Research Article

Comparative Bioavailability Assessment of Four Brands of Ciprofloxacin Tablets Marketed in South-East Nigeria

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ABSTRACT

This study evaluated the relative bioavailability of four brands of ciprofloxacin (500 mg) tablets marketed in Southeast, Nigeria using an in vivo approach. The study was carried out on twelve healthy male rabbits which were given a single dose of ciprofloxacin (500 mg) tablet of the reference (R) and three test (A, B, C) products in the fasting state in a balanced incomplete block design. Serum obtained from collected blood within 24 hours was analysed for ciprofloxacin with microbiology assay while plasma samples were analysed using UV-Vis spectrophotometric analytical method at a wavelength of 272.4 nm. The pharmacokinetic parameters were determined using non-compactmental as implemented in WinNonlin pharmacokinetic program. The 90% confident interval of the log transformed mean values of the test/reference ratios for the pharmacokinetic parameters (Cmax), (AUC0-t), and the (AUC0-âˆž) were calculated. The pharmacokinetic parameters from the UV-Vis analytical method showed no statistically significant difference between the reference and the tested brands as the mean Cmax obtained for the reference sample (R) was the highest (275.50 (Â ± 3.86) Âµg/ml) occurring at a tmax of 6.83 (Â ± 1.89) h, followed by B (222.17 (Â ± 2.11) Âµg/ml) at 5.08 (Â ± 0.98) h, C (202.00 (Â ± 0.55) Âµg/ml) at 3.63 (Â ± 1.02) h and A (192.00 (Â ± 1.10) Âµg/ml) at 7.00 (Â ± 1.11) h. The value obtained for the 90% CI for log-transformed ration for Cmax reflect that it is within the acceptable range of 80% to 125% as it is for AUC0-t and AUC0-âˆž also. The four formulations were considered to be bioequivalent as the peak plasma concentration and AUC parameter analysis of variance reflno significant difference between the reference and the tested brands.

Key words: Ciprofloxacin; Bioequivalence stud; Pharmacokinetics

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INTRODUCTION

Recent government economic policies in Nigeria are targeted at strengthening production and consumption of locally produced goods including drugs and drug products with the later resulting in the local production and clinical use of generic medicinal products in the country in addition to a handful of imported brands. One of these government policies is a huge reduction in domestic drug tariff compared to the total tariff for imported products with a reduced overall production cost for the locally manufactured drugs. Consequently, there has been a significant increase in the available brands of these drugs particularly, the antibacterial agents including ciprofloxacin, a commonly used antibiotics in the country. Although, the costs of these generic brands are lower than the branded products, ascertaining their bioequivalence with the standardized products is of paramount importance as this will guide interchange ability of the different brands in practice. In addition to the aforementioned, other identified factors including the proliferation of counterfeit and substandard products in Nigeria and the proportional increase in resistance to most anti-infective agents underscores the need for bioavailability and bioequivalence assessment of the unbranded products whereas Nigeria was rated third highest behind India and Burma in counterfeit and substandard antibacterial agents [1]. A good number of studies have reported a significant increase in resistance to anti-infective agents with huge threat to the public health [2-6]. Among the anti-infective agents, resistance to antibacterial agents including the quinolones have been extensively studied. For instance, a study reported a significant increase in the resistance of isolated E coli obtained from patients with Urinary Tract Infection (UTI) with the use of quinolones [7] similar to most other studies.

Ciprofloxacin is one of the mostly used quinolones and it belongs to the second generation fluoroquinolones with broad spectrum of activity against infective agents and its well absorbed from the gastrointestinal tract with an absolute bioavailability of 70 – 85% following oral administration [8]. It is widely distributed throughout the body with the tissue concentrations often greater than the serum concentrations and hence it serves as an excellent substitute in the therapy of gastrointestinal, skin and bone infection, complicated urinary tract infection, sexually transmitted infections and lower respiratory tract infection among others [9,10]. Among the quinolone antibacterial agents, ciprofloxacin was reported to fail in the treatment of enteric fever caused by Salmonella enterica serotype Paratyphi A in Kuwait [11]. Choosing between the numerous available brands of ciprofloxacin to achieve optimal cost effectiveness benefit is a thing of concern in medical practice. Although a couple of studies have been carried out in Nigeria to unravel this concern using selected ciprofloxacins in the Nigerian market, almost all of these studies were conducted using in vitro assessment approach which may not exactly depict what happens in vivo [12-14]. This study was therefore designed to evaluate the relative bioavailability of selected brands of ciprofloxacin tablets marketed in Southeast, Nigeria using an animal model.

