Single dose oral norfloxacin or intramuscular spectinomycin to treat gonorrhoea (PPNG and non-PPNG infections): analysis of efficacy and patient preference

K PANIKABUTRA,* C T LEE,† B HO,‡ P BAMBERG§

From the *VD Control Division, Bangrak Hospital, Bangkok, Thailand, the †STD Clinic, Middle Road Hospital, Singapore, the ‡Department of Microbiology, National University of Singapore, and the §Department of Clinical Research, Astra Pharmaceuticals International, Kings Langley, England

SUMMARY Norfloxacin, a new oral quinolone, was compared with intramuscular spectinomycin for treating culture proved gonorrhoea (caused by penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG) and non-PPNG strains.

A total of 547 infected men and women were randomly allocated to treatment with either single dose norfloxacin (800 mg by mouth) or spectinomycin (2 g intramuscularly). Patient preference for tablets or injections was noted at this visit. Patients returned four to eight days later for assessment of efficacy, safety, and preference. Of the 482 patients who attended follow up, all those treated with norfloxacin (94 infected with PPNG strains, 145 with non-PPNG strains) and all 82 infected with PPNG strains and treated with spectinomycin were cured. Of 161 infected with non-PPNG strains and treated with spectinomycin, 159 (99%) were cured.

Side effects (headache, nausea, and sleepiness) occurred in three patients receiving norfloxacin and in 17 (16 pain at injection site, 1 giddiness) receiving spectinomycin. Most patients preferred tablets to injection both on day 1 (313 v 200) and at follow up (373 v 104).

This study showed that norfloxacin was a highly effective alternative to spectinomycin, produced fewer side effects, and was the preferred mode of administration.

Infections caused by *Neisseria gonorrhoeae* remain a major health problem in many parts of the world including South East Asia, where penicillinase producing *N gonorrhoeae* (PPNG) strains cause up to 40% of gonococcal infections.¹ These infections are resistant not only to penicillin but also to various other antibiotics. The current standard treatment for PPNG infections is intramuscular spectinomycin, although there have been several reports of bacterial resistance to this treatment.²⁻⁵ A recent study conducted in Korea showed a failure rate of 8.2% in 97 American servicemen treated with spectinomycin, and the authors urged caution in the widescale use of the drug.⁶ The third generation cephalosporins provide alternative effective parenteral treatment. As with spectinomycin,

however, they are expensive and thus often beyond the means of those with low incomes, who are at greatest risk. Parenteral treatment is also less convenient to administer than oral medication and is generally less acceptable to patients. Fluorinated quinolone derivatives, such as ciprofloxacin and norfloxacin, have been developed and found to be highly effective against gonococcal infections. They produce their effect by inhibiting bacterial gyrase⁷ and thus disturbing the replication of DNA.⁸

As gonorrhoea is a highly transmissible disease, its quick and efficient eradication from patients is important. To that end, dose response studies with quinolones have focused on the efficacy of single dose administration. Ciprofloxacin is effective in a single dose for treating infections with non-PPNG strains,⁹ whereas single dose enoxacin can cure infections with both non-PPNG and PPNG strains in a population with a low incidence of PPNG.¹⁰ Norfloxacin in single dose has been shown to cure non-PPNG and PPNG

Address for reprints: Dr P Bamberg, Department of Clinical Research, Astra Pharmaceuticals International, Home Park Estate, Kings Langley, Hertfordshire, England

Accepted for publication 17 November 1987

infections with similar efficacy in a population with a high incidence of PPNG strains.¹¹ As yet, however, no single large controlled study has been performed to compare quinolones with standard intramuscular spectinomycin treatment in a population with a high prevalence of PPNG infections.

