Efficacy of various single-dose regimens of ceftriaxone in uncomplicated acute gonococcal urethritis in adult males

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Summary

The therapeutic efficacy of single intramuscular doses of ceftriaxone (Rocephin; Roche) (62,5, 125 and 250 mg), administered without probenecid, was evaluated in 167 adult males with uncomplicated acute gonococcal urethritis. Cure rates of 100% were achieved at 62,5 mg and 250 mg. In the 125 mg dose group, *Neisseria gonorrhoeae* was isolated from 1 patient at follow-up after therapy. Reinfection was suspected, since this patient returned on day 10 and admitted to sexual contact 2 days previously. Side-effects were minimal, and patient acceptance was better for ceftriaxone dissolved in lignocaine than in sterile water. *Chlamydia trachomatis* was detected at follow-up in 14,4% patients, confirming that ceftriaxone has no significant effect on chlamydial infection and additional treatment is necessary for patients with coexistent infection.

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Ceftriaxone (Rocephin; Roche), an extended spectrum cephalosporin with long plasma half-life, has been shown to give excellent cure rates for uncomplicated gonorrhoea, irrespective of the penicillin susceptibility of *Neisseria gonorrhoeae* strains.[1-7] Cure rates of 100% have been achieved with single intramuscular doses ranging from 125 mg to 500 mg. In a dose-response study, Rajan *et al.*[8] showed the efficacy of single doses as low as 32,5 mg, 62,5 mg and 125 mg, each accompanied by oral probenecid for the treatment of gonococcal urethritis (GU). Furthermore, in a pilot study using small numbers of patients, Eichmann *et al.*[2] achieved good results at a single low dose of 50 mg administered without probenecid.

In South Africa, the Medicines Control Council has licensed ceftriaxone, but only the 250 mg single intramuscular dose has approval for the therapy of gonorrhoea. With the increasing prevalence of penicillinase-producing strains of *N. gonorrhoeae* (PPNG) in patients attending the sexually transmitted diseases clinic at this hospital, the need to change to an antimicrobial agent active against both penicillin-sensitive and -resistant strains has become essential. Locally obtained proof of the efficacy of ceftriaxone would make it cost-effective as a potential first-choice agent for the treatment of GU.

Against this background and with the knowledge that probenecid does not affect the renal excretion of ceftriaxone,[9] a study was undertaken to assess the efficacy of various single low doses of ceftriaxone in the treatment of uncomplicated gonorrhoea.

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Patients and methods

Adult males presenting to the Sexually Transmitted Diseases (STD) Clinic at King Edward VIII Hospital, Durban, with a complaint of urethral discharge were considered for the study. Informed consent was obtained from all patients and the study was approved by the Ethics Committee of the Faculty of Medicine, University of Natal, and also by the Medicines Control Council of South Africa.

At the initial visit, endo-urethral swab specimens were collected from each patient for the preparation of a smear for Gram staining and for isolation of *N. gonorrhoeae*. Patients with smears in which characteristic Gram-negative intracellular diplococci were seen were included in the study and assigned randomly to receive a single intramuscular dose of 62,5 mg, 125 mg or 250 mg ceftriaxone.

All patients were asked to refrain from sexual intercourse and return after 3 days. At the follow-up visit, repeat endo-urethral swab specimens were collected for a smear for Gram staining and culture for *N. gonorrhoeae*. If 4 or more polymorphonuclear neutrophils per high-power field were seen in the Gram stain, further endo-urethral specimens were obtained for the detection of *Chlamydia trachomatis* and *Ureaplasma urealyticum*. These patients were then also given a course of oral minocycline (100 mg twice a day for 14 days).

Microbiological investigations

Endo-urethral specimens were obtained by inserting calcium alginate-tipped swabs 2-3 cm beyond the meatus and gently rotating them. Smears for Gram staining were prepared, stained and read at the clinic, while those for direct immunofluorescence staining (Microtrak; Syva Corp.) for *C. trachomatis* were fixed with acetone and processed according to manufacturer's instructions.

Specimens for the isolation of *N. gonorrhoeae* and *U. urealyticum* were inoculated onto modified New York City Medium and U9 broth respectively. All inoculated media were immediately placed in candle extinction jars and transported to the laboratory within 30 minutes. *N. gonorrhoeae* and *U. urealyticum* were identified by standard laboratory methods, as described previously.[10]

Results

The study period extended from 14 June 1988 to 12 July 1988 during which time a total of 197 adult males were enrolled. Of these, 167 patients returned for follow-up (within 3 - 7 days of receiving treatment) and could be assessed. The average age of the patients was 27 years (range 18 - 57 years).

For the first 50 patients in the study, ceftriaxone was administered dissolved in sterile water, and 24 of these men (48%) complained of moderate-to-severe pain at the site of injection. For the remaining 117 patients, ceftriaxone was administered dissolved in 1% lignocaine. Of these men, only 10 (8,6%) complained of minimal pain at the site of injection.

