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IN VITRO SUSCEPTIBILITY OF CLINICAL UROPATHOGENS TO LEVOFLOXACIN AT THE GHANA POLICE HOSPITAL

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ABSTRACT

Background: Quinolones are among drugs used in the treatment of urinary tract infections (UTIs). However, there has been an increase in quinolone-resistant uropathogens over the last decade. The aim of this study was to assess the sensitivity pattern of isolated uropathogens to levofloxacin.
Methods: Urine samples (n = 519) from suspected UTI patients were collected from July 2014 to September 2014. Microorganisms with significant growth were identified after initial culturing at 37^0C for 24 hours. Susceptibility of isolated uropathogens to levofloxacin at a break point of 5 µg was done by the Kirby-Bauer disc diffusion method.
Results: The prevalence of UTI among sampled patients was 18.3%. Predominant microbial isolates were: *Escherichia coli* (56.8%), *Coliform spp.* (24.2%) and *Staphylococcus aureus* (9.5%). Overall resistance of isolated uropathogens to levofloxacin was 51.6%. Levofloxacin resistance by predominant uropathogens was 63% for *E. coli*, 34.8% for *Coliform spp.* and 22.2% for *S. aureus*.
Conclusions: High resistance of some isolated uropathogens to levofloxacin, especially with *E. coli* was observed in this study. Thus, the need for coordinated susceptibility monitoring of clinical isolates to levofloxacin.

Keywords: levofloxacin; quinolones; susceptibility; urinary tract infections; uropathogens

INTRODUCTION

Antimicrobials play a pivotal role in the treatment of several infections which results in improved quality of life. However, increasing resistance to most conventional antibiotics has resulted in global health concerns, where antibiotic resistance has been tagged as an emerging disease by the World Health Organization [1].

Nalidixic acid, a quinolone antibiotic was among the first antibiotics primarily used for the treatment of urinary tract infections (UTIs). With time, increased bacterial resistance and its narrow antibacterial spectrum, led to the development of structural analogs of quinolones known as fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin among others known as second-generation quinolones [2, 3]. Currently, there are third-generation quinolones (like levofloxacin and sparfloxacin) with expanded activity against gram-positive bacteria and atypical pathogens, and fourth-generation quinolone drugs (trovafloxacin) with additional significant activity against anaerobes [4].

Fluoroquinolones are preferred first line agents in the treatment of UTI because of their high bacteriologic and clinical cure rates, when hypersensitivity is of concern, or where conventional agents are less desirable due to toxicity [5]. They are known for their ability to induce rapid resistance in microorganisms through induction mutations during therapy [6]. Hence, increased pressure or overuse of any type of fluoroquinolone could lead to emergence of

resistance to an entire class. However, fluoroquinolones with C-8 methoxy substitution on the fluorinated quinoloic acid cores such as levofloxacin are known to exhibit higher antibacterial activity against quinolone resistance bacteria that possess GyrA mutation [7]. Currently, ciprofloxacin and levofloxacin (*l*-isomer, or S-enantiomer of ofloxacin) are the most prescribed fluoroquinolones [8].

Ciprofloxacin is often prescribed for UTIs in Ghana because it is recommended in the national treatment guidelines and it is also affordable. Its availability in oral and intravenous formulations, favorable bioavailability and pharmacokinetics, allows twice-daily administration [5, 9]. Current studies in Ghana, Nigeria and other parts of the world reveal that, ciprofloxacin has a higher resistance rate than levofloxacin among clinical isolates [10-13]. A recent nationwide antimicrobial resistance surveillance in Ghana revealed that, ciprofloxacin and ofloxacin resistance rates were greater than 50% [13]. Furthermore, a study at the Ghana Police Hospital revealed that *E.coli*, other *Coliform*s, and mixed *Coliform* spp. with *Candida* isolates were resistant to ciprofloxacin at rates of 38.5%, 54.3% and 15% to respectively [14]. The broad therapeutic indications of ciprofloxacin and the ease of availability, over the counter although a prescription drug, appear to underpin the increased pressure on its use, misuse, and microbial resistance in Ghana. On the other hand, the once daily dosing and favorable pharmacodymanic profile of the relatively new agent, levofloxacin, coupled with its broader antibacterial spectrum, safety, good tolerance and satisfactory clinical success, makes it an alternate quinolone for UTIs [15].

