

Long-term triple tetracycline ('Deteclo') treatment of non-specific urethritis

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Non-specific urethritis (NSU) continues to be the venereologist's most perplexing problem, both diagnostically and therapeutically. The evidence available strongly suggests that the condition is due to an infection, not least because a high percentage of sufferers show prompt symptomatic response to broad-spectrum antibiotics, particularly the tetracyclines. Morton and Read (1957), and more recently Fowler (1970), have pointed out that the more favourable the response to short courses of treatment the more frequent is recurrence. Again, this observation applies particularly to the tetracyclines, although they remain the most favoured form of therapy. To offset the limitations of short courses, John (1971) used a prolonged course of oxytetracycline; he gave 500 mg. four times daily for 21 days and clearly demonstrated the advantages of this schedule over others. Recurrences requiring re-treatment after observation for 1, 2, and 3 months after treatment occurred in 5, 10, and 13 per cent., an improvement on any therapy hitherto employed. Such prolonged regimes, especially if tablets have to be taken 6-hrly, are generally considered to be beyond what some patients can cope with.

To simplify the dosage, a triple tetracycline that produces adequate blood levels with a 12-hrly dose has been used by some workers. This preparation consists of tetracycline hydrochloride, chlortetracycline hydrochloride, and demethylchlortetracycline hydrochloride in the ratio of 1:1:0.6. Each film-coated tablet contains 300 mg. of the compound. Fowler and Bernstein (1969) gave 300 mg. twice daily for 4 days, and their re-treatment rate was 34 per cent. Willcox (1972) used two dose schedules, one of 300 mg. and the other of 600 mg., twice daily for 6 days; re-treatment was required in 28.6 and 19.5 per cent. respectively during 3 months follow-up. Cohen (1973) used 300 mg. twice daily for 10 days; re-treatment was required in 13.1 per cent. after 3 months.

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The aims of the present study are 2-fold:

- (a) To assess response to 300 mg. triple tetracycline 12-hrly for 21 days.
- (b) To estimate the percentage of recurrences requiring re-treatment and to compare this finding with those following other dosages of triple tetracycline and short and prolonged courses of oxytetracycline.

Material and methods

The study group consisted of 107 men who attended because of NSU between March and September, 1972. The only element of selection was that they lived near by and were willing to co-operate. The diagnosis of NSU was made in each case by the exclusion of gonorrhoea and trichomoniasis by examination of a Gram-stained smear, a wet film, and cultures for both organisms.

The meatus was cleaned with a dry swab and the urethra 'milked' by the physician. Urethral smears were prepared from urethral discharge or scrapings. Where there was a complaint of urethral discharge but no evidence of urethritis was found, an early morning examination was carried out. If this was also negative but there was evidence of prostatitis, the case was not diagnosed as one of non-specific urethritis. Cystitis was primarily excluded by history, examination of Gram-stained smear, and macroscopic examination of the second glass of urine in the two-glass urine test.

The age range of the men was 18-53 years (average 35.5); 34 were married and 73 were single, separated, divorced, or widowed; 88 were born in the United Kingdom, eleven in the West Indies, four in Europe, and four elsewhere; 44 had a past history of NSU, eleven having had more than one attack.

The estimated incubation period was less than 10 days in seventeen, 10 days or more in 53, and doubtful or unknown in 37. The urethral discharge was purulent in 22 and mucopurulent in 85. The two-glass urine test showed a haze of pus in the first glass only in 41 and in both glasses in eleven; in the remaining 55 patients, the first glass was clear with threads or many fine shreds or specks, or a sample could not be provided.

The triple tetracycline was given in a dosage of 300 mg. 12-hrly for 21 days. The doctor making the diagnosis took time to explain to each patient the nature of the trial and the necessity of taking the tablets as near to 12-hrly as possible, and when issuing the tablets, the nurses confirmed that each man was fully conversant with the instructions. One week's supply of tablets was given at a time and each patient was examined by the doctor at each visit. After the completion of 21 days' treatment, follow-up visits were arranged at lengthening intervals up to 3 months.

The routine at each follow-up examination was similar to that used for diagnosis. When patients failed to produce a sample of urine they were instructed to attend again after holding their urine for at least 2 hours.

Where there was any doubt about the continuing presence of urethral discharge (*e.g.* a complaint of a crusted meatus in the morning, slowly resolving meatitis, or persisting inflammation of the fossa navicularis), urethral scrapings were made and/or an early morning examination was arranged. This has been departmental policy for many years.

For comparison, the records of 191 consecutive men suffering from NSU, seen during a comparable period in 1971 and treated with oxytetracycline 250 mg. 6-hrly for 4 days, were reviewed. These patients were found to match the study group in all respects except past history; their incidence of previous NSU was only half that of the present study group.

Since no evidence has been forthcoming to contradict the views of Morton and Read (1957) and Rosedale (1959), it has not been our policy to treat the consorts of men with non-specific urethritis as a routine procedure.

