

Minocycline in the treatment of non-gonococcal urethritis

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The tetracyclines have a wide spectrum of usage in venereology and are used in the treatment of gonorrhoea, syphilis, lymphogranuloma venereum, granuloma inguinale, soft sore, and non-gonococcal urethritis. For the treatment of gonorrhoea and syphilis, from considerations of effectiveness, cost, and absence of a suitable injectable tetracycline preparation, penicillin has been preferred, but for more than 20 years the tetracyclines have been the first choice for the treatment of non-gonococcal urethritis. Chlortetracycline, prepared from *Streptomyces aureofaciens*, was the earliest tetracycline to be discovered by Duggar (1948). It was soon used in the treatment of non-gonococcal urethritis in two cases by Finland, Collins, and Paine (1948) in the U.S.A. and in four cases in Great Britain by Willcox and Findlay (1949). Other compounds, notably oxytetracycline and tetracycline itself, soon followed, and as their costs were reduced they gradually assumed precedence over the cheaper but less effective regimen involving an injection of streptomycin and oral sulphonamides which were then generally used in the venereal disease clinics of Great Britain.

Since the introduction of chlortetracycline there has been much laboratory research to evolve better tetracyclines, from the discovery of new antibiotics from other actinomycetes, from cultivating the mutant strains, or by the chemical modification of the natural products. Today a considerable array of tetracycline compounds are available. These include chlortetracycline, oxytetracycline, tetracycline, lymecycline, demethylchlortetracycline, clomocycline, methacycline, and doxycycline; all have been used in the treatment of non-gonococcal urethritis.

Minocycline

One of the latest to emerge is minocycline (7-dimethylamino-6-deoxy-6-demethyl tetracycline), which has the basic tetracycline structure but with the removal of the methyl and hydroxyl groups at position 6 and with a repetition of the dimethyl amino group of the 4-position at position 7 (Martell and

Boothe, 1967) (Figure). Minocycline is claimed to be more active than conventional tetracyclines against tetracycline-sensitive bacteria and highly active against certain tetracycline-resistant bacteria, especially the staphylococcus.

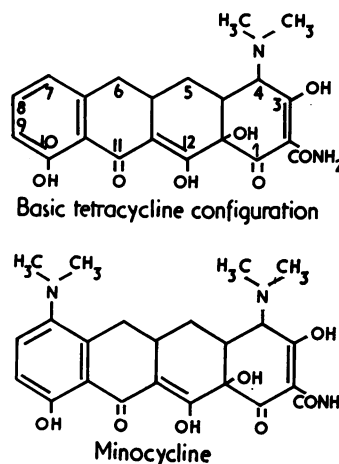


FIGURE *Chemical formulae of tetracycline and minocycline*

A number of workers, *e.g.* Thatcher, Pazin, and Domescik (1970), Pariser and Marino (1970) and Duncan, Glicksman, Knox, and Holder (1971), have used minocycline in a single oral dose in the treatment of gonorrhoea claiming success rates of 68.5 to 95.5 per cent. according to the criteria used. While clearly indicating the potent activity of minocycline against the gonococcus, these results would not appear to be as good as could be expected using single doses of penicillin or a tetracycline in multiple dosage.

However, apart from that of Fowler (1974), there are few, if any, reports of its action in non-gonococcal urethritis, which forms the subject of this paper.

As the earlier treatment regimens with oxytetracycline and other drugs which are used for comparison have usually been applied over six days this treatment has also been employed in the minocycline study.

Material

108 male patients with non-gonococcal urethritis have been treated with minocycline, the dosage comprising two 100 mg. tablets immediately followed by one twice a day for 6 days (total 1.3 gm.). The birthplace of 92 of the patients was the United Kingdom (including one with two West Indian parents), five were born in the West Indies, two were from Africa (one from West Africa and one from Tanzania), and nine were other immigrants (two each from Pakistan and Spain and one each from Eire, France, India, Italy, and Peru). 64 were single, forty were married, and four were divorced or separated. Their average age was 28.7 years (extremes 18 to 61).

Clinical particulars

Of the 108 patients, 62 had had no previous venereal incident. The remainder, however, had experienced no less than 56 previous attacks of non-gonococcal urethritis, nineteen of gonorrhoea, two of condylomata acuminata, and one each of balanitis, pediculosis pubis, and anxiety concerning venereal disease—a total of eighty incidents. Twelve of these episodes had been experienced by the sixteen immigrants (8 of whom had had no previous incident), who thus showed an average of 0.75 previous occurrences compared with 0.74 for the United Kingdom-born patients (68 episodes in 92 patients).

The duration of the discharge before treatment was 1 to 3 days in twenty cases, 4 to 7 days in 43, 8 to 14 days in nineteen, 15 to 21 days in six, 22 to 28 days in thirteen, and over 28 days in five; in two cases it was unknown. Dysuria was complained of by 79 patients but was apparently absent in 29.

