

Randomised observer blind comparative trial of ceftriaxone and penicillin in treating uncomplicated gonorrhoea in men and women

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SUMMARY Ceftriaxone is a third generation cephalosporin with a prolonged half life. It was used in doses of 500 mg intramuscularly in 27 men (group 1) and 23 women (group 2) and 250 mg in 48 men (group 3) and 45 women (group 4) with uncomplicated urogenital gonorrhoea. Similar numbers of patients in each group were treated with 2 MIU intramuscular Bicillin (procaine penicillin 1.5 g plus benzylpenicillin 300 mg (Brocades, Weybridge, Surrey, England).

Success of treatment was measured as one or two negative cultures after three or more days. The success rate for ceftriaxone was 100% in 19 evaluable men and 19 women treated with 500 mg and in 38 men and 31 women treated with 250 mg, including one infection due to penicillinase producing *Neisseria gonorrhoeae* (PPNG).

Success rates for Bicillin were 90% (19/21) evaluable patients cured in group 1, 100% (19/19) in group 2, 95% (37/39) in group 3, and 92% (33/36) in group 4. Both drugs were well tolerated. Each isolate of *N gonorrhoeae* isolated was sensitive to 0.05 mg/l or less of ceftriaxone.

Introduction

Ceftriaxone would seem to fulfil many of the criteria for single dose treatment of uncomplicated gonorrhoea. Its plasma half life is 6½ to 8½ hours, whereas other cephalosporins have half lives of 45 minutes to 2½ hours.^{1 2} Its bioavailability is 100% when given intramuscularly, 40% being excreted in bile and 60% in urine.^{1 2} Probenecid has no effect on its excretion.² It has an excellent safety record^{1 2} and is well tolerated by patients.³⁻⁵

In vitro its potency for both penicillinase producing *Neisseria gonorrhoeae* (PPNG) and non-PPNG strains exceeds that of all other cephalosporins to date and of other antibiotics with which it has been compared.⁶⁻⁸

In vivo almost all the published trials to date have shown 100% cure rates for uncomplicated urethral, cervical, and rectal gonorrhoea caused by both PPNG and non-PPNG strains, using dosages as low as 125 mg ceftriaxone.^{3-5 10-16} We report our experience with ceftriaxone, comparing it with penicillin in an observer blind trial.

Patients and methods

Patients studied attended the clinics for sexually transmitted diseases at Nottingham and Lincoln and gave informed verbal consent.

To be admitted into the trial men had to have uncomplicated urethral or rectal gonorrhoea diagnosed by the presence of Gram negative intracellular diplococci (GNICD) in smears from those sites. Swabs were taken from the urethra in heterosexual patients and from the urethra and rectum in homosexuals, and were transported in Amies' medium. *N gonorrhoeae* was isolated on modified New York City (MNYC) medium¹⁷ with added antibiotics for non-urethral specimens. Minimum inhibitory concentrations (MICs) of penicillin and ceftriaxone for the isolates were measured by agar incorporation in MNYC medium, using reference strains IRS3 and IRS5 as controls. Strains isolated at the Public Health Laboratory, Lincoln, were sent to Nottingham for ceftriaxone testing (by courtesy of the Director, Dr J G Wallace). Patients in whom the initial cultures for *N gonorrhoeae* were negative were subsequently excluded from the trial. Patients were excluded if they had received antibiotics in the previous 10 days or if they had undiagnosed genital ulcers or known renal or hepatic disease.

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Women were included if GNICD were seen on urethral, cervical, or rectal smears or *N gonorrhoeae* was cultured from urethral, cervical, or rectal swabs. The exclusions noted for men also applied to the women. In addition pregnant women were excluded, as were those not using adequate contraception (such as the contraceptive pill, an intrauterine device, or sterilisation) and any woman with evidence of salpingitis on clinical examination.

The patients were divided into four groups according to sex and the dose of ceftriaxone used; within each group about half were treated with ceftriaxone and half with penicillin according to a computer generated randomisation schedule.

