

# Double Blind Clinical Trial of Pefloxacin *versus* Ofloxacin in the Treatment of Acute Uncomplicated Gonococcal Urethritis in Men

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## Abstract

The objective of this study is to compare the effectiveness and safety of pefloxacin to ofloxacin in the treatment of gonococcal urethritis. Ninety-five male patients with uncomplicated gonococcal urethritis from the STD clinics at Ramathibodi Hospital, Mahidol University and Vachira V.D. Clinic, Department of Communicable Diseases Control, Ministry of Public Health were enrolled. They were randomly allocated to treatment regimens of either 400 mg pefloxacin or 400 mg ofloxacin as a single oral dose. Clinical, bacteriological and safety assessments were made at entry, and 3 or 7 days after treatment. *Neisseria gonorrhoeae* was eradicated in 95 percent (37/39), and 97 percent (31/32) of patients treated with pefloxacin and ofloxacin, respectively. Overall 24 percent (20 in 82) of the isolates produced penicillinase (PPNG isolates). The MIC range of both drugs was the same, between 0.03-2.0 mg/l. The MIC<sub>90</sub> of ofloxacin was 0.25 mg/l but it was 1 mg/l for pefloxacin. We concluded that 400 mg of pefloxacin was as effective as 400 mg of ofloxacin in the treatment of male gonococcal urethritis. (*J Infect Dis Antimicrob Agents* 1996;13:7-10.)

## INTRODUCTION

Sexually transmitted diseases (STD) remain a common health problem in most countries. Among these diseases, gonorrhoeae is the most prevalence (1). In Thailand the antibacterial treatment of choice for uncomplicated gonococcal urethritis in men is a single oral dose of quinolone, i.e., ofloxacin 400 mg or norfloxacin 800 mg. Pefloxacin, another quinolone, has a good *in vitro* activity against *N. gonorrhoeae* (2). Studies from Netherlands (3), and Singapore (4) also

showed that 800 mg of oral pefloxacin is safe and effective in the treatment of gonorrhoeae in male studies. Both showed that the MICs of the isolated *N. gonorrhoeae* was very low. No clinical study has been conducted on the efficacy of the lower dose of pefloxacin in this disease. The main purpose of this double blind randomised study is to compare the effectiveness and safety of pefloxacin with ofloxacin in the treatment of uncomplicated gonococcal urethritis. Both drugs were given in a single oral dose of 400 mg. Other objectives are to determine the minimal inhibitory concentrations of pefloxacin and

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ofloxacin of the gonococcal isolates and the prevalence of concomitant chlamydial infection in male patients with gonococcal urethritis.

## MATERIALS AND METHODS

### Patient selection and study design

The study was carried out at the outpatient clinics for sexually transmitted diseases of Ramathibodi Hospital, Department of Medicine, Mahidol University, and Vachira V.D. Clinic, Department of Communicable Diseases Control, Ministry of Public Health. During October 1993 to October 1994, male patients presented with urethral discharge were included in this study if the result of Gram stain from urethral smear showed Gram-negative intracellular diplococci, and they had not taken antibiotics within the previous 7 days. The exclusion criteria were; patients aged less than 16 years old, history of allergy to quinolones, or evidence of complicated gonococcal infections. There were 95 patients enrolled in this study. Only patients from whom *N. gonorrhoea* was isolated at first visit and who returned for a follow-up culture, 3 to 7 days after treatment, were included for the evaluation. At the first visit, specimens from the urethra were collected for the isolation and identification of *N. gonorrhoeae*, Gram stain and chlamydial antigen detection. At the follow-up visit, Gram stain and culture for *N. gonorrhoeae* were repeated in every patient. Chlamydial antigen detection was repeated only in patients who had positive chlamydia antigen at the first visit.

### Sample collection

Specimens were collected by inserting sterile wire loops at least 2 cm into the patients' urethra. First sample was streaked into the Thayer-Martin media Chocolate agar at our STD Clinics, and then transferred to the clinical microbiology laboratory in a candle jar where it was incubated at 35-37°C. The second sample collected in the same way was used for the Gram stain. The third sample for the detection of chlamydia antigen was collected with a cotton-tipped swab and put in to a transport tube (Chlamydiazyme kit).

