

Studies in non-gonococcal urethritis therapy

The long-term value of tetracycline

W. FOWLER

The General Hospital, Birmingham

In the majority of cases of non-gonococcal urethritis the cause is unknown, but it is widely believed to be an infectious agent, or agents, transmitted during sexual intercourse. Treatment, necessarily empirical, is mainly based on this belief and usually consists of sulphonamides, sulphonamides combined with streptomycin, or broad spectrum antibiotics. The latter, and in particular members of the tetracycline group, are most frequently prescribed, and it is generally considered that tetracycline provides the most effective treatment (Morton and Morrison, 1963) although equally good results were earlier claimed for combined sulphonamide and streptomycin therapy (Jelinek, 1957). The natural course of non-gonococcal urethritis is obscure, and it is not easy to make an accurate assessment of the effect of treatment. Although Holmes, Johnson, and Floyd (1967), by means of a short-term cross-over trial, demonstrated conclusively that tetracycline was more effective than a placebo, the ultimate efficacy of this treatment is unknown, and reported cure rates have varied from about 14 per cent. (Fowler, 1958) to over 80 per cent. (Willcox, 1957).

This is the report of a clinical trial carried out to determine, if possible, the real value of tetracycline, by comparing it with lactose and with streptomycin combined with sulphonamides. A computer was used to analyse the results of treatment and to see if any clinical or other features might be discerned which would indicate when specific therapy should be prescribed. The computer data sheets have been described previously (Fowler and Leeming, 1969).

The trial was started on January 1, 1965 and ended on December 31, 1965. During this time 833 cases of non-gonococcal urethritis were registered in the clinic. Initially, 650 patients were included in the trial; these had no past history of Reiter's disease, presented no obvious cause for the urethritis, had not recently suffered from gonorrhoea, and had received no treatment before admission. Subsequently, fifty cases were removed from the trial either because a cause was established, or because the condition was

not a primary urethritis, or because manifestations of Reiter's disease developed.

Computer analysis of cases showed no significant differences in race, age, marital status, previous history, possible incubation period, or duration of symptoms before admission. This information is not therefore given in detail, but can be provided if requested.

Methods

The investigative procedures were designed to cover the common causes of primary and secondary urethritis and were essentially the same as those described previously (Fowler, 1958), except that animal inoculations and blood examinations were not routine features of the present investigation.

Treatment and follow-up

Three types of treatment were used in the trial:

- (1) Tetracycline 250 mg. four times a day for 4 days.
- (2) Lactose one tablet four times a day for 4 days.
- (3) Streptomycin 1 g. followed by sulphadimidine 1 g. four times a day for 5 days.

The last treatment was given to every third patient, and the first two treatments (which were packed and numbered partly by the hospital pharmacist and partly by E. R. Squibb & Sons, Ltd.) were administered 'blind' by random distribution to the other patients.

Patients were advised to abstain from alcohol and to refrain from coitus for at least 2 weeks after apparent cure and were asked to attend for examination 7 days after starting treatment, weekly for the next 3 weeks, and fortnightly for the following 2 months.

At each examination, if urethral secretion was obtainable smears were taken. The urine was examined macroscopically and, if indicated, microscopically. Where there was a complaint of a residual morning discharge, slides were provided for the patient to make early-morning smears.

Assessments of results

For the purpose of this trial it was assumed that in the majority of cases resolution would be complete within 14 days of starting therapy and the results were assessed in this light. The criteria used were simple, and were thought to guard against any introduction of bias in recording the results of streptomycin + sulphadimidine treatment.

(1) CURE

There were no signs of urethritis at the second follow-up examination, *i.e.* 14 days after admission, and no recurrence of the disease during the next 10 weeks.

(2) RECURRENCE

There was no evidence of urethritis at 14 days, but the condition returned during the next 10 weeks.

(3) FAILED—NO RE-TREATMENT

Signs of urethritis were present at 14 days, but were less marked than before and cleared without further treatment, usually during the next week.

(4) FAILED—RE-TREATED

Signs of urethritis were present at 14 days and further treatment was prescribed at that time, or had to be prescribed later (usually if there were any signs of urethritis at the third follow-up examination).

Table I shows the number of patients given each treatment and the number who failed to re-attend.

