Treatment of nongonococcal urethritis with trimethoprim-sulphadiazine and with placebo

A double-blind partner-controlled study

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SUMMARY The effect of sulphadiazine and trimethoprim (T-S) was compared with that of a placebo in the treatment of 75 men with nongonococcal urethritis (NGU) and their female sexual partners. Forty (53%) men and 30 (40%) women had positive culture results for *Chlamydia trachomatis* before treatment was started. Thirty-four patients of each sex received active treatment. Of these, 19 men and 15 women had positive culture results for *C trachomatis* before treatment with T-S and one of each sex had a positive culture result after treatment. *C trachomatis* had been isolated in 21 men and 15 women before treatment with placebo. At follow up four weeks after treatment had been started, 16 men and 15 women still harboured *C trachomatis*. Five of the chlamydia-positive patients treated with placebo developed complications (epididymitis, arthritis, or salpingitis) so the trial was discontinued.

Introduction

In a critical review of the treatment of non-specific urethritis Simpoulos¹ suggested that only by comparing the results of treatment with tetracyclines and placebos or other drugs—for instance those outside the antibiotic range and with no suspected side effects—would it be reasonable to form a firm view on the desirability or effectiveness of the treatment. Furthermore, such a comparison should be carried out over a prolonged period of time.¹

Tetracyclines and erythromycin are the drugs of choice for the treatment of nongonococcal urethritis (NGU), both in chlamydia-positive and chlamydia-negative cases.² The frequently simultaneous presence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in genital infections of both men and women calls for new antimicrobial agents which are effective against both these micro-organisms. Although both tetracyclines and erythromycin are effective against *C trachomatis*, *N gonorrhoeae* is

frequently less sensitive. Penicillins and spectinomycin, commonly used for the treatment of gonorrhoea, are ineffective against *C trachomatis*.

In recent years several reports have emphasised the effectiveness of trimethoprim-sulphamethoxazole in the treatment of gonorrhoea.³⁻⁹ Carroll and Nicol¹⁰ and Willcox and Sparrow¹¹ reported favourable results with trimethoprim-sulphamethoxazole in the treatment of NGU. In-vitro studies of cell cultures have shown that genital strains of *C trachomatis* are susceptible to sulphamethoxazole.^{12 13} Trimethoprim alone has proved to be ineffective against *C trachomatis* in vitro¹³

The present study was carried out to compare the effect of a new combination of sulphadiazine and trimethoprim with that of a placebo in the treatment of male patients with NGU and their female sexual partners.

Patients and methods

STUDY POPULATION

Seventy-five men with NGU and 75 women, who were their regular sexual partners, were studied during the period from January to November 1978. All male patients were examined and treated at the

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Received for publication 18 June 1979

Outpatient Department for Venereal Diseases and their female partners at the Outpatient Clinics of the First and Second Departments of Obstetrics and Gynaecology, Helsinki University Central Hospital.

DIAGNOSIS

The diagnosis of NGU was established by the presence of urethral discharge, urethral discomfort, ≥ 10 leucocytes per high-power field in Gram-stained smears, and negative culture results for *N gonorrhoeae*.² Culture for *N gonorrhoeae* was performed for all male and female patients as described earlier.⁵ Specimens for the isolation of *C trachomatis* were collected with a sterile cotton-wool swab from both the urethra and the endocervix and placed in transport medium (2-SP). Isolation attempts were made in irradiated McCoy cells as described elsewhere.¹⁴

TREATMENT

Both partners received the same treatment, either trimethoprim-sulphadiazine (Ditrim duplo®, Neofarma, Helsinki, Finland) or placebo, one tablet twice daily for two weeks. Tablets containing trimethoprim (160 mg) and sulphadiazine (500 mg) or placebo were packed identically and randomised. The code was kept by an independent observer until the trial was completed. The patients were instructed not to have sexual intercourse without the use of a condom until re-examination at two weeks after the end of the treatment. The female partners were examined one to three days after the men, but the treatment of both partners was always started simultaneously.

All the female patients and those male patients with a positive chlamydial culture result initially or with urethral discharge or urethral discomfort or both at follow up were re-examined for the presence of *C trachomatis*. Before treatment was given all patients were informed that it might not be effective and that further treatment might be necessary. Patients who continued to be chlamydia-positive or to show evidence of urethritis when re-examined were retreated with doxycycline (Doximycin®, Orion) 100 mg twice daily for 10 days.

STATISTICAL ANALYSIS

Statistical comparisons were made using the χ^2 method with Yates's corrections.

Results

ISOLATION

C trachomatis was isolated in 40 (53%) men and in 30 (40%) women. All male patients and their partners had negative culture results for *N gonorrhoeae*. In 48

cases the present episode of NGU was the first. In five cases NGU manifested itself as a postgonococcal condition; five patients also had Reiter's disease and one acute prostatitis simultaneously.

TREATMENT

Men

A total of 34 men received trimethoprim-sulphadiazine (T-S) and 41 received a placebo (Table I). Before treatment, *C trachomatis* had been isolated in 19 (56%) of the former group and in 21 (51%) of the latter. At re-examination four weeks after the beginning of treatment one of the patients treated with T-S had not responded to treatment. In the placebo group, 21 treatment failures occurred and 16 patients continued to be chlamydia-positive when re-examined. In five cases of clinical failure after placebo treatment no attempt was made to reisolate *C trachomatis* at follow up. The difference in effect between T-S and placebo on *C trachomatis* was highly significant ($\chi^2 = 19.75$, $P < 0.001$).

