

# Perfloxacin and ciprofloxacin in the treatment of uncomplicated gonococcal urethritis in males

L L Cheong, R K W Chan, M Nadarajah

## Abstract

**Objective**—To study the effectiveness of single-dose perfloxacin and ciprofloxacin in the treatment of uncomplicated gonococcal urethritis in males.

**Setting**—Department of STD Control, Kelantan Road, Singapore.

**Method**—160 male patients with uncomplicated gonococcal urethritis were assigned alternately to receive single oral doses of either perfloxacin 800 mg or ciprofloxacin 250 mg.

**Results**—Of the perfloxacin group 98.5% (65/66 patients) and of the ciprofloxacin group 98.6% (74/75 patients) were cured of gonorrhoea. The rates of post-gonococcal urethritis were 64.3% and 67.3% in the perfloxacin and ciprofloxacin groups, respectively. Both drugs were well tolerated and reported side-effects were minor and transient. There was a high incidence of penicillinase-producing gonococci (32.3%) and tetracycline resistant isolates with MIC  $\geq$  2 mg/l (99.3%). High level tetracycline resistance (MIC  $\geq$  16 mg/l) was found in 7.4% of isolates.

**Conclusion**—The drugs in the dosages studied may be recommended for first-line treatment of uncomplicated gonococcal urethritis in males in Singapore. However, the emergence of bacterial resistance to the fluoroquinolones in the literature calls for vigilance in the monitoring of antimicrobial susceptibility.

## Introduction

The increasing incidence of penicillinase-producing *Neisseria gonorrhoeae* has spurred efforts the world over in search of alternatives to penicillin for treatment. The fluoroquinolones have been hailed as attractive drugs for this purpose as they can be administered orally, are highly bactericidal with minimal side-effects and possess a wide antibacterial spectrum.<sup>1</sup> Several clinical studies have documented high cure rates of gonococcal infection with the use of fluoroquinolone antibiotics.<sup>2-6</sup> In view of such encouraging findings, we felt it important to investigate the effectiveness of two readily available fluoroquinolones, perfloxacin and ciprofloxacin, in the eradication of *N. gonorrhoeae* infection in the local population.

## Materials and method

The study population comprised males, aged 18 years and above, with uncomplicated gonococcal urethritis attending the Sexually Trans-

mitted Diseases Clinic at the Kelantan Road Polyclinic between February and November 1990. Exclusion criteria included antibiotic therapy within the past seven days, known allergy to quinolones and renal, hepatic or haematological disorders. Verbal consent for participation in the study was obtained from all patients.

Urethral specimens were collected with sterile platinum loops and smears made for Gram-staining. A presumptive diagnosis of gonococcal urethritis was made when intracellular Gram-negative diplococci were found in the urethral smear. The diagnosis was confirmed on isolation of *N. gonorrhoeae* on culture. These patients were then assigned alternately to receive either perfloxacin 800 mg or ciprofloxacin 250 mg, in single oral doses. They were scheduled to return for test of cure on the 4th day and for screening for post-gonococcal urethritis on the 14th day. They were also advised to refrain from sexual intercourse and to report any adverse effects after taking the medication.

A negative culture for *N. gonorrhoeae* of a urethral specimen taken on the 4th post-treatment day would indicate cure while a positive culture signified treatment failure. Post-gonococcal urethritis was defined as the presence of five or more pus cells per high power field in a Gram-stained urethral smear taken on the 14th post-treatment day.

## Laboratory methods

Urethral specimens were collected with sterile platinum loops and plated immediately onto modified Thayer-Martin culture media. The plates were incubated at 36°C in a CO<sub>2</sub>-enriched environment for 24 to 48 hours. Identification was by colonial appearance, oxidase test and Gram-stained microscopic appearance. Penicillinase production was tested for by the paper acidometric method described by Sng *et al.*<sup>7</sup> Confirmed isolates were tested for susceptibility to perfloxacin or ciprofloxacin, penicillin, ampicillin, tetracycline, kanamycin and spectinomycin by the agar dilution method.<sup>8</sup> The susceptibilities were expressed as minimal inhibitory concentrations (MICs) to the various drugs.

## Results

### Clinical and laboratory results

A hundred and sixty men were enrolled in the study. Half the population was treated with perfloxacin and the other half with ciprofloxacin. Two patients treated with perfloxacin

National Skin Centre,  
Singapore  
L L Cheong  
R K W Chan

Singapore General  
Hospital  
M Nadarajah

Address for correspondence:  
Dr Cheong Lai Leng,  
National Skin Centre,  
1 Mandalay Rd, Singapore  
1130.