MATERIALS AND METHODS

Drugs

Ciprofloxacin 500 mg tablets manufactured in Nigeria were purchased

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from registered pharmacies within Awka metropolis, in Anambra State. The brands purchased are Ciprotab (Fidson healthcare plc, Lagos), Cipro-J (Juhel Ngeria Limited, Enugu), M & B Cipro tablets (May and Baker Nigeria Plc), Cipro-500 (Nuel pharmaceutical company, Ogun). Ciprotab was used as a reference drug because of previously published studies [15]. Ciprofloxacin internal standard (Zhejiang Guobang Pharmco limited, China) was obtained as gift from Pauco Pharmaceutical Limited, Nigeria.

Study animal

Twelve healthy male rabbits (weight: 2.5-3.5 kg; Age: 6-10 month) were purchased from an animal farm in Nneobi, Anambra state. The Rabbits were allowed to acclimitize in its new environment during which they were closely and then, fasted for 12 hours with free access to water before the drug administration according to the methods of Venho and Eriksson [16]. All animal experiments were conducted in line with NIH guide on the use and care of laboratory animals.

Study design

Balanced Incomplete Block Design (BIBD) with adequate washout period was adopted. In the first and second period, each of the animals was administered 500 mg of ciprofloxacin via oral route under direct observation.

Drug administration and sample collection

Five hundred milligram tablets of either the reference or test drug formulation were administered as whole tablet with the help of feeding trough with 5 mL of water. Mouth check was performed to ascertain that the animal has swallowed the medication before the water was given.

Following this, blood samples were collected from the great auricular vein of the rabbits at time interval of 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h. The samples were collected into sets of two different sample bottles (plain bottle; EDTA bottle). The blood sample in the plain bottles were allowed to stay for about 30 min to allow coagulation before been centrifuged at a speed of 3000 rpm for 10 min and the supernatant collected and stored at -180C in an eppendurf tube prior to biological assay. Meanwhile, the samples in the EDTA bottles were centrifuged immediately after collection and the supernatant plasma collected for u-v spectrophotometric analysis. Following the initial drug administration and sample collection from a particular group, a washout period of one week was allowed to pass before the second phase of drug administration and sample collection from the same group was carried out.

Drug analysis

Gradient concentrations of 0.2, 0.16, 0.12, 0.08, 0.04, 0.024, 0.016, and 0.008 µg/ml of ciprofloxacin were prepared with distilled water from the pure standard powder while the scan for the ciprofloxacin wavelength was run with distilled water as blank and these were used to prepare the calibration curve of ciprofloxacin at a scanned wavelength of 272.4 nm using the UV-Vis spectrophotometer. The plasma samples were then run on this UV-Vis spectrophotometer at the same wavelength 272.4 nm with the readings taken in duplicate and the average was determined mathematically. The serum concentration of ciprofloxacin was determined using clinically isolated Staphylococcus aureaus samples from hospitalized patients. The nutrient agar was cooled to 50^{o}C and inoculated with a 24 hour incubated Staphylococcus aureus culture (0.1 mL/100 mL agar). Holes of 8 mm were punched out of the agar after its solidification. The punch-holes were filled with 100 µL of serum in duplicate for calibrators and samples. After the incubation at 37 oC for 18 hours, the inhibition zones were measured and the concentrations were determined.