TABLE I Treatment of male patients with NGU and their female sexual partners with trimethoprim-sulphadiazine and with placebo

Treatment	Chlamydial culture results				No cultures performed
	Before treatment +	Before treatment -	After treatment +	After treatment -	
<i>Male patients</i>					
T-S	19 (56%)	15*	1	13	20
Placebo	21 (51%)	20*	16†	2	23
<i>Female partners</i>					
T-S	15 (44%)	19	1‡	32	1
Placebo	15 (37%)	26	15§	32	4

+ Positive - negative

* Men with chlamydia-negative NGU were not systematically assessed by culture after treatment

† Two patients were chlamydia-negative before treatment

‡ Initially chlamydia-negative (partner chlamydia-positive)

§ Three patients were chlamydia-negative before treatment

T-S = trimethoprim-sulphadiazine

Women

Thirty-four women received T-S and 15 (44%) were chlamydia-positive before treatment (Table I). Thirty-three of them attended for re-examination and 32 had a post-treatment negative culture result for *C trachomatis*. One woman who was chlamydia-negative initially became chlamydia-positive during the follow-up period. Her male partner was chlamydia-positive both before and after treatment. Forty-one women were given placebo and 15 (37%) of these had positive culture results for *C trachomatis* before treatment. *C trachomatis* continued to be isolated from 12 of these 15 women, as well as from three others, at follow up. T-S had a significantly better effect on *C trachomatis* in women than did the placebo ($\chi^2 = 11.87$, $P < 0.001$).

COMPLICATIONS

Complications were observed in the group treated with placebo at follow up. One of the men had developed acute arthritis and one acute epididymitis. Both of these patients harboured *C trachomatis* before and after treatment. Acute salpingitis was diagnosed in three (20%) of the 15 chlamydia-positive women treated with placebo. Because of the complications the trial was discontinued at this stage.

RETREATMENT

Twenty-three men (three from the group treated with T-S and 20 from the group treated with placebo) who either remained chlamydia-positive or showed clinical failure despite negative culture results were treated with doxycycline. Eleven of these men attended for further follow up, and only one was chlamydia-positive and clinically not cured (Table II). The female partner of the only patient with NGU with treatment failure was repeatedly chlamydia-negative. Fifteen of the female partners of the male patients treated with doxycycline attended for further follow up and were all chlamydia-negative.

TABLE II Results of doxycycline treatment in patients who failed to respond to trimethoprim-sulphadiazine and to placebo

	Chlamydial culture results				
	Before treatment		After treatment		No culture performed
	+	- (or no culture performed)	+	-	
Men with NGU	17	6	1	10	12
Female partners	15	0	0	15	0

+ Positive - negative

Discussion

It is generally agreed that approximately half of the cases of NGU are caused by *C trachomatis*. Controversy still surrounds the aetiology of chlamydia-negative NGU. There is no doubt that tetracyclines and erythromycin are the most effective antimicrobials for practical use in chlamydial infections, but the effect of these antibiotics in chlamydia-negative NGU is not generally understood. However, many studies support the concept that both tetracyclines and erythromycin are equally effective in chlamydia-positive and chlamydia-negative NGU.^{2 13 15}

The criteria for cured NGU are the eradication of symptoms and signs of urethritis together with a negative culture result for *C trachomatis*. There is still no general agreement on the length of the follow-

up period after treatment of NGU. Very long follow-up periods have been advocated by some,¹⁶ but examination months after treatment is unreliable because of high default rates, spontaneous remissions, and reinfections. Furthermore, it is not common practice to re-examine patients with uncomplicated gonorrhoea many months after treatment.

Studies of placebo treatment of infections caused by known pathogens, and with obvious risks of complications, are of doubtful value. Such studies of the treatment of NGU have been carried out previously and have shown placebo treatment to be less effective than active treatment.^{17 18}

The present study was undertaken to evaluate the difference between placebo and active therapy in a well controlled series with treatment of both partners. The study was indicated because of doubts about the effect of present treatment of NGU¹ and because the need to treat NGU at all seems to be in question.

The chlamydial isolation rate in men with NGU and in their female partners was high in the present series. The results showed that the combination of trimethoprim and sulphadiazine given for two weeks was effective in treating chlamydial NGU. Compared with the results in the placebo group the difference was statistically highly significant. The treatment of the sexual partner was even more convincing. None of the initially chlamydia-positive women remained culture-positive after active treatment.

The results in the placebo group confirmed the good reproducibility of the isolation technique for *C trachomatis*, since over 80% of the initially chlamydia-positive patients still had positive chlamydial culture results four weeks after the placebo treatment had been started. Conversely, only five initially chlamydia-negative patients were found to be chlamydia-positive after placebo treatment.

The high rate of complications in patients treated with placebo in the present series caused the trial to be discontinued. All the complications occurred in chlamydia-positive patients. The risk of ascending infection in women with cervical chlamydia was unexpected; three out of 15 patients treated with placebo developed acute salpingitis.

Thus the trimethoprim-sulphadiazine combination used in the present study is effective in the treatment of chlamydial urogenital infections provided the sexual partner is treated simultaneously. The cure rate for NGU was higher than with trimethoprim-sulphamethoxazole, as reported by Danielsson and Wikström.⁴ However, in their study *C trachomatis* was not isolated and sexual partners were not treated. The high incidence of complications in patients treated with placebo in the present series serves as a

clear warning against future placebo trials in chlamydial infections.

This study was financially supported by the Finnish Medical Foundation, Helsinki, and Orion Pharmaceuticals Co, Helsinki, Finland.

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