Treating genitourinary and pharyngeal gonorrhoea with single dose ceftriaxone

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SUMMARY The efficacy of ceftriaxone 250 mg given as a single intramuscular dose to treat genitourinary and pharyngeal gonorrhoea is compared with the outcome of the Danish standard treatment for uncomplicated genitourinary gonorrhoea, pivampicillin 1.4 g and probenecid 1 g, both given by mouth.

The study comprised 327 patients for whom the diagnosis of gonorrhoea was made by microscopy of a methylene blue stained smear at their first visit to the clinic and for whom the diagnosis was later confirmed by culture of *Neisseria gonorrhoeae*.

One hundred and seventy patients with genitourinary gonorrhoea (18 with and 152 without concomitant pharyngeal infection) were treated with ceftriaxone. One hundred and fifty seven (17 with and 140 without concomitant pharyngeal infection) were treated with pivampicillin. One week after treatment *N. gonorrhoeae* was isolated from none of 18, 1/152, (1%), 11/17 (65%), and 6/140 (4%) patients, respectively. At a second attendance two weeks after treatment no further treatment failure was found.

During the study period, a further 52 patients with pharyngeal infection (with or without concomitant genitourinary infection) that was shown by culture only were treated with a single intramuscular injection of 250 mg ceftriaxone. No treatment failure was observed in this group.

Only minor adverse drug reactions were seen.

Ceftriaxone 250 mg as a single intramuscular injection is therefore safe and effective in treating gonorrhoea, including pharyngeal infection.

In some parts of the world single dose regimens of penicillin and probenecid for treating uncomplicated genitourinary gonorrhoea can still be recommended.¹ The increasing prevalence of penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG), strains with chromosomally mediated resistance, and spectinomycin resistant strains, have stressed the need for alternative treatment regimens.² Moreover, single dose antibiotic regimens have so far been unsatisfactory for treating pharyngeal gonorrhoea.^{3,4}

Ceftriaxone, a new extended range cephalosporin, is one of the most active of all antimicrobial agents

against *N. gonorrhoeae*, and has minimum inhibitory concentrations (MICs) within the range 0.0004–0.03 µg/ml.^{5,6} This exceptional activity, combined with high blood concentrations, pronounced tissue penetration, and a plasma half life of eight hours, make it particularly favourable for treating gonorrhoea.

Clinical trials using single doses of 125–250 mg ceftriaxone have produced cure rates of 100% in uncomplicated gonorrhoea in men and women.^{6–9} The effect of single dose ceftriaxone in pharyngeal gonorrhoea is not well known, but results obtained by Judson *et al* were promising. A single intramuscular dose of 125 mg ceftriaxone cured 30 (93.8%) of 32 pharyngeal infections.¹⁰

The present study aimed to evaluate the efficacy of a single dose regimen of 250 mg ceftriaxone in pharyngeal gonorrhoea and to compare the cure rate and the

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acceptability of ceftriaxone with those of our standard initial treatment of non-PPNG infections acquired in Denmark (1.4 g pivampicillin by mouth given with 1 g probenecid).

Patients and methods

The study was undertaken as an open randomised comparative multicentre study. All patients aged over 18 who attended the clinics during March 1986 to February 1987 were invited to participate. We included patients who gave their informed consent and for whom a diagnosis of genitourinary or rectal gonorrhoea was made by microscopy of a methylene blue stained smear at the initial visit. Patients were excluded if they had received antibiotics in the previous seven days, if they had known or suspected hypersensitivity to cephalosporins, penicillins, or lidocaine or if they had known renal or hepatic insufficiency.

A total of 393 patients were randomised to treatment with either ceftriaxone 250 mg given as an intramuscular injection or pivampicillin 1.4 g plus probenecid 1 g given by mouth. Before treatment specimens were taken for culture as follows: one each from the urethra and the rectum and two from the tonsillar region of each patient; an additional specimen was taken from the cervix of each woman. Patients for whom the cultures for *N gonorrhoeae* were negative were subsequently excluded from the study.

Follow up visits were planned on days 7 and 14 after treatment. On each occasion specimens were taken for culture. If gonococci persisted or reappeared within 14 days after treatment and the patient had not had further sexual intercourse, the treatment was considered to have failed. The reappearance of gonococci after negative cultures on two occasions was considered to be due to reinfection irrespective of the patient's history.

During the study period a further 52 patients with pharyngeal infection with or without concomitant genitourinary or rectal infection, which was shown only by culture, were treated with a single intramuscular injection of 250 mg ceftriaxone. The schedule for control visits and cultures was similar to that for the first 393 patients.

