

OFLOXACIN: LABORATORY EVALUATION OF THE ANTIBACTERIAL ACTIVITY OF 34 BRANDS REPRESENTING 31 MANUFACTURERS AVAILABLE IN PAKISTAN

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ABSTRACT

Objective: To evaluate the antibacterial effectiveness of 34 competitive Ofloxacin products representing 31 manufacturers available in the local market, on 3 standard Quinolone-sensitive American Type Culture Collection (ATCC) bacterial cultures of *E.coli*, *Proteus vulgaris* and *Staphylococcus aureus*.

Design: A blind assessment of 29 Ofloxacin brands in tablet form, and 5 in pre-mixed injectable solution collected by TheNetwork for Consumer Protection in Pakistan, Islamabad, with trade and manufacturers names of the products veiled by blanking.

Setting: The appraisal was conducted in Karachi at the Department of Microbiology, Jinnah University for Women, and Dr. Essa's Lab & Diagnostic Centre, in March 2003.

Method: Direct aqueous suspensions along with 3 additional serial dilutions of each product were used to challenge the 3 target bacteria by the disc-diffusion method. The resultant inhibition-zone diameters were recorded for comparison of antibacterial activity.

Results: Comparatively effective but varying antibacterial results were seen using *Proteus* and *Staph aureus*; however, alarming differences were recorded when *E.coli* was targeted. With this organism, excellent inhibition zone diameters were observed with "Eracin" (CCL), "Ofloxacin" (Shin Poong), "Oflobid" (Hilton) & "Oflobiotic" (Zafa); others gave good, moderate or poor zones, while 4 shockingly exerted no visible effect: these included 3 single-vial injectable suspensions purported to represent Brookes ("Quinon"), Bosch ("Tariflox") and Hoechst/Aventis ("Tarivid"), and the GlaxoSmithKlein's tablet "Floxy".

Conclusion: A significant variation in antibacterial activity of marketed Ofloxacin brands, some representing pharmaceutical giants, demonstrated by simple disc diffusion zone diameter comparison raises serious questions whether the less effective ones obtained in Islamabad and also purchased in Karachi for comparison were flawed, counterfeit or sub-standard preparations.

KEY WORDS: Ofloxacin, Quinolone, Trade brands, Evaluation, Antibacterial activity

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INTRODUCTION

The Quinolones are synthetic analogs of Nalidixic acid that have an exceedingly broad spectrum of activity against many bacteria. The newer fluorinated derivatives have more potent antibacterial action and achieve useful levels in blood and tissues. A variety of such fluorinated carboxy-quinolones are available and are increasing in number, most of which have quite similar spectrums of activity. Ofloxacin, selected for study as a representative of this antibiotic group was developed by the Daiichi Pharmaceutical Corporation established in the

U.S. in 1980,¹ and currently is marketed in Pakistan under approximately 54 trade brand names.² It is basically an off-white to pale-yellow crystalline powder with empirical formula C₁₈H₂₀FN₃O₄ and 361.4 molecular weight, and is available for sale in 200 mg tablets and in sterile single-use injectable solutions in pre-mixed bottles. Our study sponsored by TheNetwork for Consumer Protection in Pakistan, Islamabad, was designed to evaluate the anti-bacterial efficacy of 34 of the 54 trade brands of Ofloxacin that are marketed in the country by 31 manufacturers; The three target bacterial species challenged were standard Ofloxacin-sensitive strains of *Escherichia coli*, *Proteus vulgaris* and *Staphylococcus aureus*. *E.coli* is a normal intestinal inhabitant but recognized as the most common cause of urinary tract infection (UTI), gram-negative sepsis and neonatal septicemia; it is also frequently associated with watery "traveler's diarrhea" and some strains cause bloody stools. *Proteus* spp are gram-negative rods that are also part of the normal intestinal flora, but can cause UTI, otitis media, pneumonia, wound infections and septicemia, while *S.aureus*, a gram-positive coccus, is found primarily in the normal human flora on and in us, but can cause boils and abscesses, various pyogenic infections (e.g. endocarditis and osteomyelitis), food poisoning, UTI, and toxic shock syndrome. It is also the most common cause of hospital acquired pneumonia, septicemia and wound infections.³

E.coli was the initial target bacterial species chosen for the comparative evaluation, and *Staph* and *Proteus* were included when significant variations in effective potency of the marketed drugs were recorded using *E.coli*.

