

Sulphamethoxazole-trimethoprim in the treatment of gonorrhoea

A. J. EVANS, GILLIAN M. CHURCHER, AND R. P. HUMAN

From Plymouth General Hospital, Greenbank Road, Plymouth

Sulphamethoxazole combined with trimethoprim was introduced for the treatment of gonorrhoea by Csonka and Knight (1967). With one exception (Wright and Grimble, 1970), published reports have described a high rate of cure with this method. Recent experience in Plymouth has not been quite so satisfactory.

Material and methods

The trial took place between September, 1969, and January, 1971.

SELECTION OF PATIENTS

All patients who attended the Plymouth clinic during that period and from whom smears and cultures yielded gonococci were included in the trial with the following exceptions:

- (i) Pregnant women
- (ii) Known prostitutes
- (iii) Men with gonococcal proctitis
- (iv) Patients who had defaulted on previous occasions
- (v) Patients who would be unable to attend for regular follow-up.

A total of 182 patients (118 men and 64 women) was admitted to the trial. Of these, 65 (40 men and 25 women) defaulted before completion of 4 weeks' follow-up. Eight men were withdrawn because they developed a post-treatment non-specific urethritis and three other patients were withdrawn for other reasons (one developed primary syphilis, one was given an antibiotic for a sore throat, and one gave half his tablets away). In addition five patients were considered to have been re-infected because of the re-appearance of gonococci after admitted re-exposure with an untreated contact.

After these cases had been excluded, 101 patients remained for analysis.

TREATMENT

Commercially available combined tablets, each containing sulphamethoxazole 400 mg. and trimethoprim 80 mg. ('Bactrim'), were used. Four of these tablets were taken in the clinic and then two night and morning to a total of 22 tablets.

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FOLLOW-UP

All patients were re-examined within 1 to 3 days of starting treatment and again after 1 week, 2 weeks, and 4 weeks.

Men

Smears were made and swabs taken of any urethral discharge at each attendance. Prostatic massage was performed at 4 weeks and a smear of the prostatic fluid examined.

Women

Smears and swabs from the urethra and cervix were taken at each attendance.

CULTURE METHODS AND SENSITIVITY TESTS

Swabs were sent in transport medium (Amies, 1967) to the laboratory where they were inoculated on to chocolate agar containing 9 per cent. horse serum, vancomycin (3 µg./ml.) and colistin (7.5 µg./ml.). If delay was inevitable they were cultured in the clinic. The plates were incubated in 5 per cent. CO₂ at 37°C. for 2 days and the gonococci identified by Gram stain, oxidase reaction, and sugar-fermentation. All strains were tested for sensitivity to, among other antibiotics, penicillin (1.5 units), streptomycin (10 µg.), sulphamethoxazole-trimethoprim (25 µg.), trimethoprim (1.25 µg.), and sulphamethoxazole (23.75 µg.), using Oxoid single and multidisks. 79 strains were also tested for sensitivity to penicillin and fifteen to sulphamethoxazole and trimethoprim, by the plate-dilution method. For sensitivity testing a modified chocolate agar was used consisting of an agar base (Marshall and Kelsey, 1960) containing 8 per cent. horse blood, 8 per cent. horse serum, and 4 per cent. lysed horse blood.

Results

Of the 101 patients, 83 (47 men and 36 women) were cured, and in eighteen (12 men and 6 women) treatment was considered to have failed because gonococci of unaltered sensitivity were isolated after treatment and further sexual exposure was denied. The failure rate was thus 18 per cent. All the failures occurred during the first 14 days after starting treatment. Even if all the patients who defaulted are presumed to have been cured, the failure rate would still be 11 per cent.

Only one gonococcal strain appeared to be resistant to sulphamethoxazole and trimethoprim by the disc diffusion method, all the others showing satisfactory zones of inhibition, with synergism. Minimum inhibitory concentration (M.I.C.) testing with these two agents gave results within the expected range and no correlation was found between the MIC and the clinical response. Penicillin sensitivity testing showed that there were two populations of gonococci, those with MICs above and those with MICs below 0.1 µg./ml. The former were regarded as relatively resistant, and the latter as sensitive, to penicillin. We found, in common with Curtis and Wilkinson (1958), Reyn, Korner, and Bentzon (1958), and Jokipii and Renkonen (1970), that while the degree of resistance could not be determined accurately by the disc method, careful measurement of the zone of inhibition enabled a strain to be relegated either to the sensitive or the relatively resistant group (Figure). Strains which gave a zone of inhibition, measured from the disc edge to the margin of inhibited growth, of 10 mm. or more were shown to be sensitive, and those with a zone of less than 10 mm. to be relatively resistant.