TABLE I *Number of cases treated*

Treatment	Lactose	Streptomycin + Sulphadimidine	Tetracycline
Total cases	217	191	192
Defaulters	24	35	31
No. of cases followed	193	156	161

Results (Table II)

- (1) 21 per cent. more 'cures' occurred with tetracycline and 10 per cent. more with streptomycin + sulphadimidine than with lactose.
- (2) 72 per cent. of patients given tetracycline, 53.2 per cent. of those given combined therapy, and 36.7 per cent. of those given lactose presented no signs of urethritis at 14 days ('cures' + 'recurrences').
- (3) 72 per cent. of the tetracycline cases, 67.3 per cent. of the combined therapy cases, and 62.7 per cent. of the lactose cases recovered without

further treatment ('cures' + 'failed—no re-treatment').

In the cases classed as 'failed—no re-treatment', recovery might have been due to therapy, although it may well have been spontaneous. At the level shown in (3), the results with tetracycline therapy are significantly better than those with lactose, but not significantly better than those with streptomycin plus sulphadimidine, which, in turn, are not significantly better than those with lactose.

RECURRENCES

These were less frequent after treatment with lactose than with either of the other treatments. Statistically, the recurrence rate after lactose was lower and that after tetracycline higher than expected, while the recurrence rate for the combined therapy was of the expected order. The recurrence rate with tetracycline in this trial was almost the same as that reported by Morton and Read (1957)—148 cases treated with tetracycline and 24 recurrences. These workers were the first to point out that the recurrence rate in non-gonococcal urethritis was much higher after 'specific' than after 'non-specific' therapy.

The interval between the urethritis clearing and recurring is shown in Table III; in the majority of cases this was one month or less.

The recurrence cleared without treatment in seven patients treated initially with tetracycline, three with streptomycin + sulphadimidine, and one with

TABLE III *Recurrences*

Treatment	Interval between disease clearing and recurring (wks)				Total cases
	2-3	4	5-7	8-10	
Tetracycline	8	15	3	1	27
Lactose	1	4			5
Streptomycin + Sulphadimidine	2	6	4	2	14

TABLE II *Results of treatment*

Treatment	No. of cases	Results							
		'Cures'		'Recurrences'		'Failed—no further treatment'		'Failed—re-treated'	
		No.	Per cent.*	No.	Per cent.*	No.	Per cent.*	No.	Per cent.*
Tetracycline	161	89	55.3	27	16.7	28	17.3	17	10.5
Lactose	193	66	34.2	5	2.5	55	28.5	67	34.6
Streptomycin + Sulphadimidine	156	69	44.2	14	8.9	36	23.0	37	23.7

*Percentage of cases followed

lactose. Five patients treated with tetracycline were re-treated with other broad spectrum antibiotics and three of them were classed as 'cures'. Similar treatment was given to four patients in the streptomycin + sulphadimidine group and two were assessed as 'cures'.

Re-treatment with tetracycline

The other patients were re-treated with tetracycline. Of fifteen cases in the tetracycline group re-treated with this antibiotic, four cases were classed as 'cures', while of seven cases in the combined therapy group and four cases in the lactose group, tetracycline was credited with 'cures' in five and one case respectively (see Table VI, below).

LATE RECURRENCES

Since this trial was completed, 112 patients, *i.e.* just over 20 per cent. of those followed in the trial, have returned to the clinic for the reasons shown in Table IV.

TABLE IV *Reasons for return to clinic*

Original treatment	Diagnosis on return to clinic		
	Gonorrhoea	Non-gonococcal Urethritis	No infection
Tetracycline	10	16	9
Lactose	12	15	4
Streptomycin + Sulphadimidine	18	17	11

Of the cases of non-gonococcal urethritis shown above, the most interesting are those in which the urethritis cleared without further treatment in the trial. These cases, and the interval which elapsed between the episode of urethritis treated in the trial and the next attack, are shown in Table V.

After the late episodes shown in Table V, the urethritis recurred at least once more in three patients in the lactose group, four in the tetracycline group, and six in the combined therapy group.

TABLE VI *Re-treatment with tetracycline (250mg. 4 times a day for 4 days)*

Original treatment	No. of cases	Results				
		Cured	Failed	Relapsed	Defaulted	
Lactose	Failures	59	17	26	2	14
	Recurrences	4	1	3	0	0
Tetracycline	Failures	12	4	7	0	1
	Recurrences	15	4	8	0	3
Streptomycin + Sulphadimidine	Failures	33	13	14	2	4
	Recurrences	8	5	2	0	1

TABLE V *Late recurrences*

Original treatment	No. of cases	Interval between urethritis clearing and recurring (mths)				
		3-4	4-6	6-12	12-24	24-36
Tetracycline	14	0	1	6	4	3
Lactose	12	2	1	4	3	2
Streptomycin + Sulphadimidine	11	0	2	2	4	3

Failures re-treated

Of the 67 cases of failure in the lactose group, 59 were treated with tetracycline; fourteen of these defaulted and seventeen were assessed as 'cures' (37.7 per cent. of cases followed).