Pharmacokinetic analysis

Pharmacokinetic parameters determination and calculation was done on concentration-time graphs with the use of WinNonlin software for pharmacokinetic studies. The area under the curve to the last measurable concentration (AUC0–t) was determined directly from the WinNonlin software while the area under the curve extrapolated to infinity (AUC0–∞) was determined as AUC0–t+Ct/Ke, where Ct was the last measurable concentration and Ke, elimination constant [17]. The elimination half-life (T1/2) was determined as 0.693/Ke. Maximal concentration of the drug (Cmax) and the time to attain the maximal concentration (tmax) were also determined.

Statistical analysis

Bioequivalence analysis utilizes mainly Cmax, AUC0–t and AUC0–∞ as its pharmacokinetic parameters and it was determined by the estimation of 90% Confidence Interval (CI) for the ratio of the log-transformed data of the mean of the test to the reference products and also by the analysis of variance of the means of those parameters [18]. These were done with SPSS version 20 with the difference between two means calculated using nonparametric paired t-test.

RESULTS

U-V Spectrophotometric analysis

The pharmacokinetic parameters of ciprofloxacin after an oral 500 mg single dose administration of the reference sample (R) and the test samples A, B and C are shown in Table 1 and the concentration-time plot are shown in Figure 1. The mean Cmax obtained for the reference sample (R) was the highest (275.50 (± 3.86) µg/ml) occurring at a tmax of 6.83 (± 1.89) h, followed by B (222.17 (± 2.11) µg/ml) at 5.08 (± 0.98) h, C (202.00 (± 0.55) µg/ml) at 3.63 (± 1.02) h and A (192.00 (± 1.10) µg/ml) at 7.00 (± 1.11) h. The AUC0-24 for the four brands, although were not statistically significant, had its highest value observed in brand R (4846.17 ± 1.43) µg.h/ml, followed by B (4445.83 ± 1.18) µg.h/ml, C (4195.67 ± 1.17) µg.h/ml, while the least is observed in brand A (4019.67 ± 0.60) µg.h/ml.

The paired-sample t-test for the equality between the means of the pharmacokinetic parameters of the reference sample A to each of the test samples is also reflected in Table 1 with a significance level (p-value) of 0.05. From the table, there were no statistically significance difference between the mean Cmax, mean tmax and AUC0-24 of R against A, B or C ($p>0.05$).

The 90% confidence interval of the log transformed mean values for the pharmacokinetic parameters of the test/reference ratios are presented in Table 2. The value obtained for the 90% CI for log-transformed ration for Cmax is A/R (94.7, 101.6), B/R (87.8, 101.6), C/R (91.2, 99.2) while that of the AUC0-24 is A/R (93.3, 102.3), B/R (96.6, 101.5), C/R (91.2, 99.2). The result is similar for AUC0-∞, as all fall within the lowest boundary of 80% and the highest boundary of 125%.

Table 1: Mean (± SD) pharmacokinetic parameters of ciprofloxacin 500 mg tablets (plasma fraction) after administration of brand R, A, B, and C (n=6) and paired-samples t-test for the equality between the means of the pharmacokinetic parameters (serum fraction)

					P-value		
Parameters	**Brand R**	**Brand A**	**Brand B**	**Brand C**	**A/R**	**B/R**	**C/R**
Cmax (µg/ml)	275.50 (± 3.86)	192.00 (± 1.10)	222.17 (± 2.11)	202.00 (± 0.55)	0.201	0.265	0.76
tmax (h)	6.83 (± 1.89)	7.00 (± 1.11)	5.08 (± 0.98)	3.63 (± 1.02)	0.551	0.735	0.568
t1/2 (h)	8.33 (± 0.66)	53.97(± 3.99)	16.35 (± 0.99)	42.84 (± 4.07)	0.149	0.219	0.82
Ke (h-1)	0.1475 (± 0.13)	0.02193 (± 0.02)	0.06047 (± 0.04)	0.04197 (± 0.04)	0.135	0.134	0.125
AUC0-24 (µg.h/ml)	4846.17 (± 1.43)	4019.67 (± 0.60)	4445.83 (± 1.18)	4195.67 (± 1.17)	0.267	0.434	0.143
AUC0-∞ (µg.h/ml)	7104.17 (± 1.72)	3959.00 (± 3.34)	5219.00 (± 3.44)	4354.33 (± 3.43)	0.212	0.395	0.79