TheNetwork for Consumer Protection in Islamabad decided to initiate and sponsor this exercise comparing the efficacy of, to begin with, one marketed antibiotic, and this preceded regular articles appearing in the daily press on the sale in Pakistan of spurious medical preparations of dubious quality – including antibiotics, painkillers, steroids, anti-depres-

sants, sedatives, laxatives, tranquilizers, cough syrups and injectables.

MATERIALS AND METHODS

Ofloxacin Trade Brands Used: A total of 29 representative trade brands were in tablet form and 5 in sterile single-use preservative-free aqueous solution in pre-mixed bottles for injections. These were purchased in duplicate by TheNetwork for Consumer Protection in Pakistan at Islamabad in March 2003, who retained one set for further reference, and recorded all the batch numbers and validity dates. Nine brands of an additional 24 registered in the 2002-03 PharmaGuide compendium were apparently not available commercially in the twin cities; these were "Bactacin" (Pharmacare), "Floxol" (P.D.H.), "Fugacin" (Remedica), "Loxin" (Dosaco), Negabact (Y.Y.Pharma), "Oflocin" (Hakimsons), "Rekoflox" (Reko), "Q-Span" (Spencer Pharma) and "Zoflox" (Pharmatec). All the available brands and manufacturers names were masked by permanent ink to ensure "blind" testing, coded, adequately packaged, and promptly dispatched by courier. The code list identifying each sample was made available to the research team in Karachi only after the results of the study, also conducted in March 2003, were tabulated and conveyed to TheNetwork. Also, four of the five injectables, "Quinox" (Brookes), "Tariflox" (Bosch), "Tarivid" (Hoechst/Aventis), and "Oflobid" (Hilton) were procured by the research team in Karachi in mid September 2003, for comparison.

Preparation of test discs: Discs (6mm in diameter) were punched out from Whatman's "12.6" filter paper, placed in Petri dishes allowing a distance of 2-4mm between each disc, and sterilized in a hot-air oven at 160C for 1hr. The injectables which were in solution were processed as such, while each 200mg Ofloxacin tablet was crushed, stirred until dissolved in 10 ml sterile distilled water, and diluted for use in three additional concentrations thus:

Direct	=	200mg
1:2	=	100mg
1:4	=	50mg
1:8	=	25mg

An aliquot of 0.02 ml of each concentration was pipetted onto a separate disc, incubated at 37C for 1 hr, placed in labeled air-tight containers and kept refrigerated at 4C until use.⁴

Bacterial cultures and Procedure: Three standard Ofloxacin-sensitive Oxford strains selected for the study included the 2 gram-negative rods *E.coli* (ATCC 25922) and *Proteus vulgaris* (ATCC 6380), and the gram-positive coccus *Staphylococcus aureus* (ATCC 6538). Overnight subcultures were suspended in sterile Nutrient broth (Oxoid, U.K.) and the final turbidity adjusted to match McFarland standard 0.5.⁴ Lawns of each bacterial suspension were made on Mueller Hinton's Sensitivity Agar (MHA; Oxoid) using sterile cotton swabs.⁵ Prepared discs of all 4 dilutions of each product were positioned at appropriate distances on the same MHA Petri dish streaked separately with each culture. All plates were incubated in one batch overnight at 37C for 24 hours, and the growth inhibition zone diameters were carefully measured with calipers and recorded according to the standard Kirby-Bauer disc diffusion method⁶ and NCCLS guidelines.⁷ All tests were run simultaneously to ensure uniformity of conditions, along with standard commercial Ofloxacin 10 ug discs (Oxoid) which were used as a control and which gave regular zones of 18-20 mm with *Staph* and 20-22mm with each of the two gram-negative cultures.⁸

