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Comparative quality of fluoroquinolone tablets marketed in some towns in Northern Nigeria

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Abstract

Survey of fluoroquinolones tablets marketed in three northern Nigeria towns revealed that in the year 2002-2003, as many as 41 brands were in circulation in this part of the country of which 92.7% were imported, and mostly from Asian countries. Only 27 of the 41 sampled brands had NAFDAC registration numbers. Analysis of the various tablet properties showed that 4 of the 18 commonly used brands sampled failed weight variation tests and had drug content below the BP limit of 90%. Drug content variation was highly significant.

Keywords: *Comparative Quality; Fluoroquinolone Tablets; Northern Nigerian*

Introduction

Quality is the sum total of all parameters and factors that ensure a product meets required standards for use. The standards set out for drugs and medicines in general are usually exerting because they are not only required to meet specifications spelt out in official /reference monographs but also be of comparable quality with other products intended for similar use. The World Health Organization estimated that 51% of drugs circulating in the world of which 77% are in developing countries, contain no active ingredient at all, 17% contained the wrong drug while 11% contained under-dose of the active drug (WHO, 1999a, 1999b).

Since the introduction of the fluoroquinolones in the 1980, several derivatives have been synthesized and evaluated for their potential use as antimicrobial agents, a substantial numbers of which are currently in use while others are at various stages of clinical screening (Anderson & MacGravey, 2003). The fluoroquinolones are currently one of the most important antimicrobials used in the management of outpatient infectious diseases (Ball, 1998). They have been successfully employed in several disease conditions such as urinary tract, respiratory tract and gastro-intestinal infections, meningitis and brain abscess. The widespread use of the fluoroquinolones have largely been due to their broad-spectrum of antimicrobial activities, their effectiveness against several emerging resistant and problematic pathogens such as *Ps. aeruginosa*, Proteus and Klebsiella spp., their ease of administration and relatively low cost. It is these factors that

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might have accounted for the availability of several brands of the fluoroquinolones in Nigeria.

It is estimated that about 90% of drugs marketed in Nigeria are imported (Adenika, 1991), principally from Asian countries, notably India, Indonesia and Malaysia. A survey of fluoroquinolones in any major drug market in Nigeria shows availability of several brands (at least ten) at a time, with some of the brands disappearing after only three months and being replaced with new ones. The presence of several brands of one product generally poses problems not only to consumers but also to the health professionals, in terms of choice, brand substitution (generic equivalence), chemical and bio-equivalence and efficacy. There is, therefore, a need to assess the quality of these various brands of the fluoroquinolones available in three cities of Northern Nigeria. Analysis of the brands would serve as a guide for possible brand substitution.

Experimental

Sample collection. Retail pharmacy outlets in Kaduna, Zaria and Kano were surveyed for their stocks of fluoroquinolone tablet preparations. Based on the survey, the most commonly available brands of the fluoroquinolones in the market were selected for laboratory analysis. For qualitative test, the sampled brands were assigned number codes not necessarily as shown in Table 1.

Quality control tests. The sampled fluoroquinolone tablet formulations were subjected to various quality control tests as described below.

a. Weight variation test

For each brand, ten tablets were selected. They were weighed together and individually on a Mettler analytical balance (Mettler GmbH). Percentage weight variation was then calculated as recommended in the (BP 2002).

b. Tablet dimensions (thickness and diameter)

Twenty tablets of each of the selected brands were selected and their thicknesses and diameters measured using Micrometer screw-gauge (Moore and Wright, England) and Vernier calipers (Preisser, UK). The mean values and deviations were then computed.

c. Tablet Hardness

Crushing strengths of ten tablets of each brand were determined as described by the British Pharmacopoeia 2002, using a Monsanto Hardness tester. From the values, mean crushing strength for each brand of fluoroquinolone was calculated.

d. Friability Test.

The Roche Friabilator was used to carry out this test as described in the BP 2002. The Friabilator was calibrated to rotate at 25 rpm for four minutes. From the weights of the ten tablets before and after friabilisation, percentage loss in weight was calculated.

e. Disintegration Test.

Disintegration times of the test samples were determined as stated in the BP 2002, using the Erweka Tablet Disintegrator. Disintegration medium was 0.1N HCl.

f. Drug Content Determination

Microbiological assay procedure was used to determine the relative drug concentrations of the selected fluoroquinolone tablet preparations. Assay of the test samples was carried out using the agar diffusion method employing the 6 x 6 (3+3) dose level Latin square design (Bloomfield, 1991; Sahm and Washington, 1990). Three dose concentrations of the test samples (2.5µg, 5µg and 10µg/ml) made with distilled water were used. *Bacillus subtilis* NCTC 10342, which was earlier, found to be sensitive to, and gave good response to increasing concentration of fluoroquinolones, was used as test organism. Overnight culture of the organism, grown in Nutrient broth (Oxoid Ltd, Basingstoke, UK), was standardized to give 10^6cfu/ml.