Table 2: 90% confidence interval for the ratios test/reference of Cmax, AUC0-24 and AUC0-∞ values (log-transformed) for plasma fraction

	Brand A/R		**Brand B/R**		**Brand C/R**	
Pharmacokinetic parameters	**Ratio of means**	**90 % CI**	**Ratio of means**	**90 % CI**	**Ratio of means**	**90 % CI**
LogCmax	0.938	94.7 101.6	0.963	87.8 101.6	0.951	91.2 99.2
LogAUC0-24	0.972	93.3 102.3	0.992	96.6 101.5	0.984	96.5 100.2
LogAUC0-∞	1.083	95.2 125.4	1.021	97.5 106.7	1.04	100.4 108.2

Cmax: maximum plasma concentration; tmax: time to reach Cmax; t1/2: elimination half-life; Ke: elimination constant; AUC0-24: total area under the plasma concentration-time curve from zero to the last measurable time; AUC0-∞: total area under the plasma concentration-time curve from zero to infinity.

Cmax: maximum plasma concentration; AUC0-24: total area under the plasma concentration-time curve from zero to the last measurable time; AUC0-∞: total area under the plasma concentration-time curve from zero to infinity.

Microbiological assay

The pharmacokinetic parameters of ciprofloxacin after an oral 500 mg single dose administration of the reference sample (R) and the test samples A, B and C are shown in Table 3 and the concentration-time plot are shown in Figure 2. The mean Cmax obtained for the sample (A) was the highest (65.96 (± 0.33) µg/ml) occurring at a tmax of 3.67 (± 0.76) h. Next to it was C (56.92 (± 1.77) µg/ml) at 1.5 (± 0.17) h, R (55.48 (± 0.76) µg/ml) at 7.33 (± 1.00) h and B (50.75 (± 2.38) µg/ml) at 10.75 (± 2.42) h. The AUC0-24 for the four brands had its highest value observed in brand A (1279.81 ± 1.26) µg.h/ml followed by R (1138.85 ± 1.53) µg.h/ml, C (1044.07 ± 2.35) µg.h/ml and B (1026.20 ± 2.88) µg.h/ml.

The paired-sample t-test for the equality between the means of the pharmacokinetic parameters of the reference sample A to each of the test samples is also reflected in Table 3 with a significance level (p-value) of 0.05. From the table, there were no statistically significance difference between the mean Cmax, mean tmax and AUC0-24 of R against A, B and C (p>0.05)

The 90% confidence interval of the log transformed mean values for the pharmacokinetic parameters of the test/reference ratios are presented in Table 4. The value obtained for the 90% CI for log-transformed ration for Cmax is A/R (101.6, 107.1), B/R (86.4, 108.4), C/R (90.1, 109.6) while that of AUC0-24 is A/R (96.9, 106.), B/R (90.1, 109.6), C/R (89.8, 107.4). The result is similar for AUC0-∞, as all fall within the lowest boundary of 80% and the highest boundary of 125%.

Table 3: Mean (± SD) pharmacokinetic parameters of ciprofloxacin (serum fraction) after administration of brand R, A, B, and C (n=6) and Paired-samples t-test for the equality between the means of the pharmacokinetic parameters (serum fraction)

					P-value		
Parameters	**Brand R**	**Brand A**	**Brand B**	**Brand C**	**A/R**	**B/R**	**C/R**
Cmax (µg/ml)	**55.48 (± 0.76)**	**65.96 (± 0.33)**	**50.75 (± 2.38)**	**56.92 (± 1.77)**	**0.37**	**0.617**	**0.997**
tmax (h)	**7.33 (± 1.00)**	**3.67 (± 0.76)**	**10.75 (± 2.42)**	**1.5 (± 0.17)**	**0.212**	**0.75**	**0.192**
t1/2 (h)	**48.56 (± 5.44)**	**22.68 (± 3.00)**	**16.67 (± 1.08)**	**6.50 (± 0.25)**	**0.651**	**0.458**	**0.33**
Ke (h-1)	**0.030 (± 0.02)**	**0.09(± 0.07)**	**0.052 (± 0.02)**	**0.12 (± 0.05)**	**0.363**	**0.406**	**0.173**
AUC0-24 (µg.h/ml)	**1138.85 (± 1.53)**	**1279.81 (± 1.26)**	**1026.20 (± 2.88)**	**1044.07 (± 2.35)**	**0.447**	**0.63**	**0.713**
AUC0-∞ (µg.h/ml)	**4763.00 (± 0.95)**	**2386.89 (± 2.41)**	**1394.27 (± 0.32)**	**1414.31 (± 0.81)**	**0.54**	**0.342**	**0.378**