RESULTS

The inhibition zone diameters observed using four concentrations of each Ofloxacin product on *E.coli* is tabulated in Table-I. Results using 200 mg discs indicated that "Oflobid" (34 mm) and "Eracin" (33 mm) gave the largest (excellent) zones, followed by "Ofloxacin" (30 mm), "Oflobiotic" (30 mm) and "Loxat" tablets (29 mm); approximately

15 products afforded "moderate" inhibition zones between 20-25 mm, while arbitrary "less effective" zones (11-19 mm diameter) were seen with 10 other trade brands. Indeed, the zones exerted by the 3 other dilutions of each product were proportionately with minor variations in keeping with the above findings, and also signalled significant individual differences in their potency. Moreover, the following striking observations were made: negligible inhibitory zones were recorded with one brand in tablet form ("Floxy": GlaxoSmithKline), and with 4 of the 5 injectables scrutinized, even when the assessment was repeated: these were "Quinon" (Brookes), "Tariflox" (Bosch), "Tarivid" (Hoechst/Aventis), and "Oflobid" (Hilton). Interestingly, "Loxat" (Siza), the fifth available injectable tested, exerted at least "fair" activity in three of the higher concentrations, while in tablet form, gave excellent inhibition zones with 200mg and 100mg discs, but none with 50mg and 25mg discs.

Table-II summarizes results when *Staphylococcus aureus* was challenged. Noteworthy is the observation that all 4 concentrations of each product gave satisfactory inhibition zones, including those that failed to do so with *E.coli*. However, individual variations in zone size were obvious: apparently the most potent anti-Staph activity was exerted by "Curitol" (Standpharm), "Eracin" (CCL), "Flovix" (Bryon), "Gyrex" (Platinum), "Kapcin" (Cirin), "Ofloxin" (Werrick) and "Ofloquin" (Global). The following five offered the least effective comparative results: "Albact" (Nabiqasim), "Floxy" (GlaxoSmithKline), "Gyrasid" (Ferozsos), "Tabroxacin" (Tabros), and "Wiloxin" (Wilson's).

Significant inhibition-zones were also recorded when *Proteus vulgaris* was targeted (Table-III). Interestingly, the best tablet results were seen with GlaxoSmithKlein's "Floxy" (which had given comparatively poor results with *Staph aureus*, and none on *E. coli*), "Ofloxacin" (Shin Poong), "Oflobid" (Hilton), "Ofloquin" (Global), "Tariflox" (Bosch), "Tarivid" (Hoechst/Aventis), and "Wiloxin" (Wilson's). However, disappointing zones

occurred with the 3 injectables “Loxat” (Siza), “Tarivid” (Hoechst/Aventis), and “Tariflox” (Bosch), even on reassessment, while “Quinon” (Brookes), the fourth one included in the study, and which had no effect on *E. coli*, exerted excellent comparable zones with all 4 suspensions.

In a final scrutiny of the overall tabulated results indicating the degree of antibiotic activity of the trade brands, it was evident that 2 of the 34 products in particular exerted the most consistent comparatively superior inhibition zones, even when in the lowest (25mg) dilution. These were tablets “Oflobid”