With widespread reports of fluoroquinolone resistance, it is prudent that the sensitivity pattern of prevailing uropathogens is periodically assessed. This would ensure that empirical treatment of UTIs with fluoroquinolones is based on evidence from local susceptibility and resistance data. Hence, this study sought to determine the antimicrobial susceptibility pattern of commonly isolated uropathogens to levofloxacin at the Ghana Police Hospital.

METHODS

Study population: This was a descriptive cross-sectional study, which involved screening of 519 urine samples of suspected UTI from both in- and outpatients who visited the Ghana Police Hospital from July 2014 to September 2014. The Ghana Police Hospital, although initially established to serve police personnel and their families, currently provides health services to the general public.

Sample collection and processing: Midstream urine samples from patients were collected into sterile urine containers, stored between 2^o – 4^oC in a refrigerator, and analyzed not later than 4 hours after collection at the Ghana Police Hospital Microbiology Laboratory. Culture of the urine was done with the aid of calibrated wire. A loop-full (0.01 mL) of each urine sample was inoculated onto a quarter-plate of Cysteine Lactose Electrolyte-Deficient [CLED] agar (Biotic Laboratories Ltd, U.K). The specimen was well streaked on the agar plate to allow discrete colonies, and incubated at 37^o C for 24 hours in Nodermann GMBH incubator (Germany). After incubation period, colonies were enumerated and those with significant growth identified. Significant microbial growth was defined as culture of a single microorganism at a concentration $\geq 1x10^5$ cfu/mL. Microbial colonies were identified using morphological features, standard biochemical and serological methods [16]. After identification, each colony, representing an isolate was emulsified in 2 mL sterile peptone water, and then transferred into sensitivity agar plates (Biotec laboratories, UK).

Susceptibility testing: The levofloxacin sensitivity disc used in this study was stored between $2^o - 8^oC$ in a refrigerator to maintain its sensitivity, till it was used for examination. Antimicrobial susceptibility testing of isolated microbes was done using the Kirby-Bauer disc diffusion method, against levofloxacin with a break point of 5 µg (Becton & Dickinson Company, USA)[Lot; 2291125]. Inhibition zone diameters pertaining to levofloxacin were measured using calipers and compared with standard interpretation charts [17], and scored as sensitive or resistant.

Data analysis: Data was checked for completeness, and descriptive statistics (percentages and frequencies) used to present findings of the study. The sensitivity of microorganisms was categorized as low (+), intermediate (++) and high (+++).

Ethical approval: Protocol for this study was approved by the Ghana Police Hospital Administration. Informed consent was obtained from all participants.

RESULTS

Of the 519 urine samples analyzed, 95 (18.3%) showed significant microbial growth. Majority of the samples with significant growth were obtained from females 68 (71.6%). The most predominant microbial

isolate was *Escherichia coli*, accounting for 54 (56.8%). *Coliforms spp* constituted 23 (24.2%), *Staphlococcus aureus* 9 (9.5%) and *Klebsiella* spp 3 (3.2%). The rest of the microbial isolates were *Pseudomonas spp, Proteus mirabilis,* mixed *Coliform* with *Candida*, and *Proteus* with *Candida* isolates. Frequencies and percentages of uropathogens isolated during the study period are presented in Table 1.

