

THERAPEUTIC TRIAL OF TRIMETHOPRIM AS A POTENTIATOR OF SULPHONAMIDES IN GONORRHOEA*

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Trimethoprim (2,4-diamino-5-(3',4',5'-trimethoxybenzyl) pyrimidine) is an antifolic acid agent developed by workers at the Wellcome Research Laboratories (Hitchings, Elion, Falco, Russell, Sherwood, and Vanderwerff, 1950a, b). It was found to inhibit the enzyme dihydrofolic acid reductase in bacteria with little or none of this activity against the corresponding enzymes of mammalian species (Hitchings and Bushby, 1961; Hitchings and Burchall, 1965). Of special interest was the observation *in vitro* and *in vivo* that the compound markedly potentiates the antibacterial activity of sulphonamides; this effect reduces the concentration of each drug required for the systemic treatment of bacterial infections and has made it possible to treat successfully infections due to sulphonamide-resistant organisms (Elion, Singer, and Hitchings, 1954, 1960).

Trimethoprim has been tried as the sole chemotherapeutic agent in a small number of patients with *Proteus* infections with encouraging results (Schneider, Schwarzenberg, Cattani, Schlumberger, Amiel, and Mathé, 1965). The combination of Trimethoprim and sulphonamide was first tested in man in a patient with *Proteus* septicaemia by Noall, Sowards, and Waterworth (1962) and in a similar case by Cooper and Wald (1964); both patients made a full recovery.

Present Investigation

Gonorrhoea in men was chosen for this trial for two reasons:

(1) The effect of antibiotic treatment can usually be simply and rapidly determined in these patients.

(2) The treatment of gonorrhoea has become less satisfactory in recent years owing to the increasing proportion of cases resistant to penicillin

and other antibiotics (Brown, 1961; Storck, Müller, and Rinderknecht, 1966).

Material and Methods

216 male patients with uncomplicated and untreated urethral gonorrhoea who were otherwise unselected, were allocated at random to one of several treatment groups which included Trimethoprim alone, sulphatriad* alone, Trimethoprim and sulphatriad in varying dosage, Gantanol (sulphamethoxazole) alone, Trimethoprim and Gantanol, Trimethoprim and Gantrisin (sulphafurazole). The patients were seen at the Venereal Disease Clinics of St. Mary's Hospital and the Central Middlesex Hospital and the diagnosis was made with the help of Gram-stained urethral smears and cultures. 43 patients defaulted early after treatment and are not further considered. Of the 173 patients followed for at least one month, 89 were from Europe, 76 were Negroes, six from Asia, and two from North America. The average age was 29 years (range 16 to 54). 102 patients were single and 71 were married. 82 patients had had no previous gonorrhoea, 83 had had one or more previous attacks of gonorrhoea, and in eight the history was uncertain.

In addition to this group of cases of untreated gonorrhoea, 29 patients who had failed to respond to the routine penicillin treatment and in some cases to other antibiotics as well, were given Trimethoprim and sulphatriad and are separately assessed.

For comparison, the results in 123 male patients with gonorrhoea treated with penicillin and 57 treated with tetracycline at these clinics during the period of trial are analysed.

Serial white blood counts were performed on thirty consecutive patients receiving Trimethoprim alone or in combination with sulphatriad. No abnormalities were observed in the total and differential count during or after treatment.

It was planned to see the patients at the end of treatment and if asymptomatic they were asked to report back at weekly intervals for 4 weeks and then monthly for the next 2 months and at any time should

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* Each 0.5 g. tablet of sulphatriad contains sulphathiazole 185 mg., sulphadiazine 185 mg., and sulphamerazine 130 mg.

the discharge recur. All recurrences were treated with a single injection of 1.2 mega units procaine penicillin unless contraindicated, when tetracycline 250 mg. four times daily for 4 days was given.

Results

The results of treatment are shown in Tables I and II.

(1) *Trimethoprim Alone* (100 mg. four times daily for 4 days). The number of patients in this group had to be curtailed when it became obvious that the compound had no appreciable effect on the clinical course of the infection. No adverse side-effects to this treatment were noted and subsequent response to penicillin or tetracycline was satisfactory.