For the assay, Ciproxin® (Bayer, Germany), Tarivid® (Aventis, Midrand) and

Peflacin® (Rhone-Poulenc, France) tablets were used as reference samples for the ciprofloxacin, ofloxacin and perfloxacin test samples respectively. The efficacies of these reference samples were earlier confirmed against sensitivity disks obtained from Becton and Dickinson (ciprofloxacin), Aventis (ofloxacin) and Pasteur Biological Laboratories, India, (perfloxacin). Nutrient agar (Oxoid Ltd, Basingstoke, UK) was used as the seeded agar on a large assay plate. Incubation was at 37°C for 24 hours.

Results

The various brands were either tablets or caplets of 250mg or 500mg strength. As shown in Table 1, forty-one (41) brands of fluoroquinolones, made up of 22 ciprofloxacin, 7 ofloxacin, 6 perfloxacin and 6 others (sparfloxacin, norfloxacin and levofloxacin) were available in the three surveyed towns. Of these brands, twenty-seven (27, i.e. 64%) were imported from Asia while three (3) had a Nigerian manufacturer label, and the rest were from Europe and the Middle East. Twenty-three (23) of the 41 available brands had NAFDAC registration number on their package, (i.e. the 3 brands produced in Nigeria, 16 of the 27 brands manufactured in Asia and 4 of the 8 Europe manufactured brands. None of the 4 brands with labels indicating they were manufactured in the Middle East had NAFDAC numbers.

Table 2 showed the results of the quality control tests performed on the test samples. Of a total of 18 brand samples analysed, 10 were ciprofloxacin, 5 ofloxacin and 3 perfloxacin. Fifteen of the analysed 18 brand samples complied with the BP limit for weight variation. Disintegration times considerably varied among the brands. Three brands, which had disintegration times exceeding 15 minutes limit time for uncoated tablets, were found to be film-coated. All the tablets/caplets had friability values well below 0.8%w/w limit. The tablets/caplets were generally hard, with crushing strengths ranging from 7.0 to 13.5 Nm^{-2}.

Result of the microbiological assay (Table 3) showed that four of the analysed brands had drug content below the minimum BP limit of 90%. Four of the brands that failed the assay test were manufactured in Asia, two being product of the same company. Interestingly, three of the four failed brands had NAFDAC registration numbers on their labels. Drug content variation was relatively high among the various brands within each of the three sub-groups. Among the ciprofloxacin brands, drug content range was as much as 36% with a standard deviation of 10.2, while among the ofloxacin and perfloxacin sampled brands, standard deviation in the drug contents was as high as 14 and 12 respectively.

Discussion

The result of this study which showed that only 3 of the 41 brands of fluoroquinolone tablets/caplets available in pharmacies in the three sampling towns had a Nigerian manufacturers' label is in agreement with the previous reports which estimated that about 90% of drugs in circulation in Nigeria are imported. This shows an overdependence of the country on foreign drug manufacturers. The qualitative tests which are not only a measure of compliance of a manufacture to laid down compendial standards but also of the level of efficiency of in-process quality control of a manufacturing plant, indicates that some of the manufacturers are non-compliant to GMP guidelines on in-process control measures.

The possession of a NAFDAC registration number is supposed to be an indication of official acceptance and authentication of quality of a product in Nigeria. The high proportion of fluoroquinolones brands in these towns without NAFDAC registration numbers

(45%) is an indication of prevalence of fake & or adulterated drugs in this region.

Table 1: List of available brands of fluoroquinolones in three Northern Nigeria towns

Brand Name	Strength (mg)	Manufacturer	Country of Origin	NAFDAC No
Ciprofloxacin				
Beso	500	Sudopharma	Korea	04-1521
Cifran	500	Ranbaxy Ltd	India	04-1434
Ciprobiotic Forte	500	Encure Pharmaceutical Ltd	India	04-2307
Ciprocin	500	Egypt International Pharm. Co	Egypt	-
Ciprocine	250	Racha Lab	Syria	-
Ciproflex	500	Alpha Pharmaceuticals Industries	Syria	-
Ciproflox	250/500	Indonesian Pharm.	Indonesia	-
Ciprogem	500	Gemini	Nigeria	04-3417
Ciprolex	500	Shield of Protection	India	-
Cipromed	500	Gracure Pharm. Ltd. New Delhi	India	-
Ciprotab	500	V.S International	India	04-0723
Ciproval	500	Nigeria-German Chemicals Plc	Nigeria	04-2433
Ciproxene	500	Massoud-Bahri & Co	Syria	-
Ciproxin	250	Bayer	Germany	-
Ciproxin	500	Bayer Istanbul	Turkey	-
Cyplox	500	Medreich Sterilab	India	04-3202
Iflos	500	PT Gauardian Pharmatama	Indonesia	04-2370
Interflox	250/500	PT Interbet	Indonesia	-
Rapidflox	500	Bharat Parenterals Ltd	India	04-3220
Siprosan	500	Drogsan	Turkey	04-2107
Vitapro	500	Vital Pharmaceuticals	India	-
Zifan forte	500	Alpha Drugs & Pharmaceuticals	India	-
Ofloxacin				
Drovid	200	Plantafarma Bitkisel Jag sanaji AS	Turkey	-
Flovid	200	Hovid	Malaysia	04-3619
Floxan	200	Korea United Pharm. Inc	Korea	04-2627
Oflomed	200	Bharat Ltd	India	04-3132
Tarivid	200	Aventis	Midrand	04-0885
Traflox	200	Nig.-German Chemical Plc	Nigeria	04-2530
Zanocin	200	Rambaxy	India	04-2491
Perfloxacins				
Abaktal	400	Lek Pharm. Company	Slovenia	04-1836
Peflacine	400	Rhone-Poulec	France	04-1015
Peflomed	400	Bharat Ltd	India	04-3133
Pefoxin	400	Alpha Pharm. Ltd	India	-
Pemax	400	Korea United Pharm Inc	Korea	-
Peflotab	400	V.S International PVT. Ltd	India	-
Norfloxacin				
Norbactin	400	Ranbaxy	India	04-2458
Norfen	400	Cadila Pharm		04-0776
Norxin	400	Korea Pharma Co. Ltd	Korea	-
Sparfloxacin				
Sparbact		Ipca Lab Ltd	India	04-3456
Sparx		Wockhardt Ltd	India	04-3204
Levofloxacin				
Tavanic		Aventis Pharm	Midrand	-