### Treatment regimens

The patients were randomly allocated to receive either treatment A (pefloxacin 400 mg and placebo of ofloxacin) or treatment B (ofloxacin 400 mg and placebo of pefloxacin). Both the doctor and the patient did not

know which treatment was given.

### Isolation and identification of *Neisseria gonorrhoeae*

The Thayer Martin plates were observed for colonies suspected of *N. gonorrhoeae* daily for 2 days. After 24 hours of incubation, the colonies appeared grey to white, opaque, raised and glistening size 0.5 to 1 mm in diameter. The suspicious colony was Gram stained and tested for oxidase by placing a few drops of oxidase reagent (1% solution of tetramethyl-p-phenylenediamine dihydrochloride) on a piece of filter paper, pick up a portion of colony with a platinum inoculating loop and rubbed the growth on the filter paper, the positive test appeared dark purple colour. The colony that is Gram-negative diplococci and oxidase positive is presumptively identified as *N. gonorrhoeae*.

### Beta-lactamase test

The  $\beta$ -lactamase production were tested by inhibition method (5). In brief, *Staphylococcus aureus* ATCC 25923 which was very sensitive to penicillin was streaked on the entire surface of the Mueller Hinton agar plate. Penicillin disc of 10 units was placed at the centre of the plate. The tested organism was streaked from the penicillin disc to the edge of the plate. The plate was incubated at 35-37°C for 18 hours.  $\beta$ -lactamase enzyme produced by the organism will destroy penicillin enable *Staphylococcus aureus* ATCC 25923 to grow in the inhibition zone.

### Determination of minimal inhibitory concentration (MIC)

The MICs of pefloxacin and ofloxacin were determined by the agar dilution technique (6). The antimicrobial agents were prepared in solution at the initial concentration of 1,280 mg/l. Two fold dilution of the antimicrobial agents were made with sterile distilled water, one ml was added to 20 ml of chocolate agar and poured into sterile petridish. The final concentration of antibiotic started from 6.4 mg/l and the last concentration was 0.03 mg/l. The inoculums were prepared to match the turbidity of 0.5 MacFarland standard and 0.03 ml were inoculated on the chocolate agar by multipoint inoculator. The plates were incubated in CO<sub>2</sub> incubator at 35-37°C for 18-24 hours. The MIC of each strain was determined as the lowest concentration of antimicrobial which inhibit 99 percent of bacterial growth.

### Enzyme immunoassay for chlamydia antigen detection

Chlamydiazyme was performed according to the manufacturer's instruction. One milliliter of specimen

dilution buffer was added to each tube containing a specimen swab. The tubes were kept at room temperature for 10 min and then agitated on a vortex mixer for three cycles of 15 seconds, after which the swabs were expressed and discarded. The sample extract (0.2 ml) and controls (positive and negative specimens supplied in the kit) were placed in the wells of plastic plates and reacted in turn with a treated polystyrene bead (1 hr), rabbit antibody to Chlamydia (1 hr), and horseradish oxidase-conjugated antibody to rabbit IgG (1 hr) according to the manufacturer's instructions. After addition of freshly prepared peroxidase substrate (ortho-phenylenediamine-hydrogen peroxide), incubation for 30 min, and addition of 1N sulphuric acid, the absorbance at 492 nm was determined. A result was considered positive if the optical density exceeded the mean of the three negative controls plus 0.10.

