

Comparison of tetracycline and minocycline in the treatment of non-gonococcal urethritis

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SUMMARY The activity of tetracycline hydrochloride and minocycline hydrochloride was compared against 12 strains of *Chlamydia trachomatis* and *Ureaplasma urealyticum*; minocycline was more active in vitro against both organisms. A group of 145 men with non-gonococcal urethritis was treated for one week with either tetracycline hydrochloride 500 mg six hourly or minocycline 50 mg twice daily. The clinical results obtained were similar: 61 of 77 (79%) men treated with tetracycline and 53 of 68 (78%) men treated with minocycline were free from urethritis one to two weeks after completing treatment. Both antibiotics were clinically effective against *C trachomatis*, but activity against *U urealyticum* was less consistent. Side effects were noted in 14 (18%) men treated with tetracycline and eight (12%) men treated with minocycline; they were predominantly gastrointestinal.

Introduction

Chlamydia trachomatis is a major cause of non-gonococcal urethritis (NGU),¹ and although the role of *Ureaplasma urealyticum* is less clear it is believed to cause some cases.² Between 25% and 50% of cases of NGU are of unknown aetiology. The tetracyclines are in general use for the treatment of NGU. *C trachomatis* is consistently sensitive,³ but between 6% and 10% of strains of *U urealyticum* are resistant, and these may cause some treatment failures.⁴ The choice of tetracycline for bacterial treatment is not unimportant; for example, tetracycline-resistant strains of *Haemophilus influenzae* are inhibited by minocycline,⁵ and anaerobic bacteria are more responsive to minocycline than to tetracycline or doxycycline.⁶ The action of tetracyclines against *C trachomatis* may be studied in cell culture. If tetracyclines are added one hour after *C trachomatis* there is little difference between the effect of tetracycline, minocycline, or doxycycline, but if they are added 48 hours after inoculation minocycline and doxycycline are much more active than tetracycline.³ The results of the action of tetracycline against *U urealyticum* in vitro are conflicting and seem to depend on the laboratory

procedure used,^{7,8} but tetracycline-resistant strains also appear to be resistant to minocycline.⁹

In this study we first compared the activity of tetracycline and minocycline against 12 fresh isolates of *C trachomatis* and *U urealyticum* and then treated a group of men with NGU with either antibiotic for one week and compared the clinical and microbiological results.

Patients and methods

The isolates of *C trachomatis* and *U urealyticum* for determination of minimum inhibitory concentrations (MICs) were obtained from unselected men with NGU. The clinical study was performed in the department of genitourinary medicine, University College Hospital, London, between September 1979 and March 1980. Men were included if (a) they were symptomatic; (b) they showed ≥ 10 polymorphonuclear leucocytes (PMNL) per high power field ($\times 100$ objective) in a Gram-stained urethral smear or ≥ 15 PMNL per high power field ($\times 40$ objective) in urine sediment, and negative cultures for *N gonorrhoeae*; (c) they did not have trichomonal or herpetic infections or intrameatal warts; (d) they had not taken antibacterial drugs for four weeks before enrolment; and (e) they had given informed assent to participate in the study.

Urethral specimens for Gram staining and for culture for *N gonorrhoeae* were collected with plastic

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loops, and endourethral swabs were used to obtain specimens for chlamydial and ureaplasma culture. Two consecutive 10 ml urine samples were passed into plastic containers and suspended material allowed to settle for five minutes at room temperature before microscopical examination for PMNL.

After NGU had been diagnosed patients were treated randomly with either tetracycline hydrochloride 500 mg six hourly or minocycline 50 mg twice daily for seven days; those taking tetracycline were advised to avoid milk products and all patients to abstain from sexual intercourse for three weeks. Follow up examinations were performed one, three, and sometimes six weeks after treatment had been completed. Patients were asked about side effects, symptoms, and further sexual intercourse, and at each attendance specimens were collected as above.