TABLE I. RESULTS OF TREATMENT WITH DIFFERENT INTRAMUSCULAR DOSES OF CEFTRIAXONE

Ceftriaxone dose (mg)	No. of patients	No. of patients returning for follow-up	Patients cured		Patients with PPNG strains	
			No.	%	No.	%
62,5	65	56	56	100	8	100
125	66	54	53	98,1*	9	100
250	66	57	57	100	9	100
Total	197	167	166	99,4	26	100

*1 patient in whom reinfection was suspected.

Only 4 patients complained of feeling nauseous and 6 of feeling slightly dizzy at the time of injection. No other adverse reactions were recorded.

The results of treatment with the different intramuscular doses of ceftriaxone are shown in Table I. Characteristic intracellular diplococci were seen in only 1 Gram-stained smear, and culture yielded *N. gonorrhoeae*; the patient from whom these smears were taken returned on day 10 and admitted to sexual contact 2 days previously. PPNG strains were detected in 26 patients (15,6%).

Results of microbiological investigation of endo-urethral specimens collected at the follow-up visit are shown in Table II. In a total of 49 patients (29,3%) $\geqslant$ 4 polymorphonuclear neutrophils per high-power field were seen. *C. trachomatis* was detected in 25 (14,9%) and *U. urealyticum* alone in 8 patients (4,8%).

TABLE II. RESULTS OF MICROBIOLOGICAL INVESTIGATIONS PERFORMED AT FOLLOW-UP VISIT

	No.	%
Patients with smears showing $\geqslant$ 4 polymorphonuclear neutrophils/high-power field	**49**	**29,3**
N. gonorrhoeae*	**1**	**0,6**
***C. trachomatis* alone**	**21**	**12,5**
***U. urealyticum* alone**	**8**	**4,8**
C. trachomatis* + *U. urealyticum	**4**	**2,3**
No agent detected	**15**	**8,9**

*Patient in whom reinfection was suspected.

At the follow-up visit, 18 patients complained of burning on micturition; endo-urethral smears of these patients showed $\geqslant$ 4 polymorphonuclear neutrophils in 13, and in 10 *C. trachomatis* was detected.

Discussion

In vitro susceptibility tests on local isolates of *N. gonorrhoeae* from patients attending the same sexually transmitted diseases clinic in which this study was undertaken, have shown a uniform sensitivity to ceftriaxone. The 90% minimum inhibitory concentration of these isolates is as low as $\leqslant$ 0,007 μg/ml.[11] This probably explains the effectiveness of the low dose ceftriaxone (62,5 mg) administered without probenecid in this study.

All patients treated, including 26 (15,6%) from whom PPNG strains were isolated, were cured with the three dosage regimen used. The exception was a patient in whom reinfection was suspected. This patient returned on day 10 after therapy and admitted to sexual contact 2 days previously.

The use of sterile water as a diluent resulted in a significant number of patients (24 of 50) complaining of moderate-to-severe pain at the site of injection. When the preparation was reconstituted in lignocaine this complaint was no longer volunteered and on enquiry only 8,6% patients stated that they experienced minimal pain at the site of injection. Side-effects were minimal, with 4 and 6 patients complaining of nauseousness and a feeling of dizziness respectively. Full blood counts, liver and renal function tests were not performed in this study, but in studies in which these tests have been undertaken, no harmful effects were noted.[4,6,12]

Although investigations for *C. trachomatis* were not included among the initial investigations performed before ceftriaxone therapy, the finding of *C. trachomatis* in 14,9% of patients at the follow-up visit is similar to prevalences of 17% and 10,7% found in two independent studies on male urethritis at the same STD clinic.[10,13] This is in agreement with the findings of other workers[1,4] that chlamydial infections are not cured by single-dose regimens of ceftriaxone. Patients with coexisting *C. trachomatis* infection ought to be adequately treated after ceftriaxone by a 7-day course of tetracycline.[13]

With the local prevalence of PPNG strains having risen steadily from the 5% reported in 1983[15] to 26% in 1986,[10] we have recommended that penicillin no longer be used for the therapy of gonococcal urethritis, and a suitable alternative be employed.[14] This study shows that ceftriaxone would be an ideal alternative because of its excellent activity against both penicillin-sensitive and -resistant strains of *N. gonorrhoeae*. Furthermore, at a dose of 125 mg, it has been projected to cost closer to the currently used regimen of 4,8 million units of procaine penicillin with oral probenecid and much less than other single-dose treatment regimens.[4] It should be noted that since the completion of this study, ceftriaxone at a single intramuscular dose of 125 mg has been made available at the STD clinic at this hospital for first-line therapy for gonococcal urethritis.

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