Acta Dermatovener (Stockholm) 51: 394–396, 1971

TRIMETHOPRIM-SULPHAMETHOXAZOLE IN GONORRHOEA

S. Ullman, A.-M. Niordson and H. Zachariae

From the Departments of Dermatology and Venereology, Rigshospital, University of Copenhagen, and Marselisborg Hospital, University of Aarhus, Denmark

Abstract. One-hundred-and-four patients, 67 men and 37 women, with non-complicated gonorrhoea were treated with two dosages of 2 g sulphamethaxozole and 400 mg of trimethoprim with an eight-hour interval. Trimethoprim is a potent inhibitor of bacterial dihydrofolic acid reductase. The cure rate of this one-day treatment was 98%. One patient developed a rash 24 hours after treatment. Otherwise no side-effects were seen. Sensitivity determinations on 91 cultures of gonococci showed only one strain which was resistant to sulphonamides *in vitro*. The patient from which this strain was isolated responded to the treatment.

Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine), a potent inhibitor of bacterial dihydrofolic acid reductase (6) and sulphamethoxazole are the active compounds of the antibacterial combination Eusaprim® (Burroughs Wellcome & Co., London, England). The synergistic effect of this combination on N. gonorrhoea has been demonstrated by Darrell et al. in 1968 (6), and good results in treatment of gonorrhoea have been reported (3, 4, 14). Csonka (3) found high cure rates after a four-day course with a daily dosage of 2 400 mg sulphamethoxazole and 480 mg trimethoprim. The present paper reports on the results of a one-day treatment.

MATERIAL AND METHODS

One-hundred-and-four patients, 67 men and 37 women, with non-complicated gonorrhoea were treated with two dosages of 2 g sulphamethoxazole and 400 mg trimethoprim with an eight-hour interval, totalling ten tablets. The patients were seen at two university clinics of skin and venereal diseases, Copenhagen and Århus. Pregnant women and patients with a history of drug reactions to sulphonamides were excluded from the trial. The diagnosis of gonorrhoea was confirmed by smear and culture. Preliminary sensitivity determinations were performed on 91 cultures. The results were graded as 0, 1, 2, and 3. Degree 3 means full sensitivity to sulphonamides, in this case sulphathiazole, while grade 0 is considered resistant. This preliminary investigation was carried out at the Neisseria Department, Statens Seruminstitute, Copenhagen by means of a disc diffusion method. The strains were lyophilized with a view to a more thorough examination by means of a plate dilution procedure. It is intended to re-examine the sensitivity of the strains on different media and to use more than one sulphonamide. The sensitivity to trimethoprim, alone and together with sulphonamides, will also be studied as part of this future more extensive study.

The patients were controlled at weekly intervals and considered cured if two consecutive cultures were negative. Blood leukocyte counts were performed in 72 patients before treatment and during control.

RESULTS

The results of the treatment are shown in Table I. Two of the 100 patients, who returned after the initial visit, had positive cultures. One of these admitted having had intercourse during the observation period, and was probably reinfected. By mistake, trimethoprim-sulphamethoxazole was not repeated. The patient received penicillin. The other "failure" denied the possibility of reinfection. However, as gonococci isolated from the patient showed high sensitivity (degree 3) to sulphonamides, treatment with trimethoprim-sulphamethoxazole was readministered, and the patient was cured.

One of the strains isolated was resistant to sulphonamides, and two other strains showed a decreased sensitivity in the preliminary testings. All 3 patients, however, were cured after the one-day treatment with trimethoprim-sulphamethoxazole.

One patient developed a rash 24 hours after treatment. Forty-seven patients had a lower leuko-

Table I. *Patients treated with trimethoprim-sulphamethoxazole (Eusaprin®)*

	No. of patients treated	No. of patients followed	No. of failures
♂	67	64	2[a]
♀	37	36	—

[a] One admitted reinfection, one denied reinfection.

cyte count 1 week following treatment, while 25 had a higher count. The average leukocyte count was 6 478 cells per µl before treatment, 5 649 cells per µl after treatment. Initial high counts tended to fall, while normal counts tended to stay normal. No patient found any difficulty in taking the tablets, nor were any subjective side-effects recorded.

DISCUSSION

Treatment with trimethoprim-sulphamethoxazole seems to be highly effective in non-complicated gonorrhoea. The results of the present study are similar to the best of those observed with large doses of penicillin (7, 8) or combined treatment with penicillin or ampicillin and probenicid (7, 9, 11). The results of this one-day treatment are equal to those obtained by Csonka (3) and Schofield et al. (4), who gave trimethoprim-sulphamethoxazole for 2 to 5 days.

In venereology it may be desirable to have a one-dose treatment. However, the one-dose treatment with 500 mg trimethoprim and 2 500 mg sulphamethoxazole as used by Kvorning (10) gave only a 73 % cure rate. We therefore recommend the present two-dosage schedule with an eight-hour interval as a simple and reliable treatment in non-complicated gonorrhoea.