At the time of sampling, products with (-) had no identifiable NAFCAC registration number.

Table 2: Tablet Properties of Various Brands of Fluoroquinolones Marketed Three Northern Nigeria Towns

Brand	% Weight Variation	Thick-ness (mm)	Diameter (mm)	Disintegrat-ion Time (min)	Friability (%)	Crushing strength (Nm^{-2})
Ciprofloxacin						
Ciproxin	375.5±9.0	4.02	11.11	1.40	0.00	9.0
C1	1014.0±21.5	7.27	19.50	2.00	0.05	10.0
C2	354.1±25.0	3.69	19.00/9.50*	1.00	0.14	12.0
C3	805.8±17.5	5.75	18.20	10.30	0.00	12.0
C4	765.5±13.5	4.57	12.00	2.80	0.07	10.5
C5	666.1±11.0	5.42	15.00/9.00*	4.30	0.23	12.5
C6	963.6±6.5	5.62	17.60	1.30	0.05	12.0
C7	381.9±3.0	4.32	11.00	1.30	0.13	9.0
C8	895.6±5.5	6.72	20.00	1.55	0.11	9.0
C9	738.6±28.0	4.61	19.00/9.50*	2.80	0.07	11.0
C10	970.4±12.9	5.87	19.80	1.45	0.05	12.0
Ofloxacin						
Tarivid	393.0±6.5	4.35	13.00/7.00*	20.20	0.26	13.5
O1	290.3±3.0	4.33	9.00	5.40	0.34	12.0
O2	373.7±10.7	5.43	10.00	9.55	0.13	10.0
O3	325.7±19.7	4.37	9.50	24.00	0.15	10.0
O4	392.8±2.5	4.35	14.00	1.40	0.12	9.5
O5	400.8±4.5	4.61	10.05	5.10	0.25	12.0
Perfloxacin						
Peflacine	778.9±7.0	4.71	18.00/9.00*	8.00	0.07	14.0
P1	762.8±3.0	4.54	18.50/9.50*	9.10	0.06	14.0
P2	845.3±20.0	5.64	20.00/9.00*	9.30	0.12	7.0
P3	943.5±50.0	6.51	19.00/9.50*	26.1	0.21	8.0

* indicates the dimension (length and width) of caplets

Table 3: % drug content of various brands of fluoroquinolone marketed in three Northern Nigerian towns.

Brand	Percentage Content (%)
Ciprofloxacin	
C1	102.6 ± 2.6
C2	80.2 ± 4.5
C3	89.0 ± 3.0
C4	104.0 ± 2.0
C5	116.3 ± 5.0
C6	89.6 ± 3.0
C7	92.0 ± 3.0
C8	102.0 ± 2.5
C9	94.9 ± 3.1
C10	90.5 ± 3.0
Ofloxacin	
O1	93.1 ± 2.6
O2	105.3 ± 3.4
O3	73.5 ± 4.6
O4	109.6 ± 5.4
O5	96.8 ± 3.2
Perfloxacin	
P1	104.0 ± 2.0
P2	98.5 ± 3.5
P3	81.0 ± 3.2

Differences in the drug content among the sub-groups was highly significant at $p \leq 0.05$

It is also worth noting that the carriage of NAFDAC registration numbers may not be a guarantee of total quality since three of the four brands that did not comply with laid down standards (USP XVII) carried NAFDAC registration numbers. This could have arisen if all batches were not subjected to certification process by the regulatory body. Monitoring of all batches would have ensured manufacturer's compliance to GMP. It must also be realized that in a country with unreliable drug distribution system, drugs available in markets may not necessarily originate from the labeled manufacturers.

The high drug content variation among the various brands implied that prescribers should be cautious when considering generic substitution of quinolones for their patients. As much as possible, none of the brands should be substituted with others unless bio-equivalence data are available.

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