Treatment of acute gonococcal urethritis in men with simultaneous infection with *Chlamydia trachomatis*

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SUMMARY Each of 201 men with symptoms and signs of acute urethritis was randomly assigned to one of two treatment regimens: ampicillin (2g) plus probenecid (1g), or sulphamethoxazole-trimethoprim (SMX-TMP) (sulphamethoxazole 1600 mg plus trimethoprim 320 mg) four tablets twice daily for two days. Before treatment *Neisseria gonorrhoeae* was isolated from 162 patients, while coexistent *Chlamydia trachomatis* was recovered from 42 (26%) men. After treatment *N gonorrhoeae* persisted in 11 (14.3%) of the 77 patients treated with ampicillin and probenecid and in three (3.5%) of the 85 treated with SMX-TMP ($p < 0.05$), while *C trachomatis* persisted in four (16%) of the 25 men treated with SMX-TMP and in all 17 patients treated with ampicillin and probenecid.

SMX-TMP was thus more effective than ampicillin in treating acute gonorrhoea in men and in eradicating concurrent *C trachomatis* infection.

Introduction

Chlamydia trachomatis is a common sexually transmitted organism causing non-gonococcal urethritis, salpingitis, and inclusion conjunctivitis, and its association with other conditions such as endometritis, epididymitis, and Reiter's disease has been documented.¹⁻³ *C trachomatis* commonly occurs in men with gonorrhoea and can be isolated from about one in four men with gonococcal urethritis.¹⁻⁴ Concurrent infection with *Neisseria gonorrhoeae* is the major cause of postgonococcal urethritis.¹⁻⁵

A high percentage of men with double infection are likely to develop postgonococcal urethritis after treatment for gonorrhoea with penicillin derivatives or spectinomycin.¹⁻⁵ The treatment of acute gonococcal urethritis with sulphamethoxazole-trimethoprim (SMX-TMP) is well documented,⁶⁻¹³ and one regimen is four tablets by mouth twice daily for two days. This regimen is particularly effective and suitable because it is relatively short term, gives high cure rates, is a possible alternative against

β -lactamase producing gonococci, does not mask concomitant syphilis, and may cure pharyngeal infection.⁶⁻⁹⁻¹² The combination of sulphamethoxazole and trimethoprim was effective against *C trachomatis* in vitro,¹⁴⁻¹⁵ and when used in clinical studies it was found to eradicate the organism and symptoms of urethritis in more than 90% of patients.¹²⁻¹⁴ Sattler and Ruskin stressed the need to undertake a study to test SMX-TMP in double infections with *N gonorrhoeae* and *C trachomatis*.¹⁰ In one such study a schedule of four doses of SMX-TMP in two days was effective in eradicating gonococci and *C trachomatis* in nine of 10 women with dual infection.¹²

Mahony *et al* found that the incidence of postgonococcal urethritis was significantly lower in patients with gonorrhoea treated with SMX-TMP than those treated with penicillin.⁷ In a study by Austin *et al* the incidence of postgonococcal urethritis following treatment with SMX-TMP was the same as after treatment of gonorrhoea with tetracycline.⁸

Despite these favourable results, SMX-TMP has not previously been the subject of a controlled clinical trial of the treatment of double infections in acute urethritis in men. This investigation studied the

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Accepted for publication 6 October 1983

efficacy of four doses of SMX-TMP in two days in eliminating both gonococci and *C trachomatis* from the urethra of men with acute gonococcal urethritis.

Patients, materials, and methods

A total of 201 consecutive male patients with symptoms of acute urethritis of less than seven days' duration were enrolled in the study. Patients were included if there was a urethral discharge and if there were Gram negative diplococci in Gram stained smears of urethral exudate.