Correlation of the results of penicillin and streptomycin sensitivity with the clinical response to sulphamethoxazole-trimethoprim (Table) showed that, of 58 patients with sensitive strains of gonococci, only one failed to respond, giving a failure rate of 1.7 per cent. Conversely, of 43 patients with strains

TABLE *Correlation between penicillin and streptomycin sensitivity of strains and therapeutic response to sulphamethoxazole and trimethoprim*

Strains	No of cases		Failure rate (per cent.)
	Treated	Failed	
Sensitive to penicillin and streptomycin	58	1	1.7
Relatively resistant to penicillin and streptomycin	43	17	39
Total	101	18	18

showing relative resistance, seventeen failed, giving a failure rate of 39 per cent.

Side-effects of the treatment were minimal. One patient developed nausea and a transient rash while taking the tablets but this was insufficient to stop her completing the course of treatment. None of the other 100 patients showed any side-effects.

The incidence of post-treatment non-specific urethritis was low. Of the 118 men treated initially, only eight (6.8 per cent.) developed this complication as opposed to 16 per cent. when a single injection of 1.2 m.u. procaine penicillin was used. Csonka (1969) reported a similar finding. It is interesting that the sulphamethoxazole-trimethoprim combination should be so ineffective in the treatment of non-specific 'urethritis' (Csonka, 1969; Carroll and Nicol, 1970) and yet be effective in reducing this complication after gonorrhoea.

Discussion

The rate of cure obtained by treating gonorrhoea with the sulphamethoxazole-trimethoprim combination in this series was 82 per cent. Wright and Grimble (1970) obtained a cure-rate of only 62 per cent. with this method but other published reports have des-

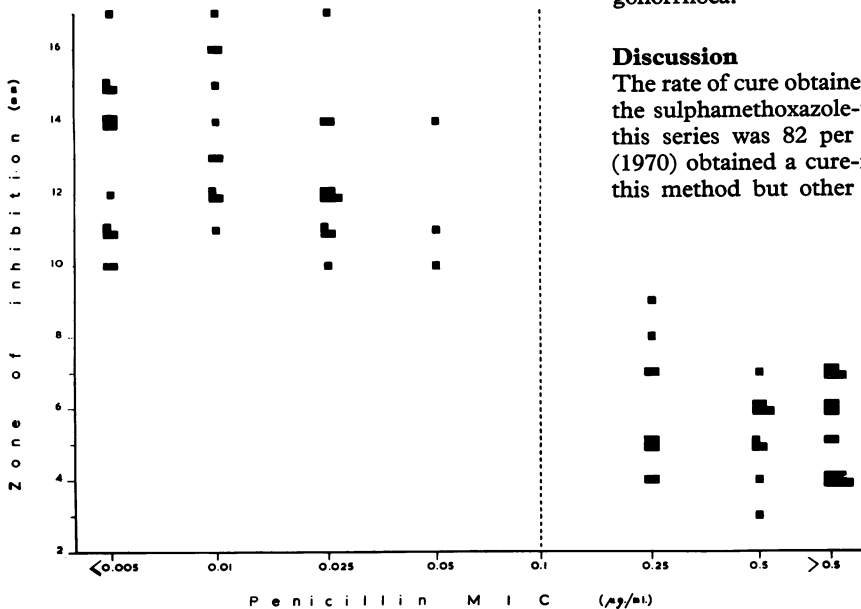


FIGURE *Comparison of MIC by plate dilution with zone of inhibition by disc to benzyl penicillin*

cribed rates in excess of 93 per cent. (Csonka and Knight, 1967; Csonka, 1969; Schofield, Masterton, Moffett, and McGill, 1969; Carroll and Nicol, 1970; Arya, Pearson, Rao, and Blowers, 1970).

Of the patients who failed with this method of treatment, 94 per cent. were infected with strains of gonococci relatively resistant to penicillin and streptomycin. This finding appears to be in direct conflict with other published results. Csonka and Knight (1967) described good results from treating with sulphamethoxazole-trimethoprim patients with gonorrhoea who had already failed to respond to penicillin. In the report from Glasgow (Schofield, Masterton, Moffett, and McGill, 1969), 27 per cent. of the strains of gonococci isolated were relatively resistant to penicillin and streptomycin and yet a cure-rate of 98.5 per cent. was obtained. Arya, Pearson, Rao, and Blowers (1970), reporting from Uganda, found that 86 per cent. of strains of gonococci showed diminished sensitivity to penicillin, but they obtained a cure-rate of 96 per cent.