Group 1 contained 27 men who received 500 mg ceftriaxone in 4 ml 1% lignocaine intramuscularly and 28 men who received 2 MIU Bicillin (Brocades, Weybridge, Surrey, England; 3 g procaine penicillin and 600 mg benzylpenicillin sodium) in 5 ml 0.5% phenol intramuscularly. Group 2 contained 23 women treated with 500 mg ceftriaxone and 25 women receiving 2 MIU Bicillin. Group 3 contained 48 men given 250 mg ceftriaxone in 2 ml 1% lignocaine and 50 men who received 2 MIU Bicillin. Group 4 contained 45 women given 250 mg ceftriaxone as above and 46 women who received 2 MIU Bicillin.

All patients were asked to attend again two to three days after treatment and after nine days and 16 days; they were asked to abstain from sexual intercourse during this period. At the first follow up visit they were asked about symptoms, sexual activity, and any side effects of their treatment. At each visit smears for microscopy and material for culture were taken from the same sites as initially.

In women, infections with other organisms, such as *Candida albicans*, *Trichomonas vaginalis*, and *Chlamydia trachomatis* were treated 10 days after giving the trial drug. In men culture for *C trachomatis* was not undertaken routinely, but postgonococcal urethritis (PGU), which was defined as 10 or more pus cells per high power field ($\times 1000$) on an urethral

smear without GNICD, was treated at the third follow up visit.

Results

Success of treatment was denoted by negative cultures for *N gonorrhoeae*; ideally two negative cultures were required but some patients only attended for one follow up visit. If that visit was on day 2 they were recorded as having been lost to follow up to exclude the possibility that the infection had been suppressed but not cured at that stage. Single negative cultures on day 3 or later were recorded as "one negative culture".

Reinfection was recorded when a patient still had gonorrhoea at the first follow up visit, but admitted having had intercourse with a sexual partner who was known to be infected.

The difference in ages and symptoms between patients treated with ceftriaxone and Bicillin within each group was not significant.

Discounting unproved initial infections and patients lost to follow up, table 1 compares the sites of infection, incidence of PGU, and success rates with the two drugs in evaluable patients in each group. In group 1 there was a treatment failure with Bicillin in a patient with a urethral infection with a PPNG strain. One rectal infection was cured by 500 mg ceftriaxone and one by Bicillin, the third patient being reinfected by first follow up. In group 2 both drugs were 100% successful, including treatment of three rectal infections with Bicillin. In group 3, 250 mg ceftriaxone cured one case of gonorrhoea caused by a non-PPNG strain that was resistant to penicillin in vitro (MIC 0.5 mg/l) and a second that was caused by a PPNG strain; both had two checks of cure. The failure with Bicillin was in a patient infected with a non-PPNG strain with an MIC of 0.5 mg/l penicillin. In group 4, the failures with Bicillin were both in patients infected with non-PPNG strains with MICs of 0.1 and 0.2 mg/l penicillin.

The figures for adverse drug reactions, which consisted of nothing more than mild pain at the

TABLE 1 Sites of infection and results of treatment with ceftriaxone 500 mg or 250 mg or Bicillin 2 MIU

	Group 1 (men)		Group 2 (women)		Group 3 (men)		Group 4 (women)	
	Ceftriaxone 500 mg	Bicillin 2 MIU	Ceftriaxone 500 mg	Bicillin 2 MIU	Ceftriaxone 250 mg	Bicillin 2 MIU	Ceftriaxone 250 mg	Bicillin 2 MIU
Evaluable patients	19	21	19	19	38	39	31	36
Urethral infections	18	19	16	13	38	38	20	24
Cervical infections			18	18			31	34
Rectal infections	1	2	0	3	0	3	0	1
Two negative cultures after treatment	16	15	15	16	30	24	22	26
One negative culture	3	4	4	3	8	13	9	7
Post gonococcal urethritis (%)	8(42)	6(28.5)			17(47)	10(25.6)		
Reinfections	0	1	0	0	0	1	0	1
Failures	0	1	0	0	0	1	0	2
Successes (%)	100	90	100	100	100	95	100	92

TABLE II *Incidence of adverse drug reactions in total trial population*

	Bicillin 2MTU	Ceftriaxone	
		500 mg	200 mg
Total men and women treated	149	50	93
No (%) adverse drug reactions	25(16.8)	9(18)	11(11.8)

injection site or transient gastrointestinal symptoms, were calculated from the total numbers of patients treated (table II). One man who had received 250 mg ceftriaxone remarked that it was less painful than Bicillin, which he had received on several occasions previously.