(2) *Sulphatriad Alone* (1 g. four times daily for 4 days). The results were highly unsatisfactory and the number of patients so treated was restricted. There were no side-effects and re-treatment of failures with penicillin was successful.

(3) *Trimethoprim and Sulphatriad.* The effect of varying the doses of the two drugs was examined

and the results show that, providing the dose of sulphatriad is kept high, it allows considerable latitude in the dose of Trimethoprim without affecting the outcome. If sulphatriad is reduced to 2 g./day, the full dose of Trimethoprim is necessary to maintain effectiveness; further reduction of sulphatriad even with a full dose of Trimethoprim gave unsatisfactory results. With the optimum dose of the combination approximately 90 per cent. of patients were cured. One patient developed a rash on the last day of treatment and this was thought to be due to sulphonamide as he recalled having had a similar rash on a previous occasion when he received sulphonamide for a septic finger. Another patient complained of marked nausea and anorexia but was able to complete the course. Re-treatment of failures with penicillin or tetracycline was successful.

(4) *Gantanol Alone* (1 g. twice daily for 4 days). This sulphonamide is rapidly absorbed and slowly excreted and maintains effective serum levels after twice daily administration (Kiser, Bormel, Young, and Silverstein, 1961). The results were no better than with sulphatriad. There were no side-effects.

TABLE I
RESULTS OF TREATMENT WITH TRIMETHOPRIM, SULPHATRIAD, AND COMBINATIONS OF THESE DRUGS

Drug and Daily Dose* (mg.)		No. Treated	No. Followed	No. of Failures	Percentage Failures of Those Followed	NGU Developed
Trimethoprim	Sulphatriad					
400	—	12	10	10	100.0	0
—	4000	18	13	9	69.2	1
400	4000	48	37	4	10.8	3
200	4000	9	9	0	0.0	2
100	4000	6	5	0	0.0	0
50	4000	3	3	1	33.3	0
400	2000	8	5	0	0.0	0
200	2000	19	14	7	50.0	1
100	2000	11	9	4	44.4	2
400	1000	6	6	4	66.6	1
200	1000	1	1	1	100.0	0
Total	141	112	40		10

* The drugs were given for 4 days.

TABLE II
RESULTS OF TREATMENT WITH GANTANOL, GANTANOL + TRIMETHOPRIM, AND GANTRISIN + TRIMETHOPRIM

Drug and Daily Dose* (mg.)			No. Treated	No. Followed	No. of Failures	Percentage Failures of Those Followed	NGU Developed
Trimethoprim	Gantanol	Gantrisin					
—	2000	—	11	9	6	66.6	2
400	2000	—	52	42	3	7.1	4
400	—	2000	12	10	6	60.0	0
Total	75	61	15		6

* The drugs were given for 4 days.

(5) *Trimethoprim and Gantanol* (Trimethoprim 200 mg. and Gantanol 1 g. twice daily for 4 days). This gave a similar cure-rate to that achieved by the combination of Trimethoprim and sulphatriad, but had the advantage of needing less frequent administration. No side-effects were noted.

(6) *Trimethoprim and Gantrisin* (Trimethoprim 200 mg. and Gantrisin 1 g. twice daily for 4 days.) The results were disappointing and therefore only a few patients were treated. One patient developed glossitis after treatment.

Comparison of Penicillin and Tetracycline Therapy with Trimethoprim/Sulphatriad and Trimethoprim/Gantanol Combinations

During this study 123 unselected male patients with gonorrhoea were treated with penicillin and 57 with tetracycline, and the results were compared with those obtained with Trimethoprim/sulphatriad and Trimethoprim/Gantanol (Table III).

There is no significant difference in the cure-rate with these different treatments ($P > 0.05$). The incidence of non-gonococcal urethritis after successful elimination of gonorrhoea was significantly higher in those receiving penicillin than in those receiving the other drugs ($0.05 > P > 0.02$).

Penicillin Failures treated with Trimethoprim/Sulphatriad Combination

Fifteen patients were initially treated with 1.2-2.4 mega units procaine penicillin but failed to respond, and fourteen of these were cured with the full dose of Trimethoprim/sulphatriad.

