Brit. J. vener. Dis. (1970) **46**, 31

Trimethoprim/sulphamethoxazole in the treatment of non-gonococcal urethritis and gonorrhoea

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SULPHONAMIDES owe their antibacterial activity to their ability to inhibit the conversion of paraminobenzoic acid to dihydrofolic acid in the metabolic pathway leading to the synthesis of purine and ultimately of desoxyribonucleic acid (DNA). Trimethoprim* interferes with purine synthesis at the stage immediately following that affected by sulphonamides and inhibits the conversion of dihydrofolic acid to tetrahydrofolic acid.

Hitchings and Busby (1961) reported that trimethoprim markedly potentiated the antibacterial activity of sulphonamides and Csonka and Knight (1967) reported the successful use of the trimethoprim /sulphamethoxazole combination in the treatment of gonorrhoea. No reports are so far available of the use of this combination in the treatment of non-gonococcal urethritis.

Present investigations

The present trials were conducted with two objects in view:

(1) To investigate the effect of trimethoprim/sulphamethoxazole combination in the treatment of non-gonococcal urethritis.

(2) To determine the cure rate yielded by this drug combination in the treatment of gonorrhoea and to discover the stage at which gonococci disappeared from the urogenital and rectal secretions.

Pilot trials were conducted first using male cases only; subsequently a main trial was carried out in cases of gonorrhoea in both men and women.

(1) Non-gonococcal urethritis

The study group was to have consisted of twenty consecutive cases of first attacks of non-gonococcal urethritis in white male patients. In fact only fourteen men entered the trial. Diagnosis was made on findings in urethral smears and cultures and 2-glass urine tests; cure was assessed on clinical improvement and on urethral smears and 2-glass urine test appearances.

Each patient was treated with 2 tablets of trimethoprim/sulphamethoxazole given twice daily for 4 days, each tablet containing 80 mg. trimethoprim and 400 mg. sulphamethoxazole.

RESULTS

Of the fourteen patients treated, two defaulted after the first day, and of the remaining twelve cases eight showed no improvement at all (Table I).

TABLE I *Results of treatment of patients with non-gonococcal urethritis*

No. treated	*No. followed*	*Improvement*		*Failure*	
		No.	*Per cent.*	*No.*	*Per cent.*
14	12	4	33·3	8	66·7

It was felt that, as the failure rate was already eight out of twelve cases, continuation of this trial was unjustified.

(2) Gonorrhoea

(a) Pilot trial

The study comprised 46 men both coloured and white (ratio 1:2). Their ages ranged between 18 and 55 years.

Diagnosis of gonorrhoea was based on the demonstration of Gram-negative intracellular diplococci in Gram-stained smears of urethral discharge. Similar smears were made during and after treatment.

DOSAGE SCHEDULES

No. of patients	*Days*	*No. of tablets in single dose/day*
10	4	4
8	3	4
26	2	4
2	1	4

Received for publication August 18, 1969
*(1) Septrin—Burroughs Wellcome.
(2) Bactrim—Roche.

RESULTS

Of the 46 cases in the pilot study, four were classified as having relapsed after treatment; one patient defaulted after receiving a single dose of 4 tablets and no further follow-up was possible.

It was found that Gram-negative diplococci were no longer detectable in smears in the remaining 41 cases by the 2nd day, *i.e.* after a single dose of 4 tablets of trimethoprim/sulphamethoxazole (Table II).

TABLE II *Results of pilot test*

No. treated	*No. followed*	*Cure*		*Failure*		*Non-gonococcal urethritis developed*	
		No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
46	45	41	91	4	9	6	13

(*b*) *Main trial*

The study group consisted of 187 persons both coloured and white. There were 136 males (age range 17 to 58 years) and 51 females (age range 15 to 45 years). In the male cases the diagnosis of gonorrhoea was made by findings in Gram-stained urethral smears and in the female cases by urethral, cervical, and rectal smears and cultures.

DOSAGE

The tablets were the same as in the previous trials. Each patient, both male and female, received a 5-day course of 4 tablets in a single dose. A single dose of 4 tablets was given in the clinic on the first day when diagnosis had been made and the patient was asked to return on the next day. On the second day tests of cure were performed and a second dose of 4 tablets was given in the clinic. The patient was then supplied with twelve tablets with instructions to take a single dose of 4 tablets on each of the succeeding 3 days. He was asked to return 6 days later for further follow-up, and thereafter routine surveillance was undertaken.

RESULTS

Of the 187 patients in the main study, 34 (25 men and 9 women) defaulted, leaving a total of 153 (111 men and 42 women) in the trial (Table III).

Of the 111 men who completed the observation period, 102 had gonococcal urethritis and nine had gonococcal proctitis (see Table III).

In the main trial, of 111 fully-observed males, 106 were cured and five were held to be failures, giving an overall cure rate of 95·5 per cent. and a failure rate of 4·5 per cent. (Table III).

Of the 42 female patients who were fully observed, 39 were cured and three were classed as failures, giving a cure rate of 93 per cent. and a failure rate of 7 per cent.