The apparent incubation period was 1 to 3 days in seventeen, 4 to 7 days in 22, 8 to 14 days in seventeen, 15 to 21 days in eight, 22 to 28 days in eight, more than 28 days in six, and unknown in 30, usually because a regular consort was involved. The disease was apparently caught from a female friend in 64 cases, from a female stranger in 29, from the wife in thirteen, and from a male friend in one; one patient denied sexual intercourse for one year. Routine Wassermann and VDRL serum tests were negative in all cases.

Case management

Urethral smears were examined before treatment by Gram stain and cultures made to exclude the gonococcus using charcoal impregnated swabs broken into Stuart's transport medium for later transfer to Thayer-Martin medium. In seven other cases excluded from the study,

although the urethral smears revealed no *Neisseria* and treatment with minocycline was begun, the cultures later proved positive (6.1 per cent. of the 115 tested).

The patients were given two 100 mg. orange tablets of minocycline to swallow in the presence of the physician and a further eleven tablets, with instructions to take them twice daily to complete a 6-day course.

The patients were instructed to return after 1 week, when a urethral smear was again taken. It was planned that they be seen subsequently at 2 and then at approximately 6 and 12 weeks from treatment; at each of these visits the urethra was examined for discharge, a smear being taken if any were present, and the urine inspected for haze and threads. Re-treatment was undertaken if a pus-containing discharge was present, if significant pus was found in the smear in the absence of visible discharge, or if the urine was hazy or contained a number of persistent threads. Patients complaining of early morning discharge but without other signs were given a slide to collect material for examination. It was planned also to make at least one examination of the prostatic secretion during surveillance and to do final serum tests for syphilis at three months.

Follow-up and results

Not all of the patients attended at the times requested, but more than half were seen over periods of 3 weeks or more. Moreover, as approximately 85 per cent. of the patients were born in the United Kingdom and were treated in the sole clinic covering a wide area, it was felt that those who failed to respond to treatment would be more than usually likely to return to the same clinic. The follow-up and results obtained are shown in Table I.

Of the 108 patients treated, 96 were followed. The status was satisfactory at the last visit in eighty, three were treated for a fresh gonococcal infection, and ten (10.4 per cent. of those followed) were re-treated for a non-gonococcal infection within 3 post-treatment months.

No attempt has been made to separate relapse from re-infection. Gonorrhoea has a short incubation period, but that of non-gonococcal urethritis is very variable, perhaps from 2 days to 6 weeks, and an arbitrary distinction of relapse from re-infection based on the time of recurrence, which is frequently used in the assessment of the results of treatment of

TABLE I *Follow-up and results*

| Duration of follow-up | No. followed | Findings | | |
|-----------------------|--------------|--------------|----------------------|--------------------|
| | | Satisfactory | Gonococcal infection | Re-treated for NGU |
| 0 | 108 | — | — | — |
| 7 days | 96 | 22 | — | — |
| 8-14 days | 74 | 11 | — | — |
| 15-21 days | 63 | 5 | — | 3 |
| 22-28 days | 55 | 7 | — | 1 |
| 1-2 mths | 47 | 11 | — | 3 |
| 2-3 mths | 33 | 15 | 3 | 3 |
| More than 3 mths | 12 | 9 | — | 3 |
| Total | 96 | 80 | 3 | 13 |

gonorrhoea, is not feasible. All cases in which re-treatment was required are therefore regarded as potential failures, except those occurring after a symptom-free period of 3 months, *i.e.* beyond the duration of planned post-treatment observation.

There was nothing to suggest a higher failure rate in the small number of immigrants included in the series (Table II).

Results according to a previous history of non-specific urethritis

In an earlier reported series of cases of non-gonococcal urethritis treated with cotrimoxazole (Willcox and Sparrow, 1974), it was noted that a higher recurrence rate was encountered amongst those patients who had previously contracted non-gonococcal urethritis than those who had not. The findings in this respect in the minocycline series are shown in Table III.

Comparison with tetracyclines under similar conditions

In Table IV the results obtained are compared with those previously reported under similar conditions in the same clinic when oxytetracycline 250 mg. was given four times a day for 6 days.

Notwithstanding any considerations of cost, the treatment with minocycline not only appeared to give somewhat better results but had the added advantage that the medication was simpler, being required only twice instead of four times daily.

Comparison with other agents

The results obtained with minocycline are compared in Table V with those previously reported with other

tetracyclines and antibiotics or chemotherapeutic drugs using the same assessment criteria (see Willcox and Sparrow, 1974; Willcox, 1972).

These convincingly indicate the superiority of the tetracyclines over other agents tested, and while it is difficult to separate with statistical significance a number of individual tetracyclines the best results combined with ease of administration were clearly provided by minocycline.

It is also of interest to observe that there are no signs of developing resistance of the causative agent of non-gonococcal urethritis to tetracyclines, for the results obtained in the more recent series using oxytetracycline were comparable to those observed in the same and another clinic 16 years earlier.