Culture for *N gonorrhoeae*, *C trachomatis*, and *U urealyticum* were by standard methods.¹⁰ Comparison of groups was by χ^2 tests with Yates's correction.

Results

SENSITIVITY STUDIES

The minimum inhibitory concentrations of tetracycline and minocycline against 12 strains of *C trachomatis* and *U urealyticum* are shown in table I. Minocycline was more active than tetracycline against *U urealyticum*, but there was little difference in their activity against *C trachomatis*.

CLINICAL STUDIES

A group of 145 men with NGU was studied, of whom 77 patients were treated with tetracycline and 68 with minocycline; their microbiological results before treatment are shown in table II.

SIDE EFFECTS

Of the 77 men treated with tetracycline, 14 (18%) reported side effects: drowsiness (4), nausea (5), epigastric pain (4), and sore tongue (1). Of the 68 treated with minocycline, eight (12%) reported side effects: drowsiness (1), epigastric pain (2), bad taste in mouth (1), flatulence (1), dizziness of less than one day's duration (2), and a fixed drug eruption (1).

RESULTS OF TETRACYCLINE TREATMENT

Tetracycline was given to 77 men with NGU; before treatment *C trachomatis* was isolated from 31 (40%) and *U urealyticum* from 28 (36%) of these men (table II). When re-examined one to two weeks after the end of treatment 61 (79%) of the 77 men were free of urethritis (table III). This result was not affected by the presence or absence of *C trachomatis* or *U urealyticum* before treatment. Thus, of the 31 men who were initially chlamydia-positive and of the 46 who were initially chlamydia-negative, 26 (84%) and 35 (76%) respectively had no urethritis after treatment. These differences were not significant ($\chi^2 = 0.291$, $p > 0.5$). Of 28 men initially ureaplasma-positive and of 49 initially ureaplasma-negative, 21 (75%) and 39 (80%) respectively showed no urethritis after treatment. These differences were not significant ($\chi^2 = 0.076$, $p > 0.5$).

TABLE I Minimum inhibitory concentrations of tetracycline and minocycline against 12 strains of *C trachomatis* and *U urealyticum*

Antibiotic	No of strains with MICs (mg/l) of:								
	0.015	0.03	0.06	0.12	0.25	0.5	1.0	2.0	>12
	<i>Chlamydia trachomatis</i>								
Tetracycline	0	0	10	2					
Minocycline	1	8	3	0					
	<i>Ureaplasma urealyticum</i>								
Tetracycline	0		0	0		1	5	5	1
Minocycline			1	9	1	0	0	0	1

TABLE II Microbiological findings in 145 patients treated for non-gonococcal urethritis

<i>Chlamydia</i> isolation	<i>Ureaplasma</i> isolation	Total No of patients	Treated with tetracycline	Treated with minocycline
Positive	Positive	22	13	9
Positive	Negative	33	18	15
Negative	Positive	38	15	23
Negative	Negative	52	31	21
Total		145	77	68

TABLE III Clinical response of men with NGU treated with tetracycline or minocycline

Drug given	No of weeks after treatment finished	Total	No of patients reattending			
			With urethritis		Without urethritis	
			Total	Admitting further sexual intercourse	Total	Admitting further sexual intercourse
Tetracycline	1-2	77	16	7	61	10
Tetracycline	≥3	48	9	9	39	14
Minocycline	1-2	68	15	5	53	6
Minocycline	≥3	40	4	3	36	17

Isolates of *C trachomatis* had been obtained from 31 of 77 men with NGU before treatment, but the organisms were not recovered from any of these patients one to two weeks after treatment. Isolates of *U urealyticum* were obtained from 28 of the 77 men before treatment. It was reisolated from four (14%) of these 28 men one to two weeks after treatment and isolated for the first time from a further two men. Of the six men yielding ureaplasmas after treatment, three had persistent urethritis and three no disease.