**RESULTS**

**Results of Treatment**

Ninety-five patients were enrolled in this study, 48 in pefloxacin and 47 in ofloxacin group. Forty-four patients in pefloxacin and forty-one patients in ofloxacin group were cultured positive. Eight patients had negative culture, 3 in pefloxacin group and 5 in ofloxacin group. The results were missing in 2 patients, one in each treatment group. Fourteen patients were lost to follow-up without apparent reason, hence only 71 patients (39 patients in pefloxacin and 32 patients in ofloxacin group) returned for follow-up at the second visit. The result of treatment was considered as cure when the symptoms resolved after treatment, and *N. gonorrhoeae* could not be isolated after treatment. The result of the two treatment regimens was similar (p=0.4, Fisher's exact test). Thirty-seven (95%) patients treated with pefloxacin compared to 31 patients (97%) treated with ofloxacin were cured.

**Antimicrobial susceptibility**

$\beta$ -lactamase test were performed in 82 strains of *N. gonorrhoeae*. There were 20 strains (24%) that produced  $\beta$ -lactamase. MIC determination were done in 72 strains. The result of MIC determination is shown in Table 1. The MICs of both pefloxacin and ofloxacin ranged from 0.03 to 2 mg/l. The MIC<sub>90</sub> of pefloxacin was 1 but it was 0.25 mg/l for ofloxacin.

**Detection of chlamydia antigen**

Table 2 summarises the results of chlamydia antigen

**Table 1. Minimal inhibitory concentration of 72 strains of *Neisseria gonorrhoeae*.**

Antimicrobial agents	MIC (mg/l)	
	Range	MIC <sub>90</sub>
Pefloxacin	0.03-2.0	1.0
Ofloxacin	0.03-2.0	0.25

**Table 2. Results of chlamydia antigen detection in gonococcal urethritis patients.**

Treatment regimens	Chlamydia antigen test			
	Positive	Negative	Not done	Total
Pefloxacin (400 mg)	6	27	15	48
Ofloxacin (400 mg)	11	23	13	47
Total	17	50	28	95

detection at the first visit. There were positive in seventeen out of sixty-seven patients tested, six patients in pefloxacin group and eleven in ofloxacin group. Therefore, concomitant chlamydial infection in gonococcal urethritis patients was 25 percent in this study.

**DISCUSSION**

This study attempted to evaluate the efficacy of a single oral dose of 400 mg pefloxacin compared to ofloxacin in the treatment of uncomplicated male gonococcal urethritis. The cure rate was 95 and 97 percent in pefloxacin and ofloxacin group, respectively. Treatment failure occurred in 3 patients due to resistant strains. All resistant strains (MIC 0.5-2 mg/l) were in the pefloxacin group. Although, the MIC<sub>90</sub> of ofloxacin was lower than that of pefloxacin, there was no statistical significant difference in the cure rate of both regimens. The cure rate of pefloxacin in our study was lower than that of Tio et al (3) (100% cured) and Cheong et al (4)

(98.5% cured). In their studies, the MIC<sub>90</sub> of *N. gonorrhoeae* to pefloxacin was 0.03 and 0.015 mg/l, respectively. These suggested that the *N. gonorrhoeae* strains are more resistant in our study. Furthermore there are reports of *N. gonorrhoeae* which decreased susceptibility to fluoroquinolones. These strains are also found in Thailand (7), the United State (8) and Australia (9). Both drugs were well tolerated. With all these informations, we suggest that 800 mg of pefloxacin should be appropriate for the treatment of uncomplicated gonococcal urethritis in men.

The prevalence of concurrent chlamydial infection in patients with gonococcal urethritis was 25 percent in this study. This is consistent with our finding in 1989 (10). The prevalence of chlamydial infection in male patients with gonococcal urethritis in our previous study was 27 percent. The number of cases was not enough to evaluate the effect of each treatment regimen on the clearance of chlamydia antigen. Due to high prevalence of chlamydial infection, we would recommend a course of anti-chlamydial antibiotic after treatment of gonococcal urethritis.

In summary, our study indicated that single dose of pefloxacin 400 mg was as effective as ofloxacin 400 mg in the treatment of male with uncomplicated gonococcal urethritis. However, we recommend that 800 mg of pefloxacin should be used since the MIC<sub>90</sub> of *N. gonorrhoeae* for pefloxacin showed more resistant than the previous reports.

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