Single-dose minocycline in the treatment of gonococcal urethritis

Clinical efficacy in relation to bacterial resistance and its effects on associated *Chlamydia trachomatis* infections

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SUMMARY Seventy-two men with gonococcal urethritis were given a single 300-mg dose of minocycline. The failure rate was 13% and the trial was terminated at an early stage. Failure was correlated with increased resistance of *Neisseria gonorrhoeae* to minocycline.

The activity of penicillin, spectinomycin, erythromycin, tetracycline, sulphamethoxazole, cefuroxime, cefotaxime, rosamicin, thiamphenicol, and piperacillin against *N. gonorrhoeae* were examined *in vitro*. With the exception of spectinomycin, parallel patterns of resistance to the other antibiotics and minocycline were found. Resistance to spectinomycin was not found, confirming the usefulness of this antibiotic in the treatment of gonorrhoea. The incidence of PGU was significantly lower after a single dose of minocycline