Re-examination at or after three weeks after treatment of 48 men who had shown no urethritis one to two weeks after treatment indicated that nine (19%) then had evidence of urethritis; all admitted to further sexual intercourse. *C trachomatis* was not recovered from any of the 48 men. *U urealyticum* was recovered from one man (previously culture-negative) without urethritis. It was not isolated from any of the nine men with urethritis, and the aetiology of their disease could not be determined.

RESULTS OF MINOCYCLINE TREATMENT

Minocycline was given to 68 men with NGU; before treatment *C trachomatis* was isolated from 24 (35%) and *U urealyticum* from 32 (47%) of these men (table II). When re-examined one to two weeks after the end of treatment, 53 (78%) of the 68 men were free of urethritis. This result was not affected by the presence or absence of *C trachomatis* or *U urealyticum* before treatment. Thus, of the 24 men who were initially chlamydia-positive and of the 44 who were initially chlamydia-negative, 22 (92%) and 32 (73%) respectively had no urethritis after treatment. These differences were not significant ($\chi^2 = 2.5, 0.5 > p > 0.1$). Of 32 men initially ureaplasma-positive and of 36 initially ureaplasma-negative, 23 (72%) and 30 (83%) respectively showed no urethritis after treatment. These differences were not significant ($\chi^2 = 0.713, p > 0.5$).

Isolates of *C trachomatis* had been obtained from 24 of 68 men with NGU before treatment, but the organisms were not recovered from any of these men one to two weeks after treatment. Isolates of *U*

urealyticum were obtained from 32 of the 68 men before treatment. It was reisolated from four of these 32 (12.5%) men one to two weeks after treatment; one showed persistent urethritis but the other three no disease.

In 40 men who had had no urethritis one to two weeks after treatment, re-examination at or after three weeks after treatment indicated that four (10%) then showed evidence of urethritis; three admitted to further sexual intercourse. *C trachomatis* was not recovered from any of these 40 men. *U urealyticum* was recovered from two of the four men with urethritis (both previously culture-negative) but from none of the 36 without urethritis.

Discussion

The in vitro results (table I) confirm previous reports of the activity of tetracycline and minocycline against *C trachomatis* and *U urealyticum*.^{3,7} The results of the clinical studies were in general consistent with this, but *C trachomatis* responded more uniformly than *U urealyticum*. All the men with chlamydia-positive NGU were culture-negative after treatment with either drug and remained so during surveillance for up to six weeks from the completion of treatment. In contrast, *U urealyticum* was reisolated one to two weeks after treatment from five of 28 men with ureaplasma-positive NGU who were treated with tetracycline and four of 32 men treated with minocycline. Reinfection after early resumption of sexual intercourse is possible (see table III), but as chlamydia were not reisolated treatment failure seems more likely.

About 80% of men with NGU were free from urethritis one to two weeks after treatment with either antibiotic, and the result was not affected by the microbiological status of the patients before treatment. On re-examination at or after three weeks after treatment urethritis was seen in some patients who had appeared to be cured earlier. This happened after treatment with either drug and did not correlate with isolation or re-isolation of *C trachomatis* or *U*

urealyticum. This recurrent disease is clearly associated with the resumption of sexual intercourse, but its cause is uncertain.

In many cases the disappearance of ureaplasmas correlated with cure, but clinical resolution accompanied by persistence of ureaplasmas and persistence of symptoms and signs of infection despite elimination of the organisms were both seen in some patients and cast doubts on the pathogenicity of *U urealyticum* in the male urethra. Further research into the complex aetiology of NGU will no doubt resolve some of these problems.

Clinically, however, both tetracycline and minocycline in the dosage used gave good results in the treatment of NGU. Side effects were not a problem with the relatively low dose of minocycline which we used and minocycline may give better compliance as its dose schedule is simple and dietary restrictions are unnecessary; its clinical and microbiological effectiveness should be evaluated in women.

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