The conduct of clinical trials of treatment for gonorrhoea is notoriously fraught with difficulties, such as the pressure in promiscuous patients (particularly prostitutes) to continue their sexual practices during treatment, despite medical advice to the contrary. Thus the true efficacy of drugs may be obscured by patients returning to the clinic apparently not cured because they have been reinfected during the follow up period. In addition, many comparative studies have been conducted with small numbers of patients, which make it impossible to validate statistically the relative cure rates obtained. The present study was set up, with these pitfalls in mind, to establish the efficacy and safety of single dose oral norfloxacin compared with standard intramuscular spectinomycin and to ascertain patient preference for one or other mode of administration. A suitably large number of men and women was included from a population with a high prevalence of PPNG infections. An interesting feature of the study was the characterisation of bacterial strains both before and after treatment that had apparently failed. By means of microbiological and biochemical tests, as well as electrophoretic identification of plasmid patterns, it was possible to assess whether or not strains obtained before and after treatment were identical. Although it is impossible to exclude the possibility of reinfection by the same partner when strains are identical, it is possible to conclude that reinfection has occurred if strains are different, and thus to eliminate misleading "treatment failures" from the efficacy analysis.

Patients and methods

The study was conducted in two centres—Bangrak Hospital, Bangkok, where both men and women were recruited, and Middle Road Hospital, Singapore, where only men were recruited.

We studied men and non-pregnant women aged 16 to 58 who had culture proved symptomatic or symptomless uncomplicated gonorrhoea of the urethra, cervix, or rectum. We excluded from the study patients with complicated gonococcal infections, known hypersensitivity to quinolones, known impaired kidney function (creatinine clearance less than 30 ml/min), known decreased liver function, blood disorders or coexistent syphilis, or those who had received concomitant treatment with any other antibacterial drugs, coumarin derivatives, phenytoin, or methotrexate. The trial was conducted in accordance with the

Declaration of Helsinki and was approved by the respective hospital ethics committees.

The study was of open parallel group design, with patients randomly allocated (in blocks of four) to receive either norfloxacin 800 mg (Astra) in a single oral dose or spectinomycin 2 g (Upjohn) given intramuscularly. From earlier studies, it seemed reasonable to assume that the true success rate for norfloxacin 800 mg was at least 95%. To show a possible equivalence between treatments within a range of 5–6%, about 250 patients were required in each group. This number was calculated according to Blackwelder, where $\alpha = 5\%$ (two-tailed) and $\beta = 80\%$.¹²

Each patient was studied for four to eight days. Patients received treatment on day 1 and were requested to return for follow up examination not earlier than day 4 and not later than day 8. All patients were advised to refrain from sexual contact during that period. At each visit patients were assessed for symptoms and signs of the disease, and Gram stained smears were prepared for microscopy. Samples were also plated directly on to selective agar (see section on microbiological assessment).

On day 1 patients were informed about the trial, and verbal consent to participate was obtained. They were also questioned about their preferences for oral or injected medication and their reasons for that preference. On day 4 to 8 they were questioned about their sexual activity during the study. If they yielded gonococcal isolates after treatment, these were compared with those obtained before treatment to assess whether or not reinfection had taken place. The safety of norfloxacin or spectinomycin regarding the production of adverse drug events was evaluated by non-specific questioning, and all adverse events described were recorded in the case record forms. Patients were also questioned again about their preference for either route of drug administration, after being informed that both treatments were equally efficacious.

MICROBIOLOGICAL ASSESSMENT

Discharge from the urethras (of men and women), cervixes or rectums, (of women only) was Gram stained and examined microscopically for intracellular diplococci in polymorphonuclear leucocytes. Patients were recruited to the study on the basis of a positive Gram stained smear, but they were only included in the efficacy evaluation if the culture for *N gonorrhoeae* was positive. Samples were also obtained for culture on selective agar (Thayer Martin agar or GC (gonococcal) agar supplemented with 1% haemoglobin, 1% Vitox, and VCN (vancomycin, colistin, and nystatin)).

