

Sulphamethoxazole combined with 2-4-diamino-pyrimidines in the treatment of gonorrhoea

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THE synergistic action of the combination of sulphonamides and 2-4-diamino-pyrimidine compounds against the gonococcus has been demonstrated clinically by Csonka and Knight (1967). It was decided to reassess the clinical efficacy of the combination of trimethoprim with sulphamethoxazole* in gonorrhoea, to examine its mode of action, and to compare the effect of a combination of another pyrimidine compound, pyrimethamine, with sulphamethoxazole. The results of using trimethoprim plus sulphamethoxazole in sulphamethoxazole resistant gonorrhoea were also studied.

Material, methods, and findings

122 men with uncomplicated acute gonorrhoea were treated with the following drugs:

- (i) Ninety-seven patients were given the combination of 400 mg. sulphamethoxazole with 80 mg. trimethoprim four times a day for 5 days; 53 of them were cured, 33 relapsed, and eleven defaulted from observation.
- (ii) Fifteen patients were given 500 mg. sulphamethoxazole four times a day for 5 days; three of them were cured and twelve relapsed. The twelve cases of failure were then re-treated with the combination of 400 mg. sulphamethoxazole with 80 mg. trimethoprim four times a day for 5 days; eight of them were cured and four relapsed.

- (iii) Ten patients were given a single dose of 100 mg. pyrimethamine, which gives a satisfactory drug level during the treatment period, and 500 mg. sulphamethoxazole four times a day for 5 days; six of them were cured and four relapsed.

The test of cure was the absence of *Neisseria* in Gram-stained urethral smears, and clear voided urines in a two-glass test, 1 week and 2 weeks after starting treatment.

Study of the records of 100 male patients who had returned for observation after treatment of gonorrhoea with 900,000 units procaine penicillin intramuscularly daily for 3 days, showed that 94 had been cured and six relapsed. In the present study, 23 of those patients whose infection relapsed after sulphamethoxazole plus trimethoprim treatment were immediately treated with the same regimen of penicillin, and of these, 22 were cured and one relapsed (Table).

Trimethoprim is known to have very little anti-gonococcal activity (Csonka and Knight, 1967), and the present results show also that sulphamethoxazole had little effect in that it failed to cure twelve of fifteen cases of gonorrhoea; yet a combination of the two drugs cured eight of twelve cases failing to respond to sulphamethoxazole alone. Resistance to sulphamethoxazole appears, therefore, to be no bar to an effective action when the two drugs are combined.

It was found in this series of fifteen cases that sulphamethoxazole used alone produced a carrier state in ten out of the twelve cases of treatment failure; the number of patients on this regime was therefore restricted to a minimum. It was further found that the combination of sulphamethoxazole + trimethoprim used in 97 cases

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*Septin
Bactrim

TABLE *Contrasted cure rates in the treatment of acute gonorrhoea*

| Treatment | No. of cases | | Cures | |
|--|--------------|----------|-------|-----------|
| | Treated | Followed | No. | Per cent. |
| (a) Sulphamethoxazole alone | 15 | 15 | 3 | 20 |
| Failures on above therapy treated by trimethoprim/sulphamethoxazole | 12 | 12 | 8 | 67 |
| Trimethoprim/sulphamethoxazole in untreated patients | 97 | 86 | 53 | 52 |
| (b) Trimethoprim/sulphamethoxazole in untreated patients (Csonka and Knight, 1967) | 52 | 42 | 39 | 93 |
| (c) Pyrimethamine/sulphamethoxazole in untreated patients | 10 | 10 | 6 | 60 |
| (d) Procaine penicillin* (retrospective study) | 100 | 100 | 94 | 94 |
| Procaine penicillin* in present study's failures on trimethoprim/sulphamethoxazole | 23 | 23 | 22 | 96 |

*0.9 mega-units intramuscularly daily for three days.

produced a similar state in fifteen out of the 33 cases of relapse; additionally two of four cases of failure among the ten treated with pyrimethamine + sulphamethoxazole showed the carrier state. No adverse reactions to the drugs were noted. Because trimethoprim was known to be ineffective in gonorrhoea it was not considered ethical to use the related substance pyrimethamine alone.