If our finding is confirmed it may be of considerable practical importance. At present one of the main uses of sulphamethoxazole-trimethoprim in the treatment of gonorrhoea is as a 'second line' drug for patients who have already failed to be cured by penicillin. Such patients will usually be infected with strains of gonococci relatively resistant to penicillin and streptomycin and the findings of this series suggest that a high failure rate can be anticipated among them.

For the successful treatment of gonorrhoea it has been suggested (Garrod, 1969) that the proportion of trimethoprim in the mixture should be increased. Such a trial has not been reported and whether it would increase the rate of cure must remain speculative.

Summary

- (1) 101 patients with gonorrhoea were treated with combined tablets of sulphamethoxazole (400 mg.) and trimethoprim (80 mg.), four tablets immediately and then two twice daily to a total of 22 tablets. Eighteen patients were not cured with this regime, a failure-rate of 18 per cent.
- (2) 94 per cent. of patients who failed with this method of treatment were infected with gonococci relatively resistant to penicillin and streptomycin *in vitro*. The failure rate in patients infected with fully sensitive strains was only 1.7 per cent.
- (3) The use of this method of treatment in patients who have already failed to respond to penicillin may be inadvisable.

(4) The incidence of post-treatment non-specific urethritis in men was lower with this method of treatment than with penicillin.

(5) Toxic reactions were minimal.

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References

- AMIES, C. R. (1967) *Canad. J. publ. Hlth*, **58**, 296
- ARYA, O. P., PEARSON, C. H., RAO, S. K., and BLOWERS, R. (1970) *Brit. J. vener. Dis.*, **46**, 214
- CARROLL, B. R. T., and NICOL, C. S. (1970) *Ibid.*, **46**, 31
- CSONKA, G. W. (1969) *Postgrad. med. J.*, **45**, Suppl. (November), 'Synergy of Trimethoprim and Sulphonamides', ed. L. P. Garrod, D. G. James, and A. A. G. Lewis, p. 77
- and KNIGHT, G. J. (1967) *Brit. J. vener. Dis.*, **43**, 161
- CURTIS, F. R., and WILKINSON, A. E. (1958) *Ibid.*, **34**, 70
- GARROD, L. P. (1969) *Postgrad. med. J.*, **45**, Suppl. (November), p. 52
- JOKIPII, A. M. M., and RENKONEN, O. -V. (1970) *Chemotherapy*, **15**, 317
- MARSHALL, J. H., and KELSEY, J. C. (1960) *J. Hyg. (Lond.)*, **58**, 367
- REYN, A., KORNER, B., and BENTZON, M. W. (1958) *Brit. J. vener. Dis.*, **34**, 227
- SCHOFIELD, C. B. S., MASTERTON, G., MOFFETT, M., and MCGILL, M. I. (1969) *Postgrad. med. J.*, **45**, Suppl. (November), p. 81
- WRIGHT, D. J. M., and GRIMBLE, A. S. (1970) *Brit. J. vener. Dis.*, **46**, 34

Sulfaméthoxazole-triméthoprime dans le traitement de la gonococcie

SOMMAIRE

- (1) 101 malades atteints de gonococcie furent traités avec des comprimés associant sulfaméthoxazole (400 mg.) et triméthoprime (80 mg.), 4 comprimés d'emblée puis 2 comprimés deux fois par jour jusqu'à un total de 22 comprimés. 18 malades ne furent pas guéris avec cette prescription (taux d'échec 18 pour cent).
- (2) 94 pour cent des malades non guéris par cette méthode de traitement étaient infectés par des gonocoques relativement résistants, *in vitro*, à la pénicilline et à la streptomycine. Le taux d'échec chez les malades infectés par des souches totalement sensibles ne fut que de 1,7 pour cent.
- (3) L'emploi de cette méthode de traitement chez les malades ayant déjà échoués à la pénicilline peut être déconseillé.
- (4) Avec cette méthode de traitement, l'incidence d'urétrites non gonococciques post-thérapeutiques chez les hommes fut plus faible qu'avec la pénicilline.
- (5) Les réactions toxiques furent minimes.