Table 4: 90% confidence interval for the ratios test/reference of Cmax, AUC0-24 and AUC0-∞ values (log-transformed) for serum fraction

	Brand A/R		**Brand B/R**		**Brand C/R**	
Pharmacokinetic Parameters	**Ratio of means**	**90 % CI**	**Ratio of means**	**90 % CI**	**Ratio of means**	**90 % CI**
LogCmax	**0.938**	**101.6** **107.1**	**0.582**	**86.4** **108.4**	**0.575**	**90.1** **109.6**
LogAUC0-24	**0.978**	**96.9** **106.8**	**0.518**	**90.1** **109.6**	**0.514**	**89.8** **107.4**
LogAUC0-∞	**1.083**	**86.9** **113.8**	**0.501**	**92.1** **103.6**	**0.512**	**84.7** **103.6**

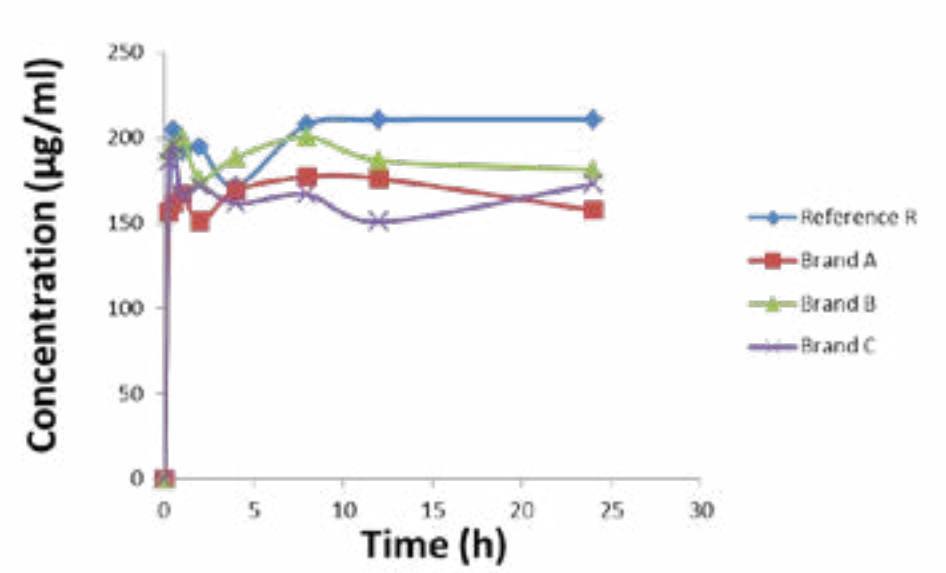

Figure 1: Graph shows mean (± SD) plasma concentration of ciprofloxacin 500 mg tablets after oral administration of single dose of Brand R, A, B and C to rabbits (n=6)