Table 1: Uropathogens isolated from samples within study period

Organisms	Numbers (n=95)	Percentages (%)
Coliforms	23	24.2
Staphylococcus aureus	9	9.5
Klebsiella spp.	3	3.1
Pseudomonas spp.	2	2.1
Proteus mirabilis	2	2.1
Candida spp. + Coliform	1	1.1
Candida + Proteus spp.	1	1.1

Overall microbial sensitivity to levofloxacin was 46 (48.4%). The susceptibility pattern of the top three microbial isolates in this study were; *E. coli* 20 (37%), *Coliforms spp* 15 (65.2%) and *S. aureus* 7 (77.8%). The results also showed that, *S. aureus, Coliforms, Klebsiella* and mixed *Coloform with Candida spp* exhibited more than 50 % sensitivity to levofloxacin. However, there was no overall clear sensitivity pattern exhibited by isolated uropathogens to levofloxacin as the uropathogens showed low, medium and high sensitivities in numbers (percentage); 19 (41.3%), 10 (21.7%) and 17 (37 %) respectively. Gross sensitivity to levofloxacin was exhibited by *Klebsiella spp,* and mixed *Candida spp* with *Coliform* isolates. On the contrary, gross resistance to levofloxacin was observed in *Proteus mirabilis,* and mixed *Candida and Proteus mirabilis* isolates. The detailed susceptibility and resistance pattern for all microbial isolates in this study is presented in Table 2.

Table 2: Microbial isolates susceptibility patterns to levofloxacin

Organisms	Pattern of sensitivity to levofloxacin (n)			Sensitivity n (%)	Resistance n (%)
	+	++	+++		
Escherichia coli	4	8	8	**20 (38 %)**	**34 (62 %)**
Coliform spp.	8	1	6	**15 (65.2 %)**	**8 (34.8 %)**
Staphylococcus aureus	5	-	2	**7 (77.8 %)**	**2 (22.2 %)**
Klebsiella spp.	1	1	1	**3 (100 %)**	-
Pseudomonas spp.	1	-	-	**1 (50 %)**	**1 (50 %)**
Proteus mirabilis	-	-	-	**-**	**2 (100 %)**
Candida spp. with Coliform	-	1	-	**1 (100 %)**	**-**
Candida with Proteus mirabilis	-	-	-	**-**	**1 (100 %)**
Total	19	10	17	**46 (48.4 %)**	**49 (51.6 %)**

DISCUSSION

The relevance of prevalence rates in UTI studies is to gain an insight of the proportion of people in a given population with laboratory diagnosed UTI. The prevalence rate of 18.3% obtained in this study was higher than 15.9% in a recent study done in Ghana [13], and the 3% obtained in a similar study in Nigeria [10]. On the contrary, the prevalence rate in this study was lower than 35.5% observed in a similar study among prison inmates in Rukuiba Military Cantonments, Nigeria [18]. The generally low prevalence of suspected UTI patients (< 20 %) observed in this study and previous studies done at the Ghana Police hospital implies that, clinicians should not be quick to treat suspected UTI empirically, unless clinical symptoms strongly lends support for empirical treatment. This would reduce pressure on use of fluoroquinolones and other antibiotics recommended for the management of UTI, and consequently reduce rate of emergence of antibiotic resistance. Prevalence of UTI is often

higher in females than males due to a myriad of factors; shortness of female urethra, poor hygiene and the antibacterial activity of prostatic fluid in males [19, 20]. In this study, prevalence of UTI was found to be higher in females than males, and corroborates findings observed in similar studies done at the Ghana Police Hospital [14, 21].