MICROBIOLOGICAL METHODS

Specimens were obtained for the culture of *N gonorrhoeae* and *C trachomatis* before and two to three weeks after treatment. Specimens for *N gonorrhoeae* were taken with a charcoal impregnated cotton swab and transported to the laboratory in Stuart's medium. The isolation medium described by Ødegaard *et al*¹⁷ was used. Suspected colonies were confirmed by sugar fermentation tests, co-agglutination tests (Phadebact Gonococcus Test, Pharmacia Diagnostics, Uppsala, Sweden), or both. Specimens for culture of *C trachomatis* were collected and transported as described by Csángó¹⁸; the organism was cultured on McCoy cells treated with cycloheximide.¹⁹

Assessment of postgonococcal urethritis

Postgonococcal urethritis was diagnosed if there were at least five polymorphonuclear leucocytes per high power field ($\times 100$ objective) in the urethral smear after treatment. The smear was collected by gentle curettage of the urethra of all patients studied.

TREATMENT

Patients were allocated at random to one of two treatment groups (A or B) and received treatment at the first visit as follows: group A: single dose oral treatment consisting of 2 g ampicillin (Doktacillin 500 mg, Astra) and 1 g probenecid (Probecid, Astra); group B: two day oral treatment with SMX-TMP (Bactrim, Hoffmann-La Roche) four tablets twice daily each tablet containing 400 mg sulphamethoxazole and 80 mg trimethoprim. Patients were excluded from the study if there had been previous or suspected allergic reactions to penicillins, sulphonamides, or trimethoprim, or if they had been treated with antibiotics within the previous 10 days.

Patients with persistent gonococcal infection (at the second or third visit) were treated with spectinomycin (Trobicin 2 g, Upjohn), and those with persistent chlamydial infection or postgonococcal urethritis received SMX-TMP two tablets by mouth twice daily for two days, erythromycin stearate

(Abbotticin, Abbott), or a tetracycline in the usual dosages for seven days.

Statistical analysis

Fisher's exact probability test was used for verification of treatment results.

Results

Of the 201 men treated on the basis of the entry criteria, 23 did not return for subsequent examination and were therefore excluded from the analysis. Among the remaining 178 patients, gonorrhoea was proved by culture in 162, 42 of whom had a simultaneous infection with *C trachomatis*.

Table I shows culture results and the allocation of patients to each treatment group. Three of the 85 patients in group A and 11 of the 77 in group B ($p < 0.05$) were still infected with gonococci after treatment. Among those with persistent *N gonorrhoeae* in group A two men were infected with β -lactamase producing strains, two admitted re-exposure, and seven cases could be ascribed to treatment failure. In group B all three treatment failures were due to resistant strains.

TABLE I Results of cultures for *N gonorrhoeae* and *C trachomatis* before treatment and assignment of patients to two treatment groups.

	Patients treated with		Total
	Ampicillin-probenecid (group A)	Sulphamethoxazole-trimethoprim (group B)	
Positive cultures for:			
<i>N gonorrhoeae</i>	77	85	162
Both organisms	17	25	42

Table II shows the effect of treatment on *C trachomatis* infection. Before treatment 42 of 162 (26%) patients with positive gonococcal isolates had co-existent *C trachomatis* infection, of whom 17 were in group A and 25 in group B.

TABLE II Eradication of *C trachomatis* in men with gonococcal urethritis (percentage cure rates in parentheses).

	Patients treated with:	
	Ampicillin-probenecid (group A)	Sulphamethoxazole-trimethoprim (group B)
Positive cultures for <i>C trachomatis</i> :		
Before treatment	17/77	25/85
After treatment		
Second visit	28*/77 (0)	4†/85 (84)
Third visit	18‡/52 (0)	8/61 (68)

*3 probable reinfections, and 11 newly culture positive patients;
†1 probable reinfection; ‡1 newly culture positive patient.

After treatment, *C trachomatis* was reisolated from 17 men in group A and 11 additional patients became culture positive. In group B, *C trachomatis* was reisolated from 4 of 25 men initially giving positive results for chlamydia, although one of them had had sexual contact in the interim. At the last visit *C trachomatis* was isolated from 8 of 61 (13.1%) men in group B. Three of these patients had persistent infection (positive results at all three visits).