Results

Successful response to treatment was defined as absence of urethral discharge together with a clear urine. Difficulty occurred when the discharge cleared satisfactorily but recurred during follow-up. In preference to the terms 'relapse' and/or 're-infection', the generic term 'recurrence requiring re-treatment' has been adopted.

Of the 107 men prescribed triple tetracycline, 101 completed the prolonged regime and made at least one post-treatment follow-up visit. All showed a successful response as defined. The six men failing

to complete the therapy were all in their first attack of NSU.

Of the 101 fully treated, 58 completed at least 3 months' follow-up after completion of treatment, by which time twelve (11.9 per cent. of the 101) had had a recurrence requiring re-treatment. This finding may be compared with the series of 191 men treated with oxytetracycline, of whom twenty defaulted immediately. Of the remaining 171, 54 (31.6 per cent.) completed 3 months follow-up and 39 (22.8 per cent.) required re-treatment (Table).

The one patient who reported side-effects developed a widespread itchy rash with swollen ankles 1½ hrs after ingesting the first tablet. He continued with the course and the condition cleared without additional treatment.

Discussion

The high percentage of men completing the prolonged regime is believed to be partly due to selection, but is more probably substantially due to the time spent with each man giving a detailed explanation and securing co-operation. The part played in the reinforcement of these instructions by the nurses is believed to have been especially valuable.

It is some measure of the concern, distress, and anxiety precipitated by repeated attacks of NSU that all those in their second or subsequent attack completed treatment; those who failed to complete (6 out of 63) were all experiencing their first attack.

The initial therapeutic success rate of 100 per cent. is perhaps less remarkable as some contribution is likely to have been made by spontaneous remission over the 21 days of therapy.

As regards recurrence, it is noteworthy that the first recurrence requiring re-treatment occurred a month after the completion of initial therapy and that the number of such cases increased over the 3 months of post-treatment follow-up. This trend contrasts with that following the short 4-day course of oxytetracycline when the majority of recurrences requiring re-treatment occurred in the first month of follow-up and the numbers fell over the 3-month

TABLE *Recurrences requiring re-treatment*

Drug	No. treated	Seen after completing treatment		Re-treatment			Total	
				Number requiring re-treatment after			No.	Per cent. ^a
		No.	Per cent.	1 ^b mth	2 ^b mths	3 ^b mths		
Triple tetracycline	107	101	94	1	5	6	12	11.9
Oxytetracycline	191	171	89.5	22	11	6	39	22.8

^aOf those seen after completing treatment

^bTime after completing treatment

follow-up period (Table). The roles of relapse and re-infection in determining these trends are far from clear and require exploration. A study employing long-term concomitant treatment of wives and/or regular consorts might help to elucidate this problem.

The re-treatment rate of 11.8 per cent. after the course of triple tetracycline compares favourably with that after the regimes employing the same drug over 4, 6, and 10 days. Whether the advantage offered is matched in terms of cost-effectiveness has not been tested, but seems to be worthy of study. The same observations apply to the prolonged regime of oxytetracycline given by John (1971). The marginally better results in the present series may well be due to the relative ease of taking the triple tetracycline. Furthermore, it is generally recommended that tetracyclines should be taken on an empty stomach and this is certainly easier to achieve with a twice daily regime.

Summary and conclusions

107 men suffering from non-specific urethritis were given 300 mg. triple tetracycline ('Deteclo') 12-hrly for 21 days.

This prolonged regime was completed by 101 of them and all made a successful response. Recurrences requiring re-treatment occurred in twelve (11.9 per cent.) before the end of a 3-month follow-up which was fulfilled by 58 (57 per cent.). These findings compare favourably with those obtained by short and prolonged regimes of oxytetracycline and by a variety of shorter courses of triple tetracycline.

With its relative ease of administration, associated high cure rate, and relatively low recurrence rate, triple tetracycline ('Deteclo') twice daily for 21 days offers a very useful regime of therapy in NSU.

Further research aimed at exploring the possibility

of further reducing the recurrence rate and minimizing the cost is recommended.

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Traitement de l'urétrite non spécifique par la tétracycline triple ("Deteclo") administrée de façon prolongée

SOMMAIRE

300 mg de tétracycline triple ("Deteclo") furent données toutes les 12 heures pendant 21 jours à 107 hommes atteints d'urétrite non spécifique.

101 malades suivirent jusqu'à la fin ce traitement prolongé et y répondirent tous favorablement. Chez 12 d'entre eux (11,9 pour cent) des rechutes obligeant à un nouveau traitement survinrent avant la fin d'une période de surveillance de trois mois, respectée par 58 malades (57 pour cent). Ces résultats se comparent favorablement avec ceux que l'on obtient par des prescriptions courtes ou prolongées d'oxytétracycline et par une variété de traitement plus courts avec la tétracycline triple.

Du fait de son administration relativement facile, du haut taux de guérison et du taux de rechute relativement faible, la tétracycline triple ("Deteclo") deux fois par jours pendant 21 jours, représente une forme de traitement très utile de l'urétrite non spécifique.

Des recherches ultérieures pour explorer la possibilité de réduire le taux de rechute et le coût du traitement sont recommandées.