Table-I: Sensitivity inhibition zones of Ofloxacin brands on *E.coli*

S.No.	Code #	Brand Name	Manufacturer	Package	Direct 200 mg (mm)	1:2 100 mg (mm)	1:4 50 mg (mm)	1:8 25 mg (mm)
1	1	ALBACT	NABIQASIM	Tabs	19	15	0	0
2	2	AVOCIN	HARMANN	Tabs	22	10	14	0
3	4	BACIVID	OMERSONS	Tabs	14	06	0	0
4	5	CIOF	REMLINGTON	Tabs	23	21	20	16
5	6	CURITOL	STANDPHARM	Tabs	17	12	0	0
6	7	ERACIN	CCL	Tabs	33	29	28	26
7	8	EXACT	SAYDON	Tabs	17	16	0	0
8	9	FLOVIX	BRYON	Tabs	15	0	0	0
9	11	FLOXY	GLAXOSMITHKLEIN	Tabs	0	0	0	0
10	13	GEOFLOX	GEOFMAN	Tabs	14	0	0	0
11	14	GYRASID	FEROZSONS	Tabs	21	16	12	10
12	15	GYREX	PLATINUM	Tabs	21	19	13	0
13	16	KAPCIN	CIRIN	Tabs	23	18	14	0
14	17	KORVID	KOREAN DRUG CO.	Tabs	13	13	0	0
15	18	LOXAT	SIZA	Tabs	29	21	0	0
16	19	LOXAT	SIZA	Injection	19	9	7	0
17	22	OFLAMAC	MACTER	Tabs	18	12	11	0
18	23	OFLOXACIN	SHIN POONG	Tabs	30	30	26	25
19	24	OFLOBID	HILTON	Tabs	34	29	25	23
20	25	OFLOBIOTIC	ZAFA	Tabs	30	30	26	25
21	26	OFLOXIN	WERRICK	Tabs	24	21	19	16
22	27	OFLOQUIN	GLOBAL	Tabs	21	16	0	0
23	28	OFLOX	INDUS	Tabs	20	20	12	11
24	30	OFTAB	KYUNG DONG/AKHAI	Tabs	21	18	17	16
25	31	OXIL	HIMONT	Tabs	21	17	15	12
26	33	QUINOX	BROOKES PHARMA	Injection	0	0	0	0
27	35	RUTIX	SQUARE/AMSTAR	Tabs	20	15	14	12
28	36	TABROXACIN	TABROS	Tabs	20	16	13	0
29	37	TARIFLOX	BOSCH	Tabs	20	17	15	13
30	38	TARIFLOX	BOSCH	Injection	0	0	0	0
31	39	TARIVID	HOECHST/AVENTIS	Tabs	23	21	17	14
32	40	TARIVID	HOECHST/AVENTIS	Injection	0	0	0	0
33	41	WILOXIN	WILSON'S	Tabs	25	23	21	0
34	43	OFLOBID	HILTON	Injection	11	0	0	0

(Hilton) and "Ofloxacin" (Shin Poong). Also eye-catching were the unexpected, conspicuously poor overall effects which were afforded by the two injectables "Tarivid" (Hoechst/Aventis) and "Tariflox" (Bosch), and also the tablet "Floxy" (GlaxoSmithKline), which are products purported to represent familiar phar-

maceutical giants. Furthermore, the 4 disappointing injectables which were procured in Karachi for crucial comparison also disturbingly exerted practically identical results when tested against the 3 target bacteria, suggesting that the products are widespread for sale in the country.

Table-II: Sensitivity inhibition zones of Ofloxacin brands on *Staphylococcus aureus*

S.No.	Code #	Brand Name	Manufacturer	Package	Direct 200 mg (mm)	1:2 100 mg (mm)	1:4 50 mg (mm)	1:8 25 mg (mm)
1	1	ALBACT	NABIQASIM	Tab	30	28	26	25
2	2	AVOCIN	HARMANN	Tab	38	36	35	33
3	4	BACIVID	OMERSONS	Tab	40	35	33	30
4	5	CIOF	REMLINGTON	Tab	40	39	35	33
5	6	CURITOL	STANDPHARM	Tab	45	40	38	32
6	7	ERACIN	CCL	Tab	44	40	37	32
7	8	EXACT	SAYDON	Tab	35	32	30	29
8	9	FLOVIX	BRYON	Tab	45	42	40	35
9	11	FLOXY	GLAXOSMITHKLEIN	Tab	32	30	26	23
10	13	GEOFLOX	GEOFMAN	Tab	40	39	36	32
11	14	GYRASID	FEROZSONS	Tab	32	31	30	30
12	15	GYREX	PLATINUM	Tab	45	40	35	32
13	16	KAPCIN	CIRIN	Tab	45	42	37	32
14	17	KORVID	KOREAN DRUG CO.	Tab	40	38	36	34
15	18	LOXAT	SIZA	Tab	39	38	32	31
16	19	LOXAT	SIZA	Injection	40	39	34	32
17	22	OFLAMAC	MACTER	Tab	35	34	32	30
18	23	OFLOXACIN	SHIN POONG	Tab	40	39	39	39
19	24	OFLOBID	HILTON	Tab	40	40	39	39
20	25	OFLOBIOTIC	ZAFA	Tab	40	44	42	37
21	26	OFLOXIN	WERRICK	Tab	45	44	43	42
22	27	OFLOQUIN	GLOBAL	Tab	45	43	38	31
23	28	OFLOX	INDUS	Tab	35	32	30	28
24	30	OFTAB	KYUNG DONG/AKHAI	Tab	40	35	32	30
25	31	OXIL	HIMONT	Tab	40	35	34	32
26	33	QUINOX	BROOKES PHARMA	Injection	37	35	33	31
27	35	RUTIX	SQUARE/AMSTAR	Tab	37	34	32	31
28	36	TABROXACIN	TABROS	Tab	31	30	30	28
29	37	TARIFLOX	BOSCH	Tab	42	40	35	32
30	38	TARIFLOX	BOSCH	Injection	35	32	31	30
31	39	TARIVID	HOECHST/AVENTIS	Tab	40	39	35	33
32	40	TARIVID	HOECHST/AVENTIS	Injection	37	35	35	34
33	41	WILOXIN	WILSON'S	Tab	31	30	27	25
34	43	OFLOBID	HILTON	Injection	41	37	35	30