Discussion

We found that trimethoprim plus sulphamethoxazole was not as effective in the treatment of gonorrhoea as Csonka and Knight (1967) appear to have found it. This could have been due to our recognition of the asymptomatic carrier state, detectable only in the early stages, at the end of the first or second week, by routine examination of urethral smears. Relapses in their series occurred within 7 days of beginning treatment, and in all such cases, the possibility of re-infection had been excluded (Curtis, 1965). If those cases of relapse which were asymptomatic are excluded from our series, it is interesting to note that our failure rates are similar to those of Csonka and Knight (1967). The finding of decreased efficacy coupled with a tendency to produce a carrier state in patients liable to default, makes the drug combination unsuitable for routine clinic use in treatment of gonorrhoea. The argument is underlined by the fact that our standard treatment with 0.9 m.u. procaine penicillin given intramuscularly daily for 3 days produces a 6 per cent. relapse rate, as against a 38 per cent. failure rate with the drug combination. The similar cure rates relating to penicillin, either as obtained in retreatment of relapsing cases in the present study or as derived from the retrospective study, suggest that the range of sensitivities of the strains of gonococci remained substantially unchanged.

In our opinion, the resistance of gonococci to sulphamethoxazole alone may be unrelated to their response to the combination of trimethoprim plus sulphamethoxazole; in our cases the combination was as effective in the sulphamethoxazole resistant cases as it was in the cases undergoing initial treatment. This could imply that sulphonamides may be inhibiting the formation of folic acid (or the later derivative in its chain) in the bacterial cell at more than one site (Wright, 1969).

Our clinical results were foreshadowed by the work *in vitro* of Garrod and Waterworth (1968), in which the minimum inhibitory concentrations of each agent and of the combination were separately determined, but it is emphasized that in our series trimethoprim plus sulphamethoxazole could be used to treat cases of gonorrhoea clinically resistant to sulphamethoxazole alone.

Inhibition of enzyme folate reductase seems to be a common property of all 2-4-diamino-pyrimidine compounds. Differences in activity of these compounds against a given target organism occur either because of slightly altered enzyme specificity or because of differences in pharmacodynamic properties (Bushby and Hitchings, 1968). These latter properties were the main consideration in selecting trimethoprim rather than pyrimethamine as an antibacterial agent (Lennox-Smith, 1968).

However, we decided that pyrimethamine plus sulphamethoxazole was worthy of a trial; first because of a similarity between the chemical structures of pyrimethamine and trimethoprim (Figure); secondly because pyrimethamine is known to be potentiated by sulphonamides, though the relevant study related to protozoal infections (Hurly, 1959; Wettingfeld, Rowe, and Eyles, 1956); and lastly because, in considering the effect against gonococci, small amounts of trimethoprim were found effective in potentiating much larger quantities of sulphonamides (Bushby, 1965; Waterworth, 1966) than was the case with other organisms (Hitchings, 1966) and there was the possibility of the same action occurring with pyri-