POSTGONOCOCCAL URETHRITIS

In group A there were 11 patients with persistent gonococcal infection, all of whom had five or more polymorphonuclear leucocytes per high power field. Of the remaining 66, 30 (45%) men cured of gonorrhoea had postgonococcal urethritis, and *C trachomatis* was isolated from 26 (86.6%) of them. Remarkably, *C trachomatis* was also isolated from two men without urethral leucocytosis.

In group B three patients had persistent gonococcal infection with five or more polymorphonuclear leucocytes per high power field. Eight of the 82 (9.8%) men cured of gonococcal urethritis had postgonococcal urethritis, and *C trachomatis* was isolated from three (37.5%) of them. Chlamydia was also isolated from one patient without postgonococcal urethritis. There was a significant ($p < 0.001$) difference in the rate of postgonococcal urethritis between group A and group B.

SIDE EFFECTS

In group A four patients had diarrhoea; one of them complained of moderate nausea and severe headache. In group B six patients experienced side effects, of whom two had mild diarrhoea, two complained of moderate nausea, and two had skin reactions, one of whom complained of itching and the other had a rash on both legs.

Discussion

This study shows that SMX-TMP in a dose of four tablets twice daily for two days was more effective than a single dose of 2 g ampicillin plus 1 g probenecid in the treatment of gonorrhoea in men ($p < 0.05$). Eleven of 87 (12.6%) patients had persistent infection after ampicillin treatment, which is a high failure rate. When it was first introduced in Norway in 1967, the combination of 2 g ampicillin and 1 g probenecid gave only a 1.2% failure rate.¹⁶ The increasing frequency of isolating penicillin resistant gonococci confirms observations from other countries.

In this study 42 of 162 (25.9%) men had concomitant infection with *C trachomatis*. This finding is in keeping with previous studies.¹⁻⁵ As in earlier observations,¹⁻⁵ ampicillin failed to eradicate *C trachomatis*, which was isolated from 28 of 77

(36.4%) men after treatment. The effect of repeated specimen collection on the rate of isolation can be explained by the fact that *C trachomatis* has a longer incubation time than gonococci. It may also be easier to obtain epithelial cells in the absence of gonococcal discharge.¹⁻⁵

This study confirms others in which very high cure rates (96-99%) were described when using SMX-TMP twice daily for two days to treat gonococcal urethritis in men.⁶⁻⁹ The same regimen seemed to be somewhat less effective in women (9% failure rate), but male partners had not been treated in these cases.¹²

Brunham *et al* isolated *C trachomatis* from only one of 10 patients treated with SMX-TMP, two tablets twice daily for two days, compared with 10 of 11 women treated with ampicillin.¹² In this study postgonococcal urethritis was usually associated with *C trachomatis*. Of the 30 men with five or more polymorphonuclear leucocytes per high power field in group A, 26 gave positive results for chlamydia after treatment.

Patients with urethral leucocytosis from whom neither gonococci nor *C trachomatis* could be isolated were equally distributed between the two treatment groups, with four such patients in group A and five in group B. None of these nine patients returned for more than one follow up visit. This suggests that postgonococcal urethritis not caused by chlamydia is more likely to be self limiting and may resolve spontaneously without further treatment.

In this study single dose treatment with ampicillin and probenecid was ineffective against *C trachomatis* in simultaneous infection with *N gonorrhoeae*. Sulphamethoxazole-trimethoprim treatment of acute, uncomplicated gonococcal urethritis in men gave a cure rate which was comparable with that in earlier studies carried out in Norway and other countries. SMX-TMP was effective in double infection with *N gonorrhoeae* and *C trachomatis*. Treatment of acute gonococcal urethritis with SMX-TMP could be particularly advantageous in younger age groups where double infections with *N gonorrhoeae* and *C trachomatis* are especially frequent.

We thank our clinical colleagues Drs Audun Gautestad, Magn-Bjørn Hornnes, Bjørnar Johansen, Rein Knoph, Gunnar Mouland, Øyvind Sørensen, and Finn-Tysland Johnsen for providing specimens and data from their patients, and Berit Sandstad, MSc for statistical consultation.

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