Table-III: Sensitivity inhibition zones of Ofloxacin brands on *Proteus vulgaris*

S.No.	Code #	Brand Name	Manufacturer	Package	Direct 200 mg (mm)	1:2 100 mg (mm)	1:4 50 mg (mm)	1:8 25 mg (mm)
1	1	ALBACT	NABIQASIM	Tabs	20	18	16	14
2	2	AVOCIN	HARMANN	Tabs	26	22	16	15
3	4	BACIVID	DR. OMERSONS	Tabs	19	12	9	8
4	5	CIOF	REMGINTON	Tabs	25	19	17	16
5	6	CURITOL	STANDPHARM	Tabs	15	14	10	8
6	7	ERACIN	CCL	Tabs	24	20	12	10
7	8	EXACT	SAYDON	Tabs	18	12	11	10
8	9	FLOVIX	BRYON	Tabs	16	15	14	11
9	11	FLOXY	GLAXOSMITHKLINE	Tabs	31	29	22	21
10	13	GEOFLOX	GEOFMAN	Tabs	20	14	11	10
11	14	GYRASID	FEROZSONS	Tabs	18	16	15	14
12	15	GYREX	PLATINUM	Tabs	21	16	16	10
13	16	KAPCIN	CIRIN	Tabs	22	20	18	16
14	17	KORVID	KOREAN DRUG CO.	Tabs	20	17	17	15
15	18	LOXAT	SIZA	Tabs	20	16	15	12
16	19	LOXAT	SIZA	Injection	12	11	11	10
17	22	OFLAMAC	MACTER	Tabs	18	14	11	7
18	23	OFLOXACIN	SHIN POONG	Tabs	30	29	27	26
19	24	OFLOBID	HILTON	Tabs	32	30	28	26
20	25	OFLOBIOTIC	ZAFA	Tabs	21	19	17	15
21	26	OFLOXIN	WERRICK	Tabs	20	16	14	13
22	27	OFLOQUIN	GLOBAL	Tabs	30	28	17	15
23	28	OFLOX	INDUS	Tabs	22	18	16	13
24	30	OFTAB	KYUNG DONG/AKHAI	Tabs	25	20	18	15
25	31	OXIL	HIMONT	Tabs	25	24	21	20
26	33	QUINOX	BROOKES PHARMA	Injection	28	26	25	21
27	35	RUTIX	SQUARE/AMSTAR	Tabs	20	18	17	16
28	36	TABROXACIN	TABROS	Tabs	20	18	16	11
29	37	TARIFLOX	BOSCH	Tabs	30	25	22	18
30	38	TARIFLOX	BOSCH	Injection	17	14	13	12
31	39	TARIVID	HOECHST/AVENTIS	Tabs	30	24	21	17
32	40	TARIVID	HOECHST/AVENTIS	Injection	15	11	8	7
33	41	WILOXIN	WILSON'S	Tabs	30	29	26	24
34	43	OFLOBID	HILTON	Injection	15	12	11	0