The characteristics of the *N gonorrhoeae* strains obtained on culture were studied using minimum

Table 1 Demographic data of 482 patients included in efficacy analysis because they fulfilled the protocol

	No	Mean age (range)	No	Mean (SD) weight (kg)
Singapore men	189*	25 (15–58)	182*	60.1 (9.43)
Bangkok men	97	25 (16–44)	97	57.4 (7.09)
Bangkok women	195	25 (16–48)	194*	49.4 (7.09)
Total	481*	25 (15–58)	473*	55.2 (9.42)

*Age of one Singapore man and weights of eight Singapore men and one Bangkok woman not known.

inhibitory concentrations (MICs) of antibiotics,¹³ plasmid profiles,¹⁴ auxotyping,¹⁵ and, if necessary, further (carbohydrate (CH) and non-enteric (NE)) biochemical tests (API 50 CH and API 20 NE microtest kits). Thus culture positive isolates obtained before and after treatment could be compared to establish whether the treatment had failed or reinfection had occurred as a result of sexual contact during the follow up period. Only patients harbouring different bacterial strains before and after treatment were classed as being reinfected, although those yielding the same strain could have been reinfected by the same partner. To establish whether reinfection had occurred before follow up, isolates obtained before and after treatment had to satisfy one or more of the following criteria: different auxotypes; different plasmid pattern (that is, plasmids with different molecular weights) and MICs of two or more antibiotics of different classes different by at least two dilution steps; MICs of two or more antibiotics of different classes different by at least three dilution steps; or different plasmid pattern (assessed electrophoretically), different MICs, and biochemical profiles of different biochemical pathways.

All bacterial strains were investigated for their

penicillinase producing properties using the nitrocefin method in Bangkok¹⁶ and the iodometric method in Singapore.¹⁷ Isolates were subsequently classified as containing PPNG or non-PPNG strains according to their penicillinase producing properties.

STATISTICAL ANALYSIS

The two treatments were compared regarding microbiological efficacy and side effects. Efficacy was also compared for PPNG and non-PPNG strains. The two tailed binomial test for proportions was used to compare cure rates and adverse events, and the χ^2 test was used to assess changes in treatment preferences.

Results

PATIENTS INCLUDED IN ANALYSIS

A total of 547 patients from both centres were entered into the study—that is, they received medication on the assumption that they were culture positive. Twenty two were subsequently found to be culture negative at day 1. Of the 525 culture positive patients, 516 were evaluable for safety, 498 for efficacy on an “intention to treat” basis (that is, they were culture positive and returned for follow up), and 482 for efficacy on the basis of fulfilling the protocol. The patients included in the per protocol analysis were 287 (60%) men and 195 (40%) women (mean age 25, mean weight 55.2 kg (table 1).

PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Of the 547 patients who entered the study, 49 could not be assessed for efficacy on an “intention to treat basis” because 27 failed to return for follow up, 21 were culture negative on entry, and one had a contaminated culture (table 2). A further 16 patients did not fulfil protocol requirements and were thus eliminated from

Table 2 Reasons for excluding 65 patients from efficacy evaluation and outcome of treatment

Reason	Outcome of treatment	Bangkok		Singapore		Total
		Norfloxacin	Spectinomycin	Norfloxacin	Spectinomycin	
Lost to follow up	n/a	2	6*	9	10	27
Initial culture negative	n/a	9	3	6	3	21
Contaminated culture	n/a				1	1
Late follow up	Cured	1		3	3	7
	Failed			1		1
Early follow up	Cured				1	1
Reinfected (interview)	Cured		3			3
	Failed		2†			2
Reinfected (laboratory report)	Failed	1‡				1
Protocol violation (concurrent syphilis)	Cured		1			1
Total/drug		13	15	19	18	65

n/a = Not assessed.

*Includes one patient who was also culture negative on day 1.

†Plasmids same, minimum inhibitory concentration (MIC) different, auxotype different (before and after treatment).

‡Plasmids different, MIC different, auxotype same (before and after treatment).

Table 3 Analysis of cure in 547 patients on basis of intention to treat* or fulfilment of all protocol requirements

	No cured/No treated	
	Intention to treat*	Protocol fulfilment
Norflloxacin	243/245	239/239
Spectinomycin	249/253	241/243
Total analysable	498	482
Non-analysable (see table 2)	49	65
Total treated	547	547

*Culture positive patients who attended follow up.

the per protocol analysis (in addition to the 49 non-assessable patients). The outcome of treatment for the 65 patients excluded is summarised for interest in table 2.

