

COTRIMOXAZOLE IN THE TREATMENT OF NON-GONOCOCCAL URETHRITIS

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Abstract. One-hundred-and-eight patients with uncomplicated non-gonococcal urethritis have been treated with trimethoprim-sulphoxazole (Cotrimoxazole) given as two tablets twice daily for 6 days. The immediate response was good—there were only 7 failures of 90 followed (7.8%) after one week. However, subsequent recurrences provided a total of 22 within 3 post-treatment months (24.4%). Since there are no criteria to distinguish relapse from reinfection, all recurrences within 3 months were classified as failures. Although these results are not as good as obtained with a 6-day course of tetracyclines, and additional data are provided that oxytetracycline has not in any way lost its powers in non-gonococcal urethritis, they are markedly superior to those achieved with sulphonamides alone or streptomycin alone and are equivalent to those previously experienced with these two drugs given in combination.

Cotrimoxazole is thus a useful addition to the armamentarium against non-specific urethritis and especially in cases (e.g. with concurrent sores) in which syphilis is under suspicion awaiting diagnosis and in those patients known to be allergic to tetracycline but not to the sulphonamides.

HISTORICAL BACKGROUND

Prior to 1937 and the introduction of the sulphonamides the treatment of non-gonococcal urethritis was the same as for gonorrhoea, i.e. urethral irrigation. Once the sulphonamides became available and provided dramatic results against the gonococcus they came to be universally used for both conditions but as they were appreciably less effective in non-gonococcal urethritis than in gonorrhoea—their effectiveness being estimated as between 55–65% (10, 16, 17) or less (3)—irrigations were still often necessary.

The condition of non-gonococcal (or “non-specific”) urethritis only gained widespread general acceptance during World War II when the early morning urethral smears of large numbers of Allied soldiery were examined, without success, for the gonococcus. The introduction of penicillin further

emphasized its identity as this antibiotic proved strikingly effective in gonorrhoea for which the sulphonamides, on account of resistance, were by now losing their usefulness but was usually conspicuously not so in non-gonococcal urethritis, for which therefore the sulphonamides remained the drugs of choice.

After the war, streptomycin was discovered. Although this then new antibiotic could by itself apparently cure only 40–60% or fewer of cases (3, 16, 17) it was soon found that a combination of one gramme of streptomycin by injection with the traditional sulphonamide course by mouth gave results superior to those generally achieved with either drug alone and cure rates varying between 70–85% could thus be obtained (6, 9, 12, 16, 17).

During the ensuing few years the broad spectrum antibiotics were introduced and a 5–6 day course of the early conventional tetracyclines raised the cure rates to 80–85% (16, 17). However, on account of the relatively much greater expense of these newer antibiotics the use of the combination of streptomycin and sulphonamides was continued for many years especially in the larger clinics, only finally being replaced by the tetracyclines once their price began to fall and widespread resistance of the gonococcus to sulphonamides and later to streptomycin had led to their discontinuance in the treatment of gonorrhoea.

INTRODUCTION OF COTRIMOXAZOLE

The sulphonamides act on the biochemical pathway concerned with the synthesis and utilization of the bacterial folates required for the synthesis of nucleic acid precursors and some essential amino-acids. It was found that trimethoprim interferes with an enzyme at an adjacent point on this pathway and

Table 1. *Follow-up and results*

Follow-up	Followed	Satisfactory	Recurrence
0	108		
1-7 days	90	18	7
8-14 days	65	5	3
15-21 days	57	8	4 ^a
22-28 days	45	1	2
1-2 months	42	13	2
2-3 months	27	11	4
Over 3 months	12	10	2
Totals	90	66	24

^a One with Reiter's syndrome.

consequently if combined with sulphonamides would provide a synergistic effect (5). This led to the introduction of cotrimoxazole "Septrin", "Bactrim") each tablet of which contains 80 mg of trimethoprim and 400 mg of sulphamethoxazole, which sulphonamide was chosen as the two substances have a similar half-life (1).