CULTURE OF *N GONORRHOEAE*

Specimens were transported from the clinics to the laboratories on charcoal impregnated sterile wooden applicators in a modified Stuart's medium. Each swab was streaked on a selective chocolate agar medium containing amphotericin B (2 µg/ml), polymyxin B sulphate (25 IU/ml), lincomycin (1 µg/ml), and trimethoprim lactate (3 µg/ml). Gonococcus like oxidase positive colonies were identified by a direct

immunofluorescence test or carbohydrate (glucose, maltose, and sucrose) utilisation tests, or both and by a Gram stained smear.

IN VITRO SUSCEPTIBILITY TESTING

Susceptibility to ceftriaxone and penicillin was tested by a plate dilution method with twofold dilution steps of the antibiotics; the results are expressed as the minimum inhibitory concentrations (MICs). The concentrations of ceftriaxone ranged from 0.064 to 0.00025 µg/ml and for penicillin from 2.4 to 0.0094 µg/ml. Isolates requiring an MIC of penicillin of 1.2 µg/ml or more were examined for the production of penicillinase by the chromogenic cephalosporin test.

During the study period, isolates from all patients attending two of the participating dermatovenereological outpatient clinics were stored in liquid nitrogen for susceptibility testing. From a third clinic, however, only isolates from patients who entered the study were stored.

Results

Table 1 shows the demographic characteristics of the study population. Of 393 patients enrolled in the study, 327 (83%), whose diagnosis was confirmed by culture of *N gonorrhoeae* and who returned for the first follow up visit, constituted the final study population. Of the remaining 66 patients, 42 were excluded because *N gonorrhoeae* was not isolated from the specimens taken at the initial visit, three were not treated according to the protocol, and 21 did not return for follow up.

The two treatment groups were comparable for age and sex. Genitourinary infection without pharyngeal infection was diagnosed in 243 (90%) of 269 men and 49 (84%) of 58 women. The remaining 26 (10%) men

Table 1 Characteristics of the study population of 393 patients (figures are numbers (percentages) except where stated)

	Treatment regimen	
	Ceftriaxone 250 mg by intramuscular injection	Pivampicillin 1.4 g and probenecid 1 g by mouth
No treated	198	195
No evaluable*	170 (86)	157 (81)
Sex distribution:		
Men	143 (84)	126 (80)
Women	27 (16)	31 (20)
Median (range) age (years):		
Men	26 (18-63)	27 (18-56)
Women	23 (18-65)	24 (18-39)

*Patients for whom diagnosis was confirmed by culture of *Neisseria gonorrhoeae* and who returned for follow up.

Table 2 Outcome of treatment with ceftriaxone or pivampicillin and probenecid in 327 patients with genitourinary gonorrhoea, 35 with and 292 without concomitant pharyngeal infection (figures are numbers (percentages) of patients not cured out of numbers treated)

Infection	Treatment regimen	
	Ceftriaxone 250 g by intramuscular injection	Pivampicillin 1.4 g and probenecid 1 g by mouth
Genitourinary	1/152 (1)	6/140 (4)
Pharyngeal	0/18 (0)	11/17 (65)

and nine (6%) women also had pharyngeal gonorrhoea.

Table 2 shows that 151 (99%) of 152 patients with uncomplicated genitourinary infection treated with ceftriaxone yielded negative cultures for *N gonorrhoeae* compared with 134 (96%) of 140 treated with pivampicillin. Concomitant pharyngeal gonococcal infection was eradicated in all 18 patients treated with ceftriaxone compared with six (35%) of 17 patients treated with pivampicillin, a significant difference ($p < 0.05$, Fisher's exact test). Of five patients infected with PPNG strains, two had pharyngeal infection. All were treated with and cured by ceftriaxone.

Of the additional 52 patients with pharyngeal infection treated with ceftriaxone, seven were excluded from analysis of efficacy because of negative culture on the day of treatment and five did not return for follow up. These patients were similar to the main study population in sex and age. All 20 evaluable women and 20 evaluable men yielded negative cultures for *N gonorrhoeae* after treatment. In 14 of the patients the evaluation was based on a positive culture from the pharynx on the day of treatment. In 26 the positive culture had been obtained within two weeks before treatment.

No serious adverse drug reactions were seen after treatment with either ceftriaxone or pivampicillin. Minor gastrointestinal complaints (mainly "loose stools" or diarrhoea) were experienced by more (10/

Table 4 Minimum inhibitory concentrations of penicillin for 17 strains of *Neisseria gonorrhoeae* isolated from patients with gonorrhoea not cured by treatment with pivampicillin 1.4 g plus probenecid 1 g

MIC ($\mu\text{g/ml}$) of penicillin		No of isolates from:	
		Genitourinary infection	Pharyngeal infection
<0.15	Susceptible	0	5
0.30-0.60	Less susceptible	4	3
1.2-2.40	Resistant	2	3

170 (6%)) patients treated with ceftriaxone than by those (3/157 (2%)) treated with pivampicillin and probenecid ($p = 0.046$).