EFFICACY ANALYSIS

Results of the two efficacy analyses are presented in table 3. There were only six treatment failures in the whole study (two received norflloxacin, four spectinomycin), and they were all included in the "intention to treat" analysis (table 3). Only two treatment failures were eligible for inclusion in the per protocol analysis, however, as their isolates from before and after treatment were found to be identical and there was no evidence of reinfection. Four treatment failures were excluded from the protocol analysis, three on the basis of reinfection (two with different strains before and after treatment and having had sexual contact, and one with laboratory assessed reinfection) and one

because of late follow up on day 9 (table 4). This last patient received norflloxacin and, as strains obtained before and after treatment seemed to be identical, treatment had possibly failed in this case.

Of the 482 patients included in the per protocol analysis, 100% (239/239) were cured with norflloxacin and 99.2% (241/243) with spectinomycin (table 3), which indicated no appreciable difference between the drugs. Similarly, when cure rates were divided by gender or penicillinase producing properties, there were no significant differences between the two drugs (table 5). No treatment failures occurred, however, after treatment with norflloxacin.

RECTAL INFECTIONS

Of the 220 Bangkok women sampled rectally at day 1, 98 were culture positive, six of whom were excluded from efficacy analysis. All the remaining patients (43 treated with spectinomycin, 49 with norflloxacin) had negative rectal cultures at follow up. Of the six patients who were excluded, two were lost to follow up, one had concurrent syphilis, and three had had sexual contact before follow up (ascertained at interview).

SIGNS OF GONORRHOEA

On entry to the study, all patients were examined for purulent or mucopurulent discharge from the urethra (men and women), cervix, and rectum (women only). Purulent discharge was present in 286/287 (99.7%) men and 149/195 (76.4%) women on entry to the study. By the end of the study, it had disappeared in 282/286 (98.6%) men and 139/149 (93.3%) women.

Table 4 Microbiological tests on gonococcal isolates from six treatment failures

Drug taken	Time of obtaining isolate related to treatment	Auxo-type*	MICs (mg/l) of antibiotics:†						No of plasmids (weight in megadaltons)	Conclusion	Included in/ Excluded from efficacy analysis
			B	A	S	K	R	N			
N	Before	NR	4	4	32	32	0.125	0.06	1 (2.6)	}	Different strain (plasmid content)
	After	NR	2	0.25	16	32	0.06	0.016	2 (2.6, 30.4)		
N	Before	P ⁻	2	0.5	16	32	0.125	0.6	2 (2.6, 30.4)	}	Same strain
	After	P ⁻	2	1	16	32	0.125	0.6	2 (2.6, 30.4)		
S	Before	NR	2	0.25	16	16	0.06	0.016	2 (2.6, 30.4)	}	Different strain (auxotype)
	After	P ⁻	8	2	32	32	0.125	0.032	2 (2.6, 30.4)		
S	Before	O ⁻	2	1	32	32	0.06	0.016	1 (2.6)	}	Different strain (auxotype)
	After	NR	4	4	32	32	0.125	0.06	1 (2.6)		
S	Before	NR	1	0.25	32	16	0.06	0.06	0	}	Same strain
	After	NR	1	0.25	32	16	0.06	0.06	0		
S	Before	NR	2	0.25	16	32	0.125	0.016	2 (2.6, 30.4)	}	Same strain
	After	NR	2	0.25	16	32	0.125	0.032	2 (2.6, 28.8)		

*NR = non requiring, P⁻ = proline requiring, O⁻ = ornithine requiring auxotypes.

†MIC = minimum inhibitory concentrations of benzylpenicillin (B), ampicillin (A), spectinomycin (S), kanamycin (K), rosoxacin (R), and norflloxacin (N).