The sulphonamides then received a new lease of life and, in gonorrhoea, provided that at least a 4-day course was given, 86-96% of cures were reported in men (2) and 98.5%, when using a 5-day course, by Schofield et al. (14) in women. The drug proved very useful in cases of gonorrhoea in which accompanying syphilis was suspect awaiting diagnosis since, like the sulphonamides, it is inactive against *T. pallidum* (2).

Few published reports are available of cases of non-gonococcal urethritis treated with this preparation, although Csonka (2) had 12 failures in a small series of 23 patients who were given three tablets twice daily for 4 days.

It has been shown that chlamydial organisms can be cultured from approximately 40% of cases of non-gonococcal urethritis (4, 11, 13). These organisms belong to sub-group A, i.e. with glycogen-containing inclusions (7) and which are sensitive to sulphonamides (8). Sulphonamides are well known to be effective in lymphogranuloma venereum due to an organism of this group (15). It was felt worthwhile, therefore, to assess the effect of combined trimethoprim and sulphamethoxazole in a larger series of cases of non-gonococcal urethritis, using a 6-day course.

CASE MATERIAL

One-hundred-and-eight male patients with uncomplicated non-gonococcal urethritis have been treated with cotrimoxa-

zole. No less than 90 were born in the United Kingdom and 18 were immigrants, 9 being Negroes (8 from the West Indies and one from West Africa) and 9 other immigrants (2 from Tunis and one each from Bahrein, Eire, Kenya, Morocco, Pakistan, the USA and Yugoslavia). Twenty-six were married, 5 others were separated, one was a widower and 76 were single. Their average age was 27.3 years (range 16-57).

Seventy-two patients had had no previous venereal incident. The remainder had experienced 65 previous attacks of non-gonococcal urethritis, 20 of gonorrhoea, 2 of syphilis and 3 of other conditions (one of warts, one of balanitis, and one of anxiety concerning venereal disease)—a total of 90 incidents.

Of the 18 immigrant patients only 3 (two West Indians and one West African) had had no previous incident while the remainder accounted for no less than 26 previous attacks of non-gonococcal urethritis, 14 of gonorrhoea and 1 of syphilis. These 41 previous incidents provided an average of 2.3 for the immigrants compared with 0.5 for those born in the United Kingdom. Although 11 of the 18 immigrants had previously been treated for non-gonococcal urethritis, as had 20 of those born in the United Kingdom, no patient was included in the study who had been treated for the condition during the previous 3 months.

The discharge had been present before treatment for 1-3 days in 25 patients, for 4-7 days in 47, 8-14 days in 17, 15-21 days in 6, 22-28 days in 2, for over this time in 7: its duration was unknown in 4 cases. Seventy-eight patients complained of some dysuria and 30 did not.

The disease had apparently been contracted from a friend in 72 instances, a stranger in 25, the wife in 10 while one patient denied sexual intercourse. The apparent incubation period was 1-3 days in 20 cases, 4-7 days in 23, 8-14 days in 18, 15-21 days in 9, 22-28 days in 6, more than 28 days in 12 and was unknown in 20 (usually because a regular partner was involved).

The Wassermann and VDRL serum tests for syphilis before treatment were both negative in 105 cases, the Wassermann was negative and the VDRL positive in one and both tests were positive in 2 cases: of the positive reactors one was a West Indian, one an other immigrant and one was born in the United Kingdom.

CASE MANAGEMENT

In all cases a Gram-stained urethral smear and a culture for the gonococcus using a charcoal impregnated swab broken into Stuart's transport medium (for later transfer to Thayer-Martin medium) were made before treatment and serological tests for syphilis were also performed.

Twenty-four cotrimoxazole tablets ('Septrin') each containing 80 mg of trimethoprim and 400 mg of sulphamethoxazole were given to the patients with instructions for two to be taken twice daily for 6 days and they were advised to refrain from sexual intercourse or alcohol at least during the first 3 weeks. They were instructed to return at approximately 1, 3, 7, and 12 weeks from the treatment date, when the urethra was examined for discharge and the urine for haze and threads. Retreatment was undertaken if the patient had visible pus-containing discharge or a hazy urine, or complaints of urethral discharge at other times (e.g. in the mornings) or of dysuria with pus cells demonstrable in the urethral

smear. Retreatment was discouraged for the existence of continuing albeit lessening dysuria by itself or for small amounts of threads if no pus was found and a potassium citrate mixture was sometimes given to anxious patients for 1 week as a holding procedure.