A total of 805 gonococcal strains were tested for susceptibility to ceftriaxone and penicillin (table 3), 380 of them were from patients who entered the study. A strong positive correlation ($r = 0.93$) was seen except for PPNG strains. The ratios between the MICs of penicillin and of ceftriaxone were 1:40 for strains with MICs of penicillin of 0.15 $\mu\text{g/ml}$ or less and 1:80 for strains with MICs of penicillin of less than 0.15 $\mu\text{g/ml}$. The MICs of ceftriaxone against isolates from the patient who was not cured after treatment with ceftriaxone were 0.002 $\mu\text{g/ml}$ before and 0.004 $\mu\text{g/ml}$ after treatment.

Table 4 shows the MICs of penicillin for strains isolated from patients who were not cured by treatment with pivampicillin 1.4 g and probenecid 1 g. None of them were PPNG strains.

Discussion

The standard treatment of uncomplicated gonorrhoea (pivampicillin 1.4 g and probenecid 1 g by mouth) was successful in 96% of our patients. A similar cure rate was found in a study from Copenhagen in 1983,¹¹ and must be considered to be satisfactory. On the other hand, the standard regimen gave an unsatisfactory cure rate (only 35%) for pharyngeal gonorrhoea as in

Table 3 Correlation between minimum inhibitory concentrations (MICs) of ceftriaxone and penicillin for 805 strains of *Neisseria gonorrhoeae*

MIC ($\mu\text{g/ml}$) of ceftriaxone	No of non-PPNG isolates with MICs ($\mu\text{g/ml}$) of penicillin of:					No of PPNG isolates	Total
	<0.01-0.04	0.08-0.15	0.30-0.60	1.2-2.4	>2.4		
<0.00025	136	0	0	0	0	0	136
0.0005-0.001	252	5	2	0	0	0	259
0.002-0.004	1	98	115	1	1	8	224
0.008-0.016	0	19	58	58	0	13	148
0.032-0.064	0	2	2	28	3	2	37
0.128	0	0	0	0	1	0	1
Total	389	124	177	87	5	23	805

PPNG = penicillinase producing *N gonorrhoeae*.

previous studies.³⁴ Our treatment failures were not associated with decreased sensitivity to penicillin in vitro (table 4).

Ceftriaxone as a single intramuscular dose of 250 mg was an effective treatment in men and women with uncomplicated gonorrhoea (including five patients infected with PPNG strains) and gave a cure rate of 99%. This finding confirmed the results of other studies that showed 100% efficacy of single doses of 125–250 mg ceftriaxone for uncomplicated gonorrhoea.^{6–9}

Single dose ceftriaxone 250 mg was also highly effective in treating pharyngeal gonorrhoea. All 58 patients, including 26 who yielded positive cultures within two weeks before treatment and two infected with PPNG strains, were cured. Judson *et al* found 125 mg ceftriaxone to be effective in 30 (94%) of 32 pharyngeal infections.¹⁰ This might indicate that a larger dose of 250 mg ceftriaxone can improve the cure rate of single dose treatment of pharyngeal gonorrhoea, although the numbers were too small to give a significant difference. (95% Confidence levels were 79.2–99.2 in the study by Judson *et al*¹⁰ and 93.8–100.0 in our study).

Ceftriaxone is also superior to other single dose regimens for treating pharyngeal gonorrhoea. Treatment with spectinomycin 2 g or 4 g as a single dose had a cure rate of only 43–46% of the pharyngeal infections treated.^{10 12} A similar low cure rate was found for two second generation cephalosporins, cefonicid and cefuroxime.^{13 14}

Epidemiological studies from the venereal diseases clinics in Copenhagen^{15 16} and the Neisseria Department, Statens Seruminstitut¹⁷ during recent years have shown a constant incidence of pharyngeal gonorrhoea of 15% in patients examined for gonorrhoea, with the highest incidence in women and homosexual men. This indicates that pharyngeal gonorrhoea is a numerically important problem. The clinical importance and the contagiousness of pharyngeal gonorrhoea has not been satisfactorily assessed. The infection seems to give throat symptoms seldom,^{4 18 19} and may in some cases be self limiting.¹⁸ Pharyngeal gonorrhoea is thus a reservoir of *N gonorrhoeae*. Until it is proved not to be contagious or a possible source of dissemination, therefore, patients with pharyngeal gonorrhoea should be treated.

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