Results in cases of gonorrhoea

The minocycline regimen outlined was also successful in the treatment of the seven cases of gonorrhoea which were excluded from the study. One of these patients defaulted immediately, the status at the last visit was satisfactory in four (at 7, 17, 70, and 98 days respectively), one was re-infected by his wife after 23 days, and another re-infected from a new source after 70 days. There were no known recurrences within 2 weeks.

Side-effects

The drug in the dosage given was well tolerated. The only side-effect reported by the 102 patients followed of the 115 treated was of soreness of the mouth at 1 week in two cases. One of these patients consulted

TABLE II *Results in immigrants and others*

| Group | No. treated | No. followed | Gonococcal infection | Re-treated within 3 months | |
|------------|-------------|-----------------|----------------------|----------------------------|-----------|
| | | | | No. | Per cent. |
| Immigrants | 16 | 15 ^a | — | 1 ^b | 6.7 |
| UK-born | 92 | 81 | 3 | 9 | 11.1 |
| Total | 108 | 96 | 3 | 10 | 10.4 |

^aThe one not followed was West Indian

^bWest Indian

TABLE III *Results according to previous history of non-gonococcal urethritis*

| Previous history of non-gonococcal urethritis | No. treated | No. followed | Gonococcal infection | Re-treated within 3 months | |
|---|-------------|--------------|----------------------|----------------------------|-----------|
| | | | | No. | Per cent. |
| Yes | 30 | 25 | — | 3 | 12.0 |
| No | 78 | 71 | 3 | 7 | 9.9 |
| Total | 108 | 96 | 3 | 10 | 10.4 |

TABLE IV *Minocycline compared with oxytetracycline under similar conditions*

| Drug | Total dosage (g.) | No. of doses each day | No. treated | No. followed | Re-treated within 3 months | |
|-----------------|-------------------|-----------------------|-------------|--------------|----------------------------|-----------|
| | | | | | No. | Per cent. |
| Oxytetracycline | 6.0 | 4 | 106 | 96 | 14 | 14.6 |
| Minocycline | 1.3 | 2 | 108 | 96 | 10 | 10.4 |

TABLE V Comparison with other antibiotics and chemotherapeutic drugs in order of effectiveness

| Therapeutic agent | Total dosage (g.) | No. of doses each day | No. treated | No. followed | Re-treated within 3 months | |
|--|-------------------|-----------------------|-------------|--------------|----------------------------|-----------|
| | | | | | No. | Per cent. |
| Minocycline | 1.3 | 2 | 108 | 96 | 10 | 10.4 |
| Tetracycline and oleandomycin ^a | 6 | 4 | 106 | 82 | 12 | 14.6 |
| Oxytetracycline (1971) | 6 | 4 | 106 | 96 | 14 | 14.6 |
| Oxytetracycline (1955) | 5-6 | 4 | 85 | 82 | 13 | 15.9 |
| Lymecycline | 4.9 | 4 | 101 | 65 | 11 | 16.9 |
| Triple tetracycline | 7.2 | 2 ^b | 71 | 57 | 10 | 17.5 |
| Tetracycline | 6 | 4 | 124 | 108 | 20 | 18.5 |
| Chlortetracycline | 5-6 | 4 | 115 | 108 | 20 | 18.5 |
| Spiramycin | 10-20 | 4 | 134 | 123 | 25 | 20.3 |
| Triacetyloleandomycin | 6 | 4 | 100 | 85 | 19 | 22.4 |
| Cotrimoxazole | 20 tabs | 2 | 106 | 90 | 22 | 24.4 |
| Streptomycin plus sulphonamides | 1+8-12 | 2-4 | 150 | 113 | 31 | 27.4 |
| Erythromycin | 6 | 4 | 207 | 177 | 49 | 27.7 |
| Sulphonamides | 8-20 | 2-4 | 215 | 195 | 73 | 37.4 |
| Penicillin | 1-3.6 m.u. | 1 | 70 | 65 | 26 | 40.0 |
| Streptomycin alone | 1-4 | 1 | 164 | 141 | 65 | 46.1 |
| Placebo | — | 3-4 | 29 | 22 | 15 | 68.2 |

^a 'Sigmamycin'

^b Each of two tablets

his general practitioner and was told that the lesions were due to thrush but no pathological confirmation was sought.

Summary and conclusions

108 male patients with non-gonococcal urethritis have been treated with minocycline given as two 100 mg. tablets initially, followed by one tablet twice a day over a period of 6 days (13 tablets). Of 96 patients followed, re-treatment for non-gonococcal urethritis within 3 months was undertaken in ten (10.4 per cent.).

The findings are compared with those previously reported in seven series involving six other tetracyclines and with nine other treatment regimens. All of the tetracyclines proved superior to other agents and the best results combined with simplicity of administration were obtained with minocycline.

Two patients complained of soreness of the mouth after 1 week but no other side-effects were reported.

Minocycline thus gives excellent results in the treatment of non-gonococcal urethritis. In the dosage used it was also successful against gonorrhoea in seven patients treated. It is therefore particularly useful

in cases in which gonorrhoea is suspected but not found in the smears or in which the smears cannot be read immediately.

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