Of another five cases of penicillin failure treated with reduced doses of Trimethoprim/sulphatriad, three were cured and two failed; one of the failures was subsequently cured with the full dose of the combined drugs, and the other with Trimethoprim/Gantanol.

Of a further nine cases of penicillin failure which also failed to respond to one or more other antibiotics, seven were cured with the full dose of Trimethoprim/sulphatriad and one defaulted.

Thus the overall results show that penicillin and other antibiotic failures respond to the Trimethoprim/sulphonamide combination as well as untreated cases.

Allergy to Penicillin Only three patients gave a clear history of allergic reactions to penicillin and they responded to Trimethoprim/sulphatriad without ill-effects.

Discussion

When assessing any treatment for gonorrhoea, the principal difficulty is to distinguish relapse from re-infection. Willcox (1964) argued in favour of evaluating therapeutic results within 1 or 2 weeks of treatment when there is less likelihood of re-infection causing confusion. It is general experience that about half of the patients who do not respond to treatment show little or no improvement from the outset and that the other half relapse after a few days, at a time when the number of re-infections is probably negligible (Dunlop, 1949; Willcox, 1964). With these considerations in mind we classed all recurrences in the first 2 weeks after treatment as failures, and the few which appeared after this period as fresh infections, provided further sexual exposure was admitted. Another source of difficulty in evaluating treatment is a high default rate. In this series a special effort was made to observe the patients for a reasonable period after treatment, and the default rate of 15 per cent. of the total of 425 patients is considered as fairly satisfactory.

Sulphonamides were successful in 80 to 90 per cent. of cases of gonorrhoea during their most effective but alas short-lived period before 1942 (Lloyd, Erskine, and Johnson, 1940; Laird, 1942).

TABLE III
COMPARISON OF TRIMETHOPRIM/SULPHATRIAD, TRIMETHOPRIM/GANTANOL, TETRACYCLINE, AND PENICILLIN IN THE TREATMENT OF GONORRHOEA

Treatment	Daily Dose (mg.)	No. Treated	No. Followed	Failures		NGU Developed	
				No.	Per cent.	No.	Per cent.
Trimethoprim/Sulphatriad	400/4000 for 4 days	48	37	4	11	3	8
Trimethoprim/Gantanol	400/2000 for 4 days	52	42	3	7	4	10
Tetracycline	1000 for 4 days	57	52	4	8	3	6
Procaine Penicillin	1.2 mega units (single injection)	123	105	12	11	21	20

Since then the results of one large clinical trial in Great Britain have been published by Dunlop (1949), who found that only 14 per cent. of 205 cases were cured by sulphathiazole given for 5 to 7 days in 1947-8. Laboratory studies by Gocke, Wilcox, and Finland (1950) showed that many strains isolated in 1947-8 in the United States were resistant to sulphadiazine. Finland and his team re-examined gonococcal strains isolated in 1953-4 (Del Love and Finland, 1955) and in 1958-9 (Hirsch and Finland, 1960) and reported on both occasions that most strains were now moderately or highly sensitive to sulphadiazine. There appear to have been no systematic clinical trials since 1949 to complement the laboratory reports, but one would have expected better results than those noted by Dunlop. Our observations suggest that sulphonamides have regained some of their former power in the treatment of gonorrhoea, though by modern standards this would be considered as quite inadequate. For the appraisal of potentiation it was an advantage to find that Trimethoprim had no noticeable effect on gonorrhoea and sulphatriad and Gantanol only a very modest one. The combined treatment gave a significantly better result than might have been expected from a simple additive action of the drug and strongly supports the original laboratory findings that Trimethoprim acts synergistically with sulphonamides. In fact, the results with the combined treatment are as good as have ever been recorded for sulphonamides in the treatment of gonorrhoea and are on a par with the present effectiveness of penicillin and tetracycline in this infection. In view of the rapidity with which sulphonamide-resistance developed in the past, this aspect will have to be carefully watched to see whether the addition of Trimethoprim prevents or delays the establishment of sulphonamide-resistant strains. We found that Gantrisin/Trimethoprim was far less potent than Gantanol/Trimethoprim. This may be due to the fact that Gantrisin gives a shorter therapeutic serum level than Gantanol and is more rapidly excreted in the urine (Kiser and others, 1961); as the absorption and excretion rate of Trimethoprim is similar to that of Gantanol these two drugs are better matched to act together.