The results of our study confirm that at present the incidence of strains of gonococci resistant *in vitro* to sulphonamides is low (1). The incidence of strains resistant to sulphonamides decreased rapidly after the introduction of penicillin in the treatment of gonorrhoea. Already in 1954 and 1962 the sensitivity level was found to be about the same as that observed before sulphonamides were introduced into therapy (12, 13). Until 1942, when sulphonamide-resistant strains appeared, sulphonamides gave acceptable results in the treatment of gonorrhoea (2). Whether trimethoprim in combination with sulphonamides will stay potent remains to be seen. Some bacteria can fairly easily be trained to resist trimethoprim, but this change is arrested at an early stage by the presence of sulphonamide, if the organism is sensitive to both. In the few instances reported where resistance developed during treatment, the organism was originally sulphonamide-resistant (6). It is noteworthy that in our only case with a sulphonamide-resistant strain of gonococci, treatment with trimethoprim-sulphamethoxazole was successful.

In our one-day treatment there was a remarkable absence of side effects. Furthermore, in long-term treatment, side effects seem to be few (5). The lack of hematologic, hepatic and renal toxicity is to be noted, especially in view of the antifolic acid activity of trimethoprim. Whether the drug can be used safely in pregnancy is beyond the scope of this article. Teratogenic effects have been found in rats following large doses of trimethoprim (15). Williams et al. (16), however, in a study on trimethoprim-sulphamethoxazole in treatment of bacteriurea in pregnant women, have so far found no evidence of teratogenicity. Nevertheless, they conclude that further studies with careful supervision are desirable.

REFERENCES

1. Amies, C.: Sensitivity of Neisseria gonorrhoeae to penicillin and other antibiotics. Brit J Vener Dis *45:* 216, 1969.
2. Batchelor, R., Murrell, M. & Thomson, G.: Sulphathiazole in the treatment of gonorrhoea. Brit J Vener Dis *17:* 244, 1941.
3. Csonka, G.: Therapeutical trial of some genital infections with trimethoprim-sulphamethoxazole. Postgr Med J, Suppl. *45:* 77, 1969.
4. Csonka, G. & Knight, G.: Therapeutic trial of trimethoprim as a potentiator of sulphonamides in gonorrhoea. Brit J Vener Dis *43:* 161, 1967.
5. Cox, C. & Montgomery, W.: Combined trimethoprim-sulfisoxazole therapy of urinary infections. Postgr Med J, Suppl. *45:* 65, 1969.
6. Darrel, J., Garrod, L. & Waterworth, P.: Trimethoprim, laboratory and clinical studies. J Clin Path *21:* 202, 1968.
7. Eriksson, G.: Oral ampicillin in uncomplicated gonorrhoea. Acta Dermatovener (Stockholm) *50:* 451, 1970.
8. Fluker, J. & Hewitt, A.: High dosage procaine penicillin combined with ampicillin in the treatment of gonorrhoea after failure with standard procaine penicillin dosage. Brit J Vener Dis *45:* 317, 1969.

9. Jensen, P., Kvorning, S. & Nørredam, K.: Probenecid as an adjuvant in the treatment of gonorrhoea with penicillin. Brit J Vener Dis *39:* 238, 1963.
10. Kvorning, S.: Treatment of gonorrhoea with sulphamethoxazole and trimethoprim. In The synergy of Trimethoprim and Sulphonamide (ed. L. Garrod, D. James & A. Lewis). Postgr Med J, Suppl. *45:* 84, 1969.
11. Olsen, G. Å. & Lomholt, G.: Gonorrhoea treated by a combination of probenecid and sodium penicillin G. Brit J Vener Dis *45:* 144, 1969.
12. Reyn, A.: Sensitivity of *N. gonorrhoeae* to antibiotics. Brit J Vener Dis *37:* 145, 1961.
13. Schmidt, H.: Neisseria gonorrhoeae's følsomhed overfor forskellige antibiotika in vitro og den kliniske behandlingseffekt. Nord Med *68:* 1479, 1962.
14. Schofield, G., Masterton, G., Moffett, M. & McGill, M.: The treatment of gonorrhoea in women with sulphamethoxazole-trimethoprim. Postgr Med J, Suppl. *45:* 81, 1969.
15. Udall, V.: Toxicology of sulphonamide-trimethoprim combinations. Postgr Med J, Suppl. *45:* 42, 1969.
16. Williams, J., Brumfitt, W., Condie, A. & Reeves, D.: The treatment of bacteriuria in pregnant women with sulphamethoxazole and trimethoprim. Postgr Med J Suppl. *45:* 71, 1969.

Received February 11, 1971

H. Zachariae, M.D.
Department of Dermatology
Marselisborg Hospital
8000 Aarhus C
Denmark