Common microbial organisms isolated from cultures obtained from patients with suspected UTIs in Ghana include *E. coli, Klebsiella,* and *Candida* [22, 23]. *E. coli* has been observed globally to be associated with 75-90% of uncomplicated UTIs, and 5-10% of UTIs are caused by *Staphylococcus saprophyticus*, and *Klebsiella, Proteus, Pseudomonas* and *Enterococcus spp* comprising a much smaller proportion [24, 25]. Findings from this aspect of the study affirmed observations from similar studies done in Ghana and other nations, as *E. coli, Coliform spp* and *Staphylococcus aureus* constituted a significant proportion of the total isolates (90.5%), and the rest; *Klebsiella spp, Pseudomonas spp, Proteus mirabilis*, mixed *Coliform* with *Candida*, and *Proteus* with *Candida* isolates constituted only 9.5%. Our study also confirmed the observation that, majority of UTI pathogens are Gram-negative bacteria. Among isolates, only *Staphylococcus aureus and Candida spp* were non-Gram-negative bacteria. Presence of mixed bacteria with *Candida spp* constituted a very small proportion of UTI cases at the hospital and was similar to findings from previous studies done at the Ghana Police Hospital [14, 21]. Hence, clinicians should consider treatment of fungal infection (specifically *Candida spp*) in recurrent UTIs when empirical treatment with conventional antibiotics fail to achieve desired therapeutic objective.

In vitro sensitivity assay of antimicrobials is a means of obtaining rapid information on the appropriate agents required for effective treatment of UTI [26, 27]. An overall resistance of 17% to levofloxacin has been reported in some emergency departments in United States of America [28]. The overall resistance of uropathogens to levofloxacin (51.6%) observed in this study was higher than one reported in USA [28]. However, overall resistance rate of uropathogens in this study was lower than the 60% reported in a similar study in Lucknow, India [29]. Findings of high resistance rate of uropathogens to levofloxacin observed in this study corroborates with findings from the nationwide surveillance of antimicrobial resistance in Ghana, which found resistance rate of uropathogens to second-generation fluoroquinolones to be greater than 50% [13].

Gram-negative bacteria are known for their diverse resistance mechanisms against the same antibiotic, single resistance mechanism against many antibiotics, and high efficiency in up-regulating or acquiring genes that code for mechanisms of antibiotic drug resistance in the presence of antibiotic selection pressure [30]. *E. coli* susceptibility to levofloxacin in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in 2009 from 14 hospitals in seven Asian countries ranged from as low as 15% in India to 83% in New Zealand [31]. Also, the overall susceptibility of *E. coli* to levofloxacin in that study was 51%, with findings from Singapore and India showing resistance rates as high as 61% and 85% respectively. Similar studies done in USA also showed increasing resistance of uropathogens to fluoroquinolones; with some hospitals reporting resistance rates of more than 25% among *E. coli* isolates [32].

Another study in USA, also reported an increase in levofloxacin resistance among *E. coli* isolates from 1-9% from 1998 to 2005 [33]. Findings from this study showed that, *E.coli* isolates showed very high resistance (62%) to levofloxacin similar to findings in Singapore, but lower than the 85 % resistance rate in India observed in the 2009 SMART study. Resistance of *E.coli* isolates in this study was also found to be higher than findings observed in studies done in USA, and another study that reported 24.4% in Nigeria [32, 34]. The high resistance to levofloxacin in this study could have been due to the breakpoint for levofloxacin used, 5 μg, unlike other studies that used ≥ 8 μg [8, 35]. Also the high resistance rate (50-90%) of uropathogens to second generation quinolone (ciprofloxacin) observed in the recent nationwide survey [13], coupled with the high selection pressure on ciprofloxacin in Ghana suggests that uropathogens may have acquired resistant genes against levofloxacin. The reason for this assertion is that, both ciprofloxacin and levofloxacin exert their antibacterial action by rapid inhibition of DNA gyrase and type IV topoisomerase [36]. With selection pressure on ciprofloxacin in Ghana, Gram-negative organisms like *E.coli,* known for their high efficiency in up-regulating or acquiring genes that code for mechanisms of antibiotic resistance are likely to develop resistance against levofloxacin.

On the contrary, *Coliforms spp* isolates, *Klebsiella spp*, and *Coliforms spp* with *Candida spp* mixed isolates in this study showed high susceptibility to levofloxacin 65.2%, 100% and 100%, respectively. Also, findings from a study in Nigeria with a larger sample size (n = 223) found similar susceptibility (95.1%) of uropathogens to levofloxacin [37].