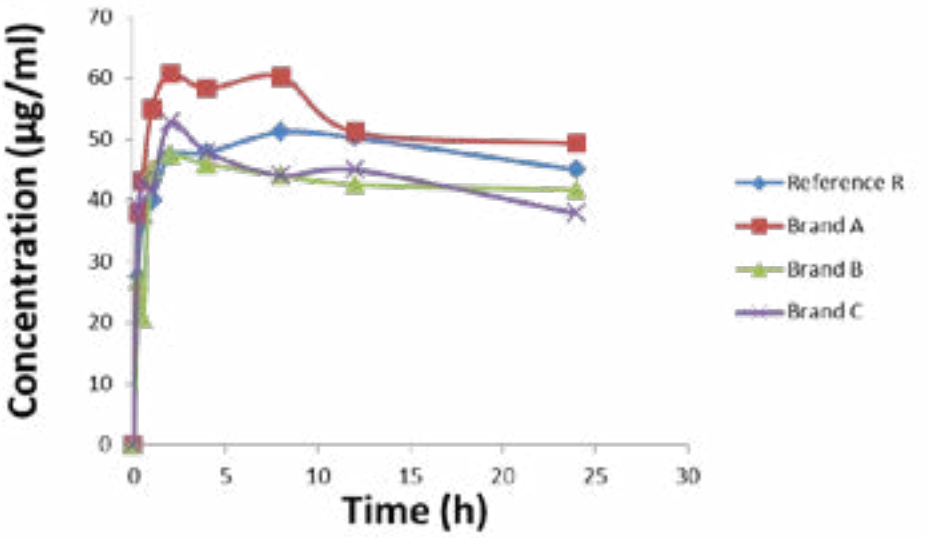

Figure 2: Graph shows mean (± SD) serum concentration of ciprofloxacin 500 mg tablets after oral administration of single dose of Brand A, B, C and D to rabbits (n=6)

Cmax: maximum serum concentration; tmax: time to reach Cmax; t1/2: elimination half-life; Ke: elimination constant; AUC0-24: total area under the plasma concentration-time curve from zero to the last measurable time;

AUC0-∞: total area under the plasma concentration-time curve from zero to infinity. Cmax: maximum serum concentration; AUC0-24: total area under the plasma concentration-time curve from zero to the last measurable time; AUC0-∞: total area under the plasma concentration-time curve from zero to infinity.

DISCUSSION

The measurement of the rate and extent of drug's systemic availability is been referred to as bioavailability and its assessment is by the Tmax that reflect the time required to get to the systemic circulation (rate), Cmax and AUC that are indicative of the amount of drug reaching the systemic circulation (extent) [19,20]. Hence, bioequivalence studies compare the Cmax, AUC and Tmax of the reference or standard sample with the test samples. The examined brands showed statistically insignificant difference for the required pharmacokinetic parameters for the two analytical methods utilized in this study. This is similar to a work carried out in Pakistani where two brands of ciprofloxacin tablets were examined for bioequivalence and the paired sample t-test showed that there is no statistically significant difference in the pharmacokinetic parameters of the two brands at a $p<0.05$ [21]. This is indicative of effective concentration of ciprofloxacin in the plasma and serum which will ultimately result into the therapeutic effectiveness of the drug in the various brands tested. The 90% CI of the log transformed mean values for the test/reference ratios for the plasma and serum fractions are between the lowest boundary of 80% and the highest boundary of 125% which is within the regulatory acceptable ranges for bioequivalence [22,23]. Two independent studies conducted in Singapore and Pakistani respectively

on ciprofloxacin brands assessed the brands to be bioequivalence as the 90% CI of the log transformed mean values for their test/reference ratios fall within the regulatory acceptable ranges of 80 to 125% [21-24]. Meanwhile, a study conducted in Nigeria utilized the Microbial Inhibition Zones (MIZ) revealed that none of the four tested brands can be used to replace the innovator brand in Staphyloccocal infections [25,26]. The difference in the outcome of these studies can be attributed to the fact that the brands tested in the two cases were from different manufacturer.

CONCLUSION

The four formulations were considered bioequivalent as the peak plasma concentration (Cmax) and AUC parameter analysis of variance reflected no significant difference between the reference brand and the three test brands. The tablet formulations were well tolerated by rabbits at the given dose and no adverse effects reported during the study. The analytical methods (UV-Vis spectroscopy and microbiological assay) were simple, cost effective and gave comparable result. The three local brands tested can substitute the reference ciprofloxacin tablet.

RECOMMENDATION

The animal subject served the purpose while a human subject would be very much appropriate and the analyses with a high specificity instrument such as HPLC are recommended.

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