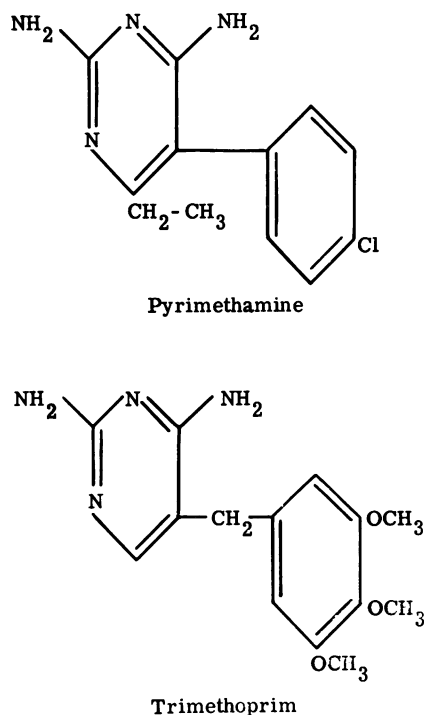


FIGURE Structural formula of pyrimethamine and trimethoprim

methamine. This last effect occurred despite the fact that the absolute degree of potentiation ('FIC') was less than that occurring with other organisms (Bushby and Barnett, 1967).

However, in practice, it was found in the present trial that pyrimethamine plus sulphamethoxazole was only moderately effective in treating gonorrhoea, as was trimethoprim plus sulphamethoxazole, both combinations giving failure rates of the order 30 to 40 per cent. We conclude that it is unjustifiable to employ these drug combinations for routine treatment of gonorrhoea.

Summary

A series of 97 male patients with uncomplicated gonorrhoea was treated with a combination of sulphamethoxazole 400 mg. plus trimethoprim 80 mg. given orally 4 times daily for 5 days. 86 cases were followed and failure of treatment occurred in 38 per cent. Furthermore, because conventional tests for cure were supplemented by examination of Gram-stained urethral smears in all cases followed, a carrier state was detected in 45 per cent. of the cases of treatment failure.

Two small series of cases of gonorrhoea in men were also investigated, as follows:

(1) Fifteen cases were treated with sulphamethoxazole 500 mg. given orally 4 times daily for 5 days; failure of treatment occurred in twelve cases, ten of which exhibited a carrier state. The twelve cases of failure were re-treated with the combination of sulphamethoxazole and trimethoprim as prescribed above; failure occurred in four.

(2) Ten cases were treated with the combination of sulphamethoxazole 500 mg. 4 times daily for 5 days with pyrimethamine in a single dose of 100 mg. Failure of treatment occurred in four cases, two of which exhibited a carrier state.

It is concluded that the unsatisfactory cure rate obtained with sulphamethoxazole plus trimethoprim and the tendency of this drug combination to produce a carrier state are major contraindications to its use in the routine treatment of gonorrhoea.

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Sulfaméthoxazole associé aux 2-4-diaminopyrimidines dans le traitement de la gonococcie

SOMMAIRE

97 hommes atteints de gonococcie non compliquée furent traités par une association de sulfaméthoxazole 400mg. + triméthoprime 80 mg. donnée par voie buccale 4 fois par jour pendant 5 jours; 86 cas furent suivis, le traitement échoua dans 38 pour cent de ceux-ci. De plus, du fait qu'aux tests conventionnels de guérison s'ajouta l'examen au Gram de la sécrétion urétrales dans tous les cas suivis, on découvrit que dans 45 pour cent des cas ayant échoués le malade restait porteur de germes.

Deux petites séries de cas de gonococcie chez l'homme furent également étudiés, comme il suit:

(1) 15 cas furent traités par le sulfaméthoxazole, 500 mg. donnés par voie buccale 4 fois par jour pendant 5 jours; le traitement échoua dans 12 cas dont 10 trouvés porteurs de germes. Ces 12 cas d'échec furent retraités avec l'association sulfaméthoxazole et triméthoprime décrit plus haut; on nota 4 échecs.

(2) 10 cas furent traités avec une association de sulfaméthoxazole, 500 mg. 4 fois par jour pendant 5 jours, avec la pyriméthamine donnée en une seule fois à la dose de 100 mg. Ce traitement échoua dans 4 cas dont 2 furent trouvés porteurs de germes.

On conclut que le taux de résultats non satisfaisants obtenus avec sulfaméthoxazole + triméthoprime et la tendance à produire un état de porteur de germes avec cette association médicamenteuse sont des contre indications majeures à son utilisation comme traitement de routine de la gonococcie.