.33	0.13
β (h^{-1})	0.12	0.09	0.34	0.054	0.059	0.6
K_{10} (h^{-1})	3.5	0.3	0.03*	0.59	0.09	0.12
K_{10} -HL (h)	0.78	3.64	0.0001**	4.25	7.92	0.007*
Alpha-HL (h)	0.17	1.3	0.001*	0.75	3.54	0.005*
Beta-HL (h)	7.52	15.14	0.026*	13.75	13.6	0.96
<i>AUC</i> ($\text{mg} \cdot \text{h/l}$)	9.5	10.16	0.74	7.81	6.87	0.5
C_{max} (mg/l)	2.3	1.2	0.005*	0.81	0.42	0.007*
Volume (l/kg)	0.35	1.39	0.003**	2.85	5.8	0.2

* Significant, ** highly significant.

lowing $t_{1/2}$ correction. It could also be seen that the half-life and Cl_r correction method resulted in a considerable decrease in the standard deviation of the mean values. For this reason the corrected values are considered the most appropriate. As mentioned earlier the half-life correction method has been found useful in an effort to minimize the effect of intra-individual variation in BA studies, following the two different dosing intervals involved. This approach assumes that a change in half-life from one study to the next in the same subject reflects solely a change in clearance and is not mediated by a change in the apparent volume of distribution. The alternative correction method (Kwan-Till) is based on the variability of Cl_r , and assumes that changes in total clearance (Cl_t) are solely the result of changes in renal clearance and that non-renal clearance remains constant from study to study. It is most useful for, but not limited to drugs that are substantially excreted unchanged in the urine.⁽⁶⁾

Generally the bioavailability of fleroxacin was higher than that of ciprofloxacin as has been previously established.^(1,7,9,13,14) The value of 37% obtained for ciprofloxacin in this study is considered quite low and calls for a possible reappraisal of the bioavailability of ciprofloxacin in black Africans. The mean C_{max} obtained for ciprofloxacin following oral administration in this study was 1.52 mg/l. This value is about 50% that obtained following i.v. administration and in line with those obtained from previous studies, 0.94–1.69 and 1.51–2.91 mg/l.^(7–10) In these earlier studies, large within-group variability in absorption was observed for ciprofloxacin⁽¹⁰⁾; this was also the case in this present study adjudged by the large coefficient of variation and standard deviation obtained for the various parameter estimates. It has also been suggested that ciprofloxacin absorption may not follow a first order kinetics.⁽¹¹⁾ Indeed, in this study the data obtained for a majority of the volunteers on ciprofloxacin was best fitted to the model describe by a zero order absorption process, corroborating the findings of Tartaglione *et al.*,⁽¹¹⁾ Vance-Bryan *et al.*⁽¹²⁾ and Wingender *et al.*⁽¹⁰⁾ Although we were able to determine K_a independently by the method of residuals, the value obtained (0.61 ± 0.1) was relatively high and close enough to α and K_{10} (1.11 ± 0.37 and 0.29 ± 0.1 , respectively (values derived from compartmental analysis)), prompting us to wonder if a flip-flop phenomenon

may not be at play.

Fleroxacin, on the other hand, exhibited a different trend from that observed in the literature with respect to C_{max} and *AUC* where the values observed in this study were 3–4 fold lower than expected following identical doses as reported by Cullmann *et al.*⁽¹³⁾; 2.2–3.0 mg/l compared to the 0.42–0.81 mg/l obtained in this study.

The difference between the blood level profile following oral and i.v. administration was significant with ciprofloxacin but not with fleroxacin. In fact with fleroxacin the profile following oral administration closely approximated that of the i.v. dose, confirming earlier reports in this regard.⁽¹⁴⁾

The reasons for the differences in the disposition profile between our study population and those previously studied cannot be immediately ascertained. However, a closer look at the absorption and elimination profile of both drugs gives some indications for speculation on the possible reasons for the observed differences. In our study the 'absorption rate constant' (K_a) for ciprofloxacin was 10-fold higher than that of fleroxacin thus explaining the differences in the values of C_{max} obtained following oral absorption. It has previously been postulated that ciprofloxacin is more lipophilic than fleroxacin,⁽¹⁵⁾ this may explain the significant differences in the C_{max} value following i.v. administration, more so in view of the fact that the iso-electric point (IP) for ciprofloxacin is at the physiological pH of 7.4. One would expect this property of ciprofloxacin (IP at pH 7.4) to greatly enhance its extent of distribution in comparison to fleroxacin, but our findings were contrary to this speculation. As discussed in an earlier publication,⁽¹⁶⁾ we are of the opinion that fleroxacin is more widely distributed than ciprofloxacin, at least in the population we studied.

Some of the reasons that may have given rise to this profile derive from the fact that the neutral species of ciprofloxacin predominant at the IP is the doubly charged molecule, which may be amenable to interaction in the presence of any competing species. Indeed, the clearance profile of ciprofloxacin from the urinary recovery studies seems to suggest that it is very rapidly cleared within the first hour following i.v. administration. Also, in three instances we found no detectable levels of ciprofloxacin in the serum of some of the volunteers at 8 h following i.v. administration. The rate plot (urinary excretion rate (dX_u/dt vs. $t_{\text{mid-point}}$) for both ciprofloxacin and fleroxacin did not yield a straight line as expected, rather, the resulting curve was bi-phasic. Similarly, the plot of dX_u/dt vs. $C_{\text{mid-point}}$ did not yield a straight-line, rather, a scatter plot was obtained with the regression line indicating a strong correlation, the Cl_r estimated using this method was quite close to that estimated using the relationship: $Cl_r = X_u^\infty / AUC_0^\infty$.

One of the possible confounding variables between the population we studied and others is the possibility of traces of chloroquine (CQ) being present in the blood of our volunteers. There exists a potential for interaction since CQ is a 4-amino-quinoline, a group somewhat structurally related to the 4-quinolones. Chloroquine and other antimalarials are routinely taken for malaria chemoprophylaxis and therapy in our environment. Chloroquine has a very long half-life and studies have shown that levels of CQ persist in plasma long after the last administration of the drug.⁽¹⁷⁾ There is thus an urgent need to study the possible interactions between the quinoline anti-malarials and the quinolones, particularly in a

malaria endemic environment such as Nigeria.

Our study also seems to suggest that the elimination profile of ciprofloxacin in our population distinguishes two groups of people. The Cl_r profile of our study population identifies two distinct groups of volunteers, one with Cl_r values lower than the filtration rate and the other with higher values. The range of Cl_r was 4.38–19.2 l/h following oral administration and 7.24–20.5 l/h following i.v. administration. The distribution profile was clearly bi-modal. Fleroxacin exhibited a similar trend but less profound than ciprofloxacin. With fleroxacin the range was 6.8–20.1 l/h following oral administration and 10.6–23.4 l/h following i.v. administration (a value of 65.1 l/h was computed for one volunteer and there was no justifiable reason why this value should be regarded as an aberration hence it was included in the analysis).

We have been able to establish that there are significant differences in the disposition profile of ciprofloxacin and fleroxacin between our study population and those studied previously in the literature. We have also been able to justify the need for more work to be done, in particular, focusing on the interaction potentials between the 4-amino quinolones and the 4-quinolones.

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