It was planned also to make at least one examination of the prostatic fluid during surveillance and to perform a final serum test for syphilis after 3 months.

FOLLOW-UP AND RESULTS

By no means all patients attended at the times requested but sufficient time elapsed for all patients to have been able to have done so for 3 months, had they cooperated fully. The follow-up and results achieved are shown in Table I.

As the venereal diseases clinic at which the patients were treated is the only one in a large area, and was already known to a considerable number, it is felt highly probable that the usual reason that defaulters did not return was because they were free from symptoms.

However, of 108 patients treated 90 were followed up, whom the status at last visit was satisfactory in 66 and 24 had a recurrence, 22 (22.4% of those followed) within the period of 3 months. One of the failures developed Reiter's syndrome.

With gonorrhoea it is extremely difficult to distinguish relapse from reinfection and the criteria usually applied are either a history or otherwise of further sexual exposure or the grouping as failures of all recurrences in the first one or two weeks regardless of history, and those arising after this time as recurrences. With the often longer and extremely variable incubation period of non-gonococcal urethritis even these criteria cannot be satisfactorily relied upon and therefore in this study both suspected relapses and reinfections have been grouped together as recurrences. However, all recurrences known to have occurred after 3 months from treatment are assumed to be reinfections.

Table II. Results in immigrants and non-immigrants

Group	Treated	Followed	Recurrences within 3 months	
			No.	%
Immigrants	18	13	3	23.1
Non-immigrants	90	77	19	24.7
Total	108	90	22	24.4

Table III. Results according to previous history of non-gonococcal urethritis

Previous history of N.G.U.	Treated	Followed		Recurrence	
		No.	%	No.	%
Yes	31	29	93.5	9	31.3
No	77	61	79.2	13	21.3
Total	108	90	83.3	22	24.4

It is noteworthy that only 7 failures (7.8% of those followed) occurred during the first week, thus indicating a good general initial response.

Results in immigrants and non-immigrants

No significant differences in the results were noted between immigrants and those born in the United Kingdom (Table II).

Results according to a previous history of non-gonococcal urethritis

The results in patients with and without a previous history of non-gonococcal urethritis are shown in Table III. It is noted that those who had suffered from the condition before were more likely to have a recurrence than those who had not. Such recurrences contributed to an apparently better follow-up.

Comparison with other treatments

The results are compared with those of a number of schedules involving different drugs on earlier occasions (16, 17) in Table IV.

Table IV. Comparison of results with those earlier obtained by other methods

Drug	Dosage	Treated	Followed	Retreated within 3 months	
				No.	%
Oxytetracycline	5-6 g	85	82	13	15.9
Cotrimoxazole	20 tabs.	106	90	22	24.4
Streptomycin plus sulphonomides	1.0 g+ 8-12 g	150	113	31	27.4
Sulphonamides	8-28 g	215	195	73	37.4
Streptomycin	1-4 g	164	141	65	46.1
Placebo	—	29	22	15	68.2

Table V. *Oxytetracycline in non-gonococcal urethritis*

Year	Dose (g)	Duration (days)	Treated	Followed	Recurrences within 3 months	
					No.	%
1950-55	5-6	5-6	85	82	13	15.9
1971	6	6	106	96	14	14.6

The current results with cotrimoxazole were not as good as those previously obtained with oxytetracycline (and indeed other tetracyclines) but are better than previously achieved with sulphonamides and approximately equal to those of the combination of 1.0 g streptomycin plus sulphonamides.

As the tetracycline series recorded in Table IV was undertaken more than 15 years ago it was considered desirable to compare these earlier results with those obtained in the same clinic immediately prior to the present study. The two series are compared in Table V.

No suggestion is forthcoming from this data that the clinical effectiveness of the tetracyclines in non-gonococcal urethritis has in any way diminished.

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