Our experience with varying the proportion of Trimethoprim to sulphatriad showed that a comparatively small dose of Trimethoprim is effective in potentiating a much larger amount of sulphonamide and this is in line with the results of *in vitro* experiments using the gonococcus (Bushby, 1965; Waterworth, 1966). In this respect the gonococcus appears to behave differently from other organisms tested (Hitchings, 1966).

The good response to the combined treatment of patients who had failed on penicillin and sometimes on tetracycline is noteworthy as it indicates an absence of cross resistance. Patients known to be allergic to penicillin showed no side-effects to the combined treatment. It is therefore suggested that Trimethoprim/sulphonamide therapy might be useful in cases of penicillin-resistant gonorrhoea and in penicillin-hypersensitivity.

There are clearly several important questions to be investigated, such as the efficacy of this treatment of gonorrhoea in women and of rectal gonorrhoea in men, and the effect of the combined drugs on early syphilis. The possibility of giving the preparations in a single dose is receiving attention at present.

Whilst the long-term prospects of Trimethoprim/sulphonamide therapy in gonorrhoea may be uncertain, the clinical results fully substantiate the laboratory prediction of synergism and should encourage therapeutic trials also in other fields where sulphonamides are or were considered of merit such as in urinary, respiratory, and alimentary tract infections.

Summary

Earlier laboratory studies showed that 2,4-diamino-5-(3',4',5'-trimethoxybenzyl) pyrimidine (Trimethoprim), which is an antifolate agent with antibacterial properties, markedly potentiates the antibacterial activity of sulphonamides. It was decided to test for this potentiation in the treatment of gonorrhoea. Trimethoprim and sulphonamides were given singly and in combination to 245 male patients with urethral gonorrhoea. Trimethoprim alone had no therapeutic effect, sulphatriad and Gantanol (sulphamethoxazole) alone cured 31-33 per cent. of patients, Trimethoprim with sulphatriad was successful in 89 per cent., and Trimethoprim with Gantanol in 93 per cent.

These figures suggest that the significantly better results of the combined drugs were due to synergism and not to a simple additive action. The combined drugs are as successful in the treatment of gonorrhoea as sulphonamides ever were during their most effective period before 1942, and are comparable to current therapeutic results with penicillin or tetracycline.

Some of the outstanding problems and future prospects are briefly discussed.

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L'essai thérapeutique de la Triméthoprime comme un stimulant des sulfamides dans la blennorragie

RÉSUMÉ

Les études antérieures de laboratoire avaient montré que le 2,4-diamino-5-(3',4',5'-triméthoxybenzyl) pyrimidine (Triméthoprime), qui est un agent antifolique ayant des propriétés bactéricides, augmente d'une façon marquée l'activité bactéricide des sulfamides. Il fut décidé de tester cette stimulation dans le traitement de la blennorragie. La triméthoprime et les sulfamides avaient été donnés séparément et aussi en combinaison à 245 patients atteints d'urétrite blennorragique. La triméthoprime seule n'avait pas eu d'effet thérapeutique, la sulfatriade et le gantanol (sulfaméthoxazole) avaient guéri 31 à 33 pour cent des patients, la triméthoprime combinée au sulfatriade avait eu l'effet thérapeutique désiré chez 89 pour cent et la triméthoprime combinée au gantanol chez 93 pour cent.

Ces chiffres suggèrent que les résultats sensiblement supérieurs des médicaments combinés étaient dus au synergisme et non à une action simplement additive. Les drogues combinées réussissent aussi bien dans le traitement de la blennorragie que les sulfamides l'ont fait à leur période la plus efficace avant 1942, et leurs résultats thérapeutiques sont comparables à ceux de la pénicilline ou de la tétracycline obtenus aujourd'hui.

Certains des problèmes saillants et les perspectives sont brièvement discutés.