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Table 1 Clinical and laboratory data of the study population

	Treatment			
	Perfloxacin		Ciprofloxacin	
No. of Patients (n)	66		75	
Mean Age (years)	24.5	(R: 18-58)	23.3	(R: 17-52)
Race:				
Chinese (%)	40	(60.6)	43	(57.3)
Malay (%)	12	(18.2)	19	(25.3)
Indian (%)	11	(16.7)	11	(14.7)
Others (%)	3	(4.5)	2	(2.7)
No. of patient with Reactive VDRL	3		3	
No. of patient with PPNG infection	22		24	
No. of patient with Non-PPNG infection	44		51	

Table 2 Overall cure rates with perfloxacin and ciprofloxacin

	<i>N. gonorrhoeae</i>		
	PPNG n (%)	Non-PPNG n (%)	Overall cure rate (%)
Cured with perfloxacin	22/22 (100)	43/44 (97.7)	65/66 (98.5)
Cured with ciprofloxacin	23/24 (95.8)	51/51 (100)	73/74 (98.6)

were excluded as the urethral cultures were negative for *N. gonorrhoeae*. An additional 12 patients in the perfloxacin group and five in the ciprofloxacin group were excluded from further analysis as they defaulted both post-treatment reviews. Sixty-six in the perfloxacin treatment group and 75 in the ciprofloxacin group were assessable for the study. The clinical and laboratory features of these patients are presented in table 1.

One treatment failure occurred in each treatment group. Pre-treatment urethral cultures isolated non-PPNG in the patient given perfloxacin and PPNG in the other. The overall cure rates with perfloxacin and ciprofloxacin were 98.5% and 98.6% respectively (table 2).

At the second follow-up visit, 38 of 66 patients (57.6%) treated with perfloxacin and 37 of 75 patients (49.3%) given ciprofloxacin had normal urethral smears on microscopy. However, some of these patients had received antibiotics such as tetracycline and erythromycin at the first follow up visit. After the exclusion of those patients who had received a second course of antibiotics, the rate of post-gonococcal urethritis was found to be 64.3% (27 of 42) in the perfloxacin group and 67.3% (37 of 55) in the ciprofloxacin group. The final evaluation is presented in table 3.

#### Drug Tolerance

The drugs were generally well tolerated with adverse effects occurring in a small minority. One patient who received perfloxacin complained of swelling of the lower eyelids lasting 3 hours after ingestion of the drug. Adverse

Table 3 Outcome of patients treated with perfloxacin or ciprofloxacin

Final Evaluation	Perfloxacin n (%)	Ciprofloxacin n (%)
Cured	38 (48.5)	37 (49.3)
Cured with PGU	27 (40.9)	36 (48.0)
Defaulted	13 (19.7)	5 (6.7)
Reinfected	0 (0)	1 (1.3)
Failed treatment	1 (1.5)	1 (1.3)
Total no. of patients	66 (100)	75 (100)

Table 4 Antimicrobial susceptibility of 148 isolates of *N. gonorrhoeae* to perfloxacin or ciprofloxacin

	MIC (mg/l)		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
Perfloxacin	0.0005 - > 0.125	0.0008	0.015
Ciprofloxacin	0.002 - > 0.125	0.015	0.03

Table 5 Antimicrobial susceptibility of the 2 isolates of *N. gonorrhoeae* that did not respond to treatment with perfloxacin or ciprofloxacin

	MIC (mg/l) of isolates of <i>N. gonorrhoeae</i> that failed treatment with	
	Perfloxacin	Ciprofloxacin
Perfloxacin	> 0.125	—
Ciprofloxacin	—	> 0.125
Penicillin	0.25	> 32
Ampicillin	0.25	> 8
Tetracycline	8	4
Kanamycin	8	8
Streptomycin	16	8

effects attributed to ciprofloxacin in six patients were dryness of the mouth, urticaria, thirst, hunger, genital itch in the absence of a rash and an increase in the frequency of asthmatic attacks in the week following ingestion of the drug.

#### Antimicrobial susceptibility of *N. gonorrhoeae*

One hundred and forty-six isolates of *N. gonorrhoeae* were tested for beta-lactamase production and susceptibilities to either perfloxacin or ciprofloxacin, and, penicillin, ampicillin, tetracycline, kanamycin and spectinomycin.

The MICs of perfloxacin and ciprofloxacin for 50% and 90% of the isolates are presented in table 4. The antibiograms for the two isolates resulting in infection not eradicated with the test medication are shown in table 5.