Twelve of the seventeen patients whose cases failed to respond to tetracycline initially were re-treated with this antibiotic; one of these defaulted and four were cured.

Of the 37 patients requiring re-treatment after combined streptomycin + sulphadimidine therapy 33 were given tetracycline; four defaulted and thirteen (44.8 per cent. of the cases followed) were regarded as 'cures'.

The cases of treatment failure not given tetracycline were treated with other broad spectrum antibiotics. This was successful in three out of eight cases in the lactose group, two out of five cases in the tetracycline group, and three out of four cases in combined therapy group. Table VI shows the results of tetracycline therapy in treatment failures and recurrences.

COMPLICATIONS

The only complication which occurred in this trial was acute posterior urethritis which developed in one patient treated with tetracycline, one treated with combined therapy, and two who received lactose.

INDICATIONS FOR SPECIFIC THERAPY

Analysis of age, marital status, consort, past history, clinical, urethroscopical, microscopical, and laboratory findings revealed no feature which might

indicate the cases in which 'specific' therapy would be successful. One interesting fact produced by the analysis was that the results of tetracycline therapy were significantly better in British than in West Indian or African patients ($P < 0.05$).

Discussion

The well-known tendency for non-gonococcal urethritis to clear spontaneously is well illustrated in this trial in which 34.2 per cent. of the cases in the lactose series recovered within 14 days, while another 28.5 per cent. improved by the 14th day and their urethritis cleared later, usually during the next week, without further treatment.

It is against this background that potentially 'specific' therapy has to be evaluated. If this is done at the end of the follow-up period, as is usual, the number of patients who recovered and remained well after initial treatment was 10 per cent. higher for tetracycline and 5 per cent. in the streptomycin + sulphonamide series than in the lactose series. This difference between the spontaneous recovery rate and that after treatment with tetracycline is hardly striking. However, as mentioned earlier, it is extremely doubtful if the recoveries which occurred after 14 days in the tetracycline and streptomycin + sulphonamide series (Table II—'Failed—no further treatment') were due in any way to the use of these drugs and a much better idea of the value of 'specific' therapy might be obtained from the findings at 14 days, when the full effect of such therapy is likely to be apparent. At 14 days, 72 per cent. of the patients treated with tetracycline were free from signs of urethritis, compared with 36.7 per cent. of those given lactose (Table II—'Cures' and 'Recurrences'). Subsequently, these percentages were reduced to 55.3 per cent. for tetracycline and 34.2 per cent. for lactose as the urethritis recurred in 27 of the tetracycline-treated series and five of the lactose series. It would seem, then, that tetracycline is of long-term value in between 21 and 35 per cent. of cases of non-gonococcal urethritis, depending upon whether the recurrences are relapses or re-infections.

Antibody formation in patients recovering spontaneously might explain the low recurrence rate in the lactose series, if the recurrences were in fact re-infections. The same argument can hardly be used to explain the difference between the recurrence rates following tetracycline and streptomycin + sulphonamide therapy. Nor, from the later history, is there any suggestion that the sexual habits of patients in the tetracycline series differed significantly from those of the patients in the other two series and that patients in the tetracycline group were more likely to become re-infected than the others.

In favour of relapse rather than re-infection, it can be argued that the rates at which the urethritis recurred in the three series indicated suppression of infection by streptomycin + sulphonamide and, to a greater extent, by tetracycline. That the recurrences were of short duration and cleared spontaneously in seven patients treated with tetracycline and four patients in the streptomycin + sulphonamide series is in keeping with this argument. So too is the fact, best illustrated in the tetracycline series, that the interval between the urethritis clearing and recurring was less than seven weeks in all three series and was four weeks or less in the majority of cases, and that after 4 to 6 months the rate was the same for all three treatment series. The results of re-treatment with tetracycline might have helped to answer this question of relapse or re-infection (Morrison, 1967), but too few cases were involved for this to be possible. However, the pattern of results in these cases is hardly that of tetracycline in fresh infections.