Table 5 Cure in 482 patients analysed by gender, penicillinase producing properties, or geographical location

Patient sub-groups	No cured/No treated with:	
	Norfloxacin (239/239)	Spectinomycin (241/243)
Men	142/142	144/145
Women	97/97	97/98
PPNG Strain	94/94	82/82
Non-PPNG strains	145/145	159/161
Bangkok patients	147/147	144/145
Singapore patients	92/92	97/98

SIDE EFFECTS

Of the 547 patients recruited to the study, 520 returned for follow up, of whom 516 were evaluable from a safety point of view. They were 303 men and 213 women, who were questioned about the occurrence of adverse drug events (side effects) after treatment. Of 20 events recorded in 20 patients, 13 were judged as mild and seven as moderate. The side effects reported were pain at injection site (15 patients), numbness after injection (1), and giddiness (1) after spectinomycin treatment as opposed to sleepiness (1), nausea (1), and headache (1) after norfloxacin treatment. If pain and numbness at the site of injection are regarded as being simply signs of local intolerance, there was no significant difference between treatments concerning the incidence of adverse events.

PREFERENCE FOR METHOD OF TREATMENT

Most (220/227) patients recruited in Singapore and all 320 patients recruited in Bangkok completed the preference survey on day 1. At follow up, on day 4 to 8, the survey was carried out again in 195 of the Singapore patients and 312 of the Bangkok patients. Thus the numbers completing the survey before and after treatment were closely similar and could be compared statistically. Table 6 gives a summary of treatment preferences at each visit for individual and combined centres. The results indicate a clear preference for tablets at day 1, with that preference increasing further by day 4 to 8. The main reason for patients preferring tablets was that their administration was painless, whereas patients' preference for injection was mainly connected with their previous experience that injection was more effective. By day 4 to 8, however, preference for injection had declined 48%. The apparent change in preference towards tablets by day 4 to 8 was contributed largely by the patients from Bangkok, where all changes recorded were towards tablets. In Singapore, however, changes in preference occurred in both directions and when these directions of change were compared statistically using a χ^2 test, preferences shifted significantly

($p < 0.001$) towards the treatment type received. Presumably this trend occurred as a result of the high efficacy obtained with both treatments.

Discussion

This study represents the largest comparison of oral norfloxacin with intramuscular spectinomycin, the generally accepted standard treatment for penicillin resistant gonorrhoea. It is also the first study known to the authors that has attempted to differentiate objectively between true treatment failures and those caused by reinfection from a sexual contact before follow up. When studying infections associated with promiscuous behaviour, it is important to establish this point.

The results of this study indicate a very low failure rate for both drugs, and it is noteworthy that only two out of the six treatment failures were valid for the per protocol analysis. Exclusion of three treatment failures on the basis of reinfection was based on different bacterial strains obtained before and after treatment, as well as sexual contact in two cases and the appearance of a strain with an extra plasmid and requiring a lower MIC of norfloxacin in the third case.

Thus both spectinomycin and norfloxacin were highly effective in eradicating PPNG and non-PPNG infections at all anatomical sites and could not be differentiated on an efficacy basis. Both preparations appeared to be safe, as very few adverse events were reported during the study. Injections of spectinomycin did, however, produce more patient discomfort.

The results of the preference analysis indicated an overall patient preference for tablets on entry to the study, which increased by the end of the study. The main reason for preferring tablets was that their administration was painless, and this is documented by the relatively high incidence of pain at the site of injection reported by patients in this study and the consequent 48% decline in preference for injection on day 4 to 8. From the doctor's point of view, it is easier to administer a single oral dose than an injection.

Thus, provided that no resistance to norfloxacin develops, it should provide the first simply administered and inexpensive treatment for both PPNG and

Table 6 Summary of treatment preferences

	Tablets		Injection		No preference	
	Day 1	Day 4-8	Day 1	Day 4-8	Day 1	Day 4-8
Bangkok men	69	87	31	12	0	0
Bangkok women	132	178	88	35	0	0
Singapore men	112	108	81	57	27	30
Total	313	373	200	104	27	30

Total who replied at Day 1 = 540, total who replied at Day 4-8 = 507.

non-PPNG infections and should be a valuable tool for limiting the spread of these infections.