Forty-seven (32.2%) of the isolates were penicillinase producing. Penicillin resistance (MIC  $\geq$  1 mg/l) was seen in 89 of 146 (61%) isolates, 42 (47%) of which were non-PPNG.

Only a single isolate showed susceptibility to tetracycline at 0.5 mg/l. The rest (99.32%) were resistant to tetracycline at  $\geq$  2 mg/l. High level tetracycline resistance (MIC  $\geq$  16 mg/l) was present in 11 of 146 (7.4%) isolates. Thirty-two isolates of non-PPNG (21.9% of 146) were resistant to penicillin and tetracycline at  $\geq$  2 mg/l, indicating chromosomally mediated resistance (CMRNG).

Kanamycin resistance (MIC  $\geq$  32 mg/l) was seen in 20 of 146 (13.7%) isolates. No in-vitro resistance to spectinomycin (MIC  $\geq$  128 mg/l) was detected.

#### Discussion

The successful eradication of gonococcal infections with the fluoroquinolones has been well documented in the literature. The majority of the reports were on the use of single-dose ciprofloxacin therapy which achieved cure rates of up of 100%.<sup>9</sup> Other fluoroquinolones used with somewhat lower efficacy include norfloxacin, ofloxacin and enoxacin. The cure

rates of 98.5% and 98.6% with pefloxacin and ciprofloxacin in our study are comparable to those of the above reports. As such, the recommendation that either of these drugs be used as first-line therapy for uncomplicated gonococcal urethritis in males appear to be amply justified. The oral route of administration offers an added advantage over the use of drugs such as ceftriaxone and spectinomycin which necessitate parenteral administration.

The high rates of post-gonococcal urethritis (64.3% and 67.3% for the pefloxacin and ciprofloxacin groups respectively) in our study provide some cause for concern. A previous local study<sup>10</sup> had documented a rate of 48.8% in men after treatment of gonorrhoea with spectinomycin. In view of these findings, we would recommend the institution of routine treatment for post-gonococcal urethritis at first presentation for gonococcal urethritis, a practice which has not gained widespread acceptance in this part of the world.

In a review of data gathered from studies on penicillin susceptibility of *N. gonorrhoeae*, countries in South East Asia have been found to have the highest percentage of strains with reduced susceptibility.<sup>11</sup> The percentage of PPNG in the region has been reported to be in the range of 17.8 to 44.4%.<sup>10 12 13</sup> We found 32.6% of PPNG among our isolates. Although chromosomal analysis was not performed, there was evidence of chromosome mediated resistance (CMRNG) in 21.9% of the isolates. The inference was based on the finding of MICs of penicillin and tetracycline of  $\geq 2.0$  mg/l in strains without plasmid mediated resistance.<sup>14</sup>

The gonococci isolated in the region are also relatively resistant to other common antibiotics. In 1981, Brown *et al*<sup>12</sup> found tetracycline resistance at MIC  $\geq 2.0$  mg/l in 70.1% of gonococcal isolates in Bangkok. In our more recent study, we were able to document the same level of in-vitro tetracycline resistance in 99.3% of the isolates. In addition, 7.4% demonstrated high level tetracycline resistance (MIC  $\geq 16$  mg/l) which is most probably plasmid mediated (TRNG). Although tetracyclines have long ceased to be used in the treatment of gonorrhoea in this region, it has been postulated that their use in chlamydial infections and pelvic inflammatory disease probably assist the establishment of TRNG.<sup>15</sup>

The disturbing spectre of fluoroquinolone resistance in gonococci has done much to dampen the initial enthusiasm in the use of these drugs. Turner *et al* reported an isolate of penicillinase-negative chromosomally mediated resistant strain of *N. gonorrhoeae* (CMRNG) with an MIC of 0.1 mg/l for ciprofloxacin.<sup>16</sup> The strain was isolated from a man on his return to the UK from Thailand.

Later reports of reduced susceptibility of *N. gonorrhoeae* to ciprofloxacin found MICs of up to 0.5 mg/l.<sup>17</sup> Ciprofloxacin-resistant strains of gonococci with an MIC of 1.0 mg/l have apparently been isolated in the United States.<sup>18</sup> It has been shown that strains resistant to one fluoroquinolone have increased resistance to other fluoroquinolones as well.<sup>19</sup> Given the ease of travel to and from Singapore and her location within a region reputed to have high gonococcal antimicrobial resistance, the fluoroquinolones may well be doomed to outlive their usefulness as anti-gonococcal agents even before their widespread local use for this purpose.

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