Through our lack of knowledge of the cause of non-gonococcal urethritis, it is impossible to determine with certainty whether the recurrences are relapses or re-infections, and so to ascertain the true value of tetracycline. Because of the tendency of non-gonococcal urethritis to clear spontaneously, information of real value concerning the efficacy of tetracycline cannot be obtained from the cases in which this antibiotic was given as a second treatment. However, the pattern of results in cases in the lactose series re-treated with tetracycline suggests that this antibiotic is of value in no more than 35 per cent. of cases. If, as seemed probable, the majority of recurrences were relapses, then tetracycline was of long-term value in nearer 21 than 35 per cent. of cases. This contention receives tentative support from the finding that the recurrence rate in 205 consecutive patients given double the amount of tetracycline (*i.e.* 500 mg. four times a day for 4 days) was significantly lower than the rate observed in the present trial. It would seem likely that carefully controlled trials using a varied dosage of tetracycline would help to decide if the recurrences were relapses or re-infections.

So far as streptomycin + sulphonamide is concerned, this treatment would seem to be effective in the long-term in from 10 to 16 per cent. of cases of non-gonococcal urethritis depending upon whether the recurrences are relapses or re-infections.

If, as this trial suggests, only about one-third of patients with non-gonococcal urethritis derive long-term benefit from 'specific' therapy, there is an obvious need for some means of knowing when such treatment should be prescribed. Analysis of the various clinical and other features presented by

the cases in this trial confirmed the findings of Morton and Read (1957) that none of these indicated the likely response to 'specific' therapy. Until such information is available it seems reasonable to continue the current practice of prescribing potentially 'specific' therapy to all cases of non-gonococcal urethritis of obscure origin, although it might well be that the dosage should be higher or more prolonged than at present.

Summary and conclusions

600 patients suffering from non-gonococcal urethritis of uncertain aetiology were included in a therapeutic trial carried out in an attempt to assess the long-term value of tetracycline and of streptomycin + sulphamide in comparison with placebo treatment. The trial was partly double-blind involving tetracycline or lactose, while every third patient was given streptomycin 1g. intramuscularly followed by sulphadimidine 1g. four times a day for 5 days. The dosage of tetracycline was 250 mg. four times a day for 4 days. If the cases were assessed in the usual manner 14 days after beginning treatment, the cure rate yielded by tetracycline appeared to be 72 per cent., that by streptomycin + sulphamide 53 per cent. and that by the placebo (lactose) 37 per cent. However, with a longer follow up and assuming that recurrences of urethritis were due to relapse and not to re-infection, the 'cure' rate for tetracycline fell to 55 per cent. Furthermore, by the end of the follow-up period of 3 months, it appeared that tetracycline benefited only 10 per cent. more patients than the number judged to be 'cured' by placebo treatment. Computer analysis of clinical and other data failed to indicate which cases were likely to benefit most from 'specific' treatment.

References

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Étude sur le traitement des urétrites non gonococciques. Valeur à long terme de la tétracycline

SOMMAIRE

Un essai thérapeutique fut entrepris sur 600 malades atteints d'urétrite non gonococcique d'étiologie incertaine dans le but de fixer la valeur à long terme de la tétracycline et de la streptomycine associée au sulfamide par rapport à un placebo (lactose). Cet essai fut partiellement à double insu, pour la tétracycline et le lactose, alors que chaque troisième malade recevait 1 g. de streptomycine par voie musculaire, suivie de sulfadimidine 1 g. quatre fois par jour pendant 5 jours. La dose de tétracycline fut de 250 mg. quatre fois par jour pendant 4 jours. En jugeant des cas selon la manière habituelle, 14 jours après le début du traitement, le taux de guérison obtenu avec la tétracycline sembla être de 72 pour cent, celui de la streptomycine associée au sulfamide de 53 pour cent, et de 37 pour cent pour le placebo. Cependant, en suivant les malades plus longtemps et en s'assurant que les reprises de l'urétrite étaient dues à une rechute et non à une ré-infection, le taux de 'guérison' pour la tétracycline baissa à 55 pour cent. Plus encore, à la fin d'une période de surveillance de 3 mois, il apparut que la tétracycline n'a été supérieure que de 10 pour cent seulement par rapport au nombre des cas considérés comme 'guéris' par le placebo. L'analyse mathématique des données cliniques ou autres ne réussit pas à indiquer quels sont les cas susceptibles de tirer le plus avantage du traitement 'spécifique'.