TABLE III *Analysis of patients treated and followed-up, by sex*

Sex			*Males*	*Females*	*Total*
No. starting treatment			136	51	187
Defaulters	Total		25	9	34
	(After 2 days treatment)		(21)	(9)	
Fully treated	White		59	26	—
	Non-white		52	16	—
Total			111	42	153
Cures	Urethritis	No.	97	—	—
		Per cent.	95	—	—
	Proctitis	No.	9	—	—
		Per cent.	100	—	—
	Total	No.	106	39	145
		Per cent.	95·5	93	94·8
Failures	Urethritis	No.	5	—	—
		Per cent.	5	—	—
	Proctitis	No.	0	—	—
		Per cent.	0	—	—
	Total	No.	5	3	8
		Per cent.	4·5	7	5·2

Thus, of the total of 187 patients entering the main trial, 153 were known to have been fully treated and observed, and 145 of them were cured, so that the overall cure rate was 94·8 per cent. of 153 cases and the overall failure rate 5·2 per cent. (Table III).

Gram-negative diplococci were no longer detectable on the second day in the urethral and rectal smears of 126 (95·4 per cent.) of the 132 males, *i.e.* after a single dose of 4 tablets of trimethoprim/sulphamethoxazole (Table IV).

Negative smears and cultures were obtained on the second day in 48 (94·1 per cent.) of the 51 women, *i.e.* after a single dose of 4 tablets of trimethoprim/sulphamethoxazole (Table IV).

TABLE IV *Analysis of patients with negative smears and cultures after one day's treatment, by sex*

Sex		*Males*	*Females*
No. starting treatment		136	51
No. seen in 2nd day		132	51
Negative tests	No.	126*	48†
	Per cent.	95·4	94·1

*Males had urethral and rectal smears done.
† Females had smears and cultures done.

Discussion

Trimethoprim/sulphamethoxazole did not seem to be sufficiently effective in the treatment of non-specific

urethritis to justify continuing with the pilot trial. It may be of some relevance that studies *in vitro* (Bushby, 1969) have shown that this drug combination has little or no effect on the growth of the 'T' strain mycoplasmas, even in concentrations much in excess of those possible in tissues under clinical conditions.

Trimethoprim in combination with sulphamethoxazole in the treatment of gonococcal infection in both males and females, however, is a different proposition, and there is no doubt that this combination of drugs is very effective. In the small pilot trial the failure rate was 9 per cent., comparing well with the results of a single injection of 1·2 mega units of procaine penicillin. In the main trial there was a failure rate of only 4·5 per cent. of the 111 men who were followed-up and of 7 per cent. of the 42 women who were kept under surveillance (overall cure rate 94·8 per cent. of 153 cases.)

We do not feel able to recommend a single dose of 4 tablets of trimethoprim/sulphamethoxazole as routine therapy for gonococcal infection in all cases, but nonetheless the main trial did show that, in 95·4 per cent. of the men and 94·1 per cent. of the women, the gonococci had disappeared from the site of infection after one such dose.

Summary

Trimethoprim/sulphamethoxazole was used in the treatment of 187 cases of gonorrhoea; 136 in men and 51 in women. The tablets used each contained 80 mg. trimethoprim together with 400 mg. sulphamethoxazole, all patients being given 4 tablets taken in one dose each day for 5 days. Cure resulted in 106 (95·5 per cent.) of 111 male cases followed and in 39 (93 per cent.) of 42 female cases followed. Male patients were re-examined by smears and females by smears and cultures, during as well as after treatment, and it was found that the gonococci had disappeared from the secretions of 126 of 132 men and 48 of 51 women examined after only one day's treatment (a single dose of four tablets). A dose as small as this is not, however, recommended for general use.

This drug combination was also tried in non-gonococcal urethritis, but after a failure of treatment in eight of twelve cases a pilot trial was discontinued.

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Association de triméthoprime et de sulfaméthoxazole dans le traitement de l'urétrite non gonococcique et de la gonococcie

SOMMAIRE

Cette association fut employée dans le traitement de 187 cas de gonococcie; 136 hommes, 51 femmes. Chaque comprimé contenait 80 mg de triméthoprime et 400 mg de sulfaméthoxazole. Chaque malade recevait 4 comprimés en une fois, chaque jour, pendant cinq jours. La guérison fut obtenue chez 106 (95,5 pour cent) des 111 cas masculins suivis et dans 39 (93 pour cent) des 42 cas féminins suivis. Les hommes furent suivis par les colorations, les femmes par les colorations et les cultures, ceci aussi bien lors du diagnostic qu'après traitement. On constata que les gonocoques avaient disparus des sécrétions après seulement un jour de traitement (c'est-à-dire après une dose unique de quatre comprimés) chez 126 hommes sur 132 et chez 48 femmes sur 51. Une aussi faible dose n'est cependant pas recommandée pour l'emploi général.

Cette association médicamenteuse fut également essayée dans l'urétrite non gonococcique mais, après échec de ce traitement pour huit cas sur douze, l'étude d'orientation fut interrompue.