DISCUSSION

Our evaluation of the efficacy of competitive trade brands of only one of numerous common antibiotics available in the local market was an unexpected eye-opener. Indeed, faced with a choice of multiple antibiotic groups, each with several generic varieties, and each of the varieties with numerous competitive trade brands, it is only a few selected members of the

fluoroquinolones in particular that emerge as popular prescriptions for treating patients who present with varying problems ranging from UTI and soft-tissue infection to typhoid fever. The newer fluorinated derivatives (e.g. Ciprofloxacin, Enoxacin, Levofloxacin, Lomefloxacin, Gatifloxacin, Moxifloxacin, Ofloxacin and Sparfloxacin) have potent antibacterial activity and can achieve clinically useful levels in blood and tissues.⁹ That is, if

the product available over-the-counter is not imitation or substandard – necessities vital to the patient whose cure depends on the potency of the drug it is expected to contain. Furthermore, choosing the trade brand from so many is another hurdle: for example, there are apparently 54 competitive Ofloxacin products that are currently advertised as marketed in Pakistan, 59 Ciprofloxacin, 18 Norfloxacin, etc.² The choice is usually influenced by manufacturer's representatives who move around from doctor to doctor bearing attractive gifts and spouting praise for their particular brand.

Our results comparing the antibiotic strength of 34 obtainable Ofloxacin trade brands on three selected bacterial species not only indicates significant differences in the extent of antibacterial effect exerted, which suggests variations in effective drug unit content of the samples, but also alarmingly specified “zero” discernable activity on a known ATCC Ofloxacin-sensitive *E. coli* strain, the first selected bacterial specie targeted, by products purported to be marketed, among others, by pharmaceutical giants such as GlaxoSmithKline (“Floxy”) and Hoechst/Aventis (“Tarivid”). That these two brands did indeed have some effect on *Proteus* and *Staph* suggests that the products were not entirely devoid of “antibiotic” activity, except when *E.coli* was challenged. Furthermore, the four injectables, Quinox, Tariflox, Tarivid and Oflobid procured in Karachi for comparison gave matching zone diameters as those recorded for TheNetwork samples, suggesting that the products are not available for sale only in Islamabad. The question then arises is whether the profound variations observed in effectiveness reflect the option that the trade brands were indeed substandard preparations, or imitation, or that they had somehow suffered loss of potency due to mishandling by unknown hands or through defective storage conditions in transit or in the retailing pharmacy. The observation, however, that identical results were obtained with pertinent merchandise procured in Islamabad and also in

Karachi suggests that “mishandling” is a remote possibility; that these are counterfeit or substandard products seems to be logically more reasonable. We ruled out the likelihood that the tablets, including “Floxy” which had done poorly, were not completely dissolved in water, by ascertaining that a minimum of 10ml of liquid was essential for the purpose, or else saline or buffer would have been employed; moreover, the injectables that performed feebly were purchased and processed in ready-to-use suspension form. Whatever the explanation, it appears that competitive shoddy drugs abound in our environment, and that our conclusions which are backed by simple corroborative data encourage awareness and the evaluation of other antibiotics. Indeed, illicit imitators would logically tend to profit more by counterfeiting those drugs which are more popular in sale, or represent well-known manufacturers, as our exercise has indicated.

A relevant article adding pertinent weight entitled, “Local companies producing sub-standard drugs” appeared in the daily *Dawn* (July 23, 2003) which detailed a research study carried out at the Department of Pharmaceutics, University of Karachi, in which 15 different brands of Ofloxacin tablets were randomly selected from the local market, using probability sampling tools, and assayed for physical parameters such as weight variation, hardness, friability, dissolution, disintegration, etc in accordance with the methods and guidelines given in both the British and US Pharmacopoeia. Two of the 15 tablets are reported to have failed to meet the obligatory standard, and 4 samples had significantly less ingredient than the required specification to be effective for therapeutic use.

Therefore, the reality that medical preparations of dubious quality ranging from antibiotics and injectables to sedatives, analgesics, laxatives and cough syrups are being marketed in the country, as well as contaminated blood for transfusion, adulterated food-stuff and so-called mineral waters, to list a few, is indeed an issue that merits alertness, concern and appraisal.

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