We thank Drs A Chitwarakorn and C Wongba of Bangrak Hospital, Bangkok, Drs S N Tham, K S Wong, K B Lim, and T Thirumoorthy of Middle Road Hospital, Singapore, and Dr E H Sng of Singapore General Hospital for their help during the study, and Dr M Frame for help with the manuscript.

References

- 1 Panikabutra K. Epidemiology of gonorrhoea in Thailand. *JAMA* 1986;special supplement:33-8. (ASEAN symposium on quinolones in the treatment of gonorrhoea. Science Press Congress Archives 86001.)
- 2 Centres for Disease Control. Spectinomycin resistant penicillinase-producing *Neisseria gonorrhoeae* in California. *MMWR* 1981;30:221-2.
- 3 Easmon CSF, Ison CA, Bellinger CM, Harris JW. Emergence of resistance after spectinomycin treatment for gonorrhoea due to β -lactamase-producing strains of *Neisseria gonorrhoeae*. *Br Med J* 1982;284:1604-5.
- 4 Centres for Disease Control. Spectinomycin-resistant *Neisseria gonorrhoeae*—worldwide. *MMWR* 1982;31:632-8.
- 5 Centres for Disease Control. Spectinomycin-resistant penicillinase-producing *Neisseria gonorrhoeae*. *MMWR* 1983;32:51-2.
- 6 Boslego JW, Tramont EC, Takafuji ET, et al. Effect of spectinomycin use on the prevalence of spectinomycin-resistant and of penicillinase-producing *Neisseria gonorrhoeae*. *N Engl J Med* 1987;317:272-8.
- 7 Benbrook DN, Miller RV. Effects of norfloxacin on DNA metabolism in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1986;29:1-6.
- 8 Crumplin GC, Smith JT. Nalidixic acid and bacterial chromosome replication. *Nature* 1976;260:643-5.
- 9 Roddy RE, Handsfield HH, Hook EW. Comparative trial of single-dose ciprofloxacin and ampicillin plus probenecid for treatment of gonococcal urethritis in men. *Antimicrob Agents Chemother* 1986;30:267-9.
- 10 van der Willigen AH, van der Hoek JCS, Wagenvoort JHT, et al. Comparative double-blind study of 200 and 400 mg enoxacin given orally in the treatment of acute uncomplicated urethral gonorrhoea in males. *Antimicrob Agents Chemother* 1987;31:535-8.
- 11 Panikabutra K, Lee CT, Antonio-Velmonte M, Bamberg P. Efficacy and safety of norfloxacin in uncomplicated gonorrhoea—a double-blind dose response study. *JAMA* 1986;special supplement:54-6. (ASEAN symposium on quinolones in the treatment of gonorrhoea. Science Press Congress Archives 86001.)
- 12 Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Controlled Clinical Trials* 1982;3:345-53.
- 13 Ho B, Sng EH. Characteristics of resistance in *Neisseria gonorrhoeae* isolated in Singapore. *JAMA* 1986;special supplement:26-9. (ASEAN symposium on quinolones in the treatment of gonorrhoea. Science Press Congress Archives 86001.)
- 14 Kado CI, Liu ST. Rapid procedure for detection and isolation of large and small plasmids. *J Bacteriol* 1981;145:1365-73.
- 15 Hendry AT, Stewart IO. Auxanographic grouping and typing of *Neisseria gonorrhoeae*. *Can J Microbiol* 1979;25:512-21.
- 16 Panikabutra K, Ariyarat C, Chitwarakorn A, Wongba C, Saensanoh C. Susceptibility of recently isolated strains of *Neisseria gonorrhoeae* in the Bangkok area. *JAMA* 1986;special supplement:18-22. (ASEAN symposium on quinolones in the treatment of gonorrhoea. Science Press Congress Archives 86001.)
- 17 Sng EH, Yeo KL, Rajan VS. Simple method for detecting penicillinase-producing *Neisseria gonorrhoeae* and *Staphylococcus aureus*. *British Journal of Venereal Diseases* 1981;57:141-2.