The sensitivities to penicillin of strains of *N gonorrhoeae* in Nottingham and Lincoln were similar to those found in a previous study.¹⁸ The MICs for organisms isolated from patients in this trial were similar to those encountered in the Public Health Laboratories at the time of the trial. The minimum concentrations that inhibited 90% of all strains were 0.5 mg/l penicillin and 0.005 mg/l ceftriaxone. Similar 100-fold differences were found between penicillin and ceftriaxone for the MIC₅₀ and mean concentrations. All strains of *N gonorrhoeae* isolated were inhibited by 0.05 mg/l or less of ceftriaxone, whereas some β lactamase producing strains had MICs of penicillin greater than 100 mg/l.

Discussion

Ceftriaxone has shown consistently high success rates in treating uncomplicated urogenital gonorrhoea in all reports published to date; the doses used compare, in many cases, with those used to treat the gonococcus with penicillin in the early days of antibiotic treatment.

Table III summarises those trial results where ceftriaxone has been 100% successful in doses of 125 mg to 500 mg. At the much lower doses of 32.5 mg and 62.5 mg the cure rate was still 100% for urethral infections with PPNG strains;¹¹ in non-PPNG urethral infections the cure rates were 96.2% with 62.5 mg, 95%

TABLE III *Numbers of patients treated with different doses of ceftriaxone for uncomplicated gonorrhoea with 100% success in the present and previous trials*^{3-5 10-16 20-21}

Sites of infection	Strains	Dose of ceftriaxone:		
		125 mg	250 mg	500 mg
Men: ^{3 5 10,16 21}				
Urethra	PPNG	19	80	
	Non-PPNG	123	361	141
Rectum	Non-PPNG	65	10	3
Women:				
Cervix ^{4 20}	Non-PPNG		53	18
Urethra	Non-PPNG		32	16
Rectum	Non-PPNG	20	10	
	PPNG	3		

with 50 mg, and 97.3% with 32.5 mg.^{11 12} The trial by Clay *et al*, however, reports the only treatment failures with a dose of 500 mg ceftriaxone; one out of 100 men and two out of 86 women given 500 mg ceftriaxone were not cured.¹⁹ In the same trial five out of 109 men were not cured by 250 mg ceftriaxone. Collier *et al* reported one failure in 55 cervical infections treated with 125 mg ceftriaxone.²⁰

Fewer cases of pharyngeal gonorrhoea have been treated; in all, published data show four out of four cures with 500 mg, six out of six cures with 250 mg, and 44 out of 48 cures with 125 mg.^{3 4 10 19-21}

Because of the low doses used, it was possible to use very small amounts of lignocaine diluent, thus minimising pain at the injection site without affecting the bioavailability of the drug.²² Though in our trial we used 2 ml lignocaine for 250 mg ceftriaxone and 4 ml for the 500 mg dose, other trials have used half these amounts, with only 0.5 ml lignocaine for 125 mg ceftriaxone, and in some cases the injections were given into the deltoid muscle almost painlessly.^{4 10 20} In our trial the incidence of local pain was less with the lower dose of ceftriaxone.

We did not perform tests of liver and kidney function or full blood counts before and after treatment, but in the trials where these have been undertaken no harmful effects were noted.^{3-5 13 20 21}

It is recognised that cephalosporins do not cure chlamydial infections, and other trials have shown no difference in the incidence of PGU after ceftriaxone and after spectinomycin³ or kanamycin.¹¹ In our trial a higher incidence of PGU was noted after ceftriaxone than after Bicillin.

Another infection that may coexist with gonorrhoea is early syphilis, and ceftriaxone has been shown to be effective in treating syphilis in rabbits,²³ so incubating seronegative syphilis could be aborted by single dose ceftriaxone treatment.

In the United Kingdom the incidence of infections with PPNG strains has risen yearly until 1983 (the last available date),²⁴ but it has not yet approached 5% of all cases of gonorrhoea. If that level is reached McCutchan *et al* have recommended that penicillin should no longer be used as a routine treatment for gonorrhoea.²⁵ If such a situation arose then ceftriaxone would be a suitable alternative. In the meantime, ceftriaxone is an excellent drug for treating known or suspected penicillin resistant strains.

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