Another study by Onoh *et al*. in Nigeria [10], showed *Klebsiella spp* having 100% susceptibility to levofloxacin as seen in this study. This suggests high efficacy of levofloxacin against *Klebsiella spp* implicated UTI.

Levofloxacin is known to exhibit greater antimicrobial activity against gram-positive organisms than ciprofloxacin [8]. In this study, *Staphylococcus aureus* and *Candida spp*. were the only non-Gram-negative organisms. In a study among patients attending University of Abuja Hospital in Nigeria, *Staphylococcus aureus* was found to be 67.7% sensitive to levofloxacin [34]. With *Staphylococcus aureus* showing 77.8% sensitivity to levofloxacin in this study, tends to agree with the assertion by Fu *et al.* [8]. that, levofloxacin is known to exhibit greater microbial activity against gram-positive organisms.

According to Martin *et al*. [38], although levofloxacin exhibits lower *in vitro* activity against *P. aeruginosa* than ciprofloxacin, levofloxacin is more effective in UTI treatment. A recent review on the clinical use of levofloxacin over a decade found that, it was the only marketed drug among the quinolones with sufficient activity against susceptible strains of *P. aeruginosa* [39]. Of the two isolates of *Pseudomonas spp* isolated in this study, one (50%) showed susceptibility to levofloxacin. This finding was similar one reported by Omigie *et al.* [37] where resistance to levofloxacin was found to be 54%. It was also observed in that study that, resistance of *P. aeruginosa* to quinolones increased by 14.2 % (35.3 to 49.8%) from 2001 to 2004. Hence, our finding also confirms the observation by Omigie *et al*. that, *Pseudomonas spp* although isolated in few numbers, are gradually becoming a public health concern because of their high resistance rates to quinolones [37]. However, in another study by Onoh *et al*.,[10] although percentage of *Pseudomonas spp.* was low (1.2%), there was 100% susceptibility to levofloxacin. It is worth noting that, this study by Onoh *et al*. [10] did not state the breakpoint of levofloxacin used, thus, further analysis can't be done. A study at the Ghana Police Hospital on ciprofloxacin susceptibility by isolated clinical uropathogens revealed that all three *Pseudomonas spp*. isolates were sensitive (100%) to ciprofloxacin [14], whilst this study found 50 % susceptibility to levofloxacin. Although the number of *Pseudomonas spp*. isolates were few in both studies, the lower susceptibility to levofloxacin observed appears to agree with observations from similar studies that, ciprofloxacin remains the most active quinolone against *P. aeruginosa* [6, 40].

Antibiotic sensitivity studies done among patients with UTI in Nigeria revealed that *Proteus spp.* susceptibility to levofloxacin was greater than 95% [10, 37]. On the contrary, our study showed 100% resistance. This high resistance could be attributed to the 5 μg levofloxacin break point used. Although the break points for levofloxacin used in other studies were not indicated [10, 37], we presumed the high susceptibility of *Proteus spp.* observed in those studies could be attributed to use of levofloxacin with breakpoint of 8 μg.

According to the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID), empirical treatment with fluoroquinolones should not be recommended in communities where resistance rate of uropathogens exceeds 10% [41]. With the recent findings of high resistance (greater than 50%) of clinical isolates to fluoroquinolones across the country [35], coupled with high resistance of *E. Coli* to levofloxacin in this study, we suggest that levofloxacin and ciprofloxacin should be used rationally for empirical treatment of UTIs in Ghana. Furthermore, high-dose treatment (750 mg) of levofloxacin once daily as suggested in other studies is recommended for treatment of mild-moderate UTIs.

CONCLUSION

Based on high resistance of uropathogens to levofloxacin especially among *E. coli* isolates, empirical treatment of UTIs with relatively new levofloxacin should be done judiciously. Additionally, the need for culture and antimicrobial sensitivity tests for suspected UTI patients before treatment cannot be overemphasized. We also recommend that, break points of fluoroquinolones used in similar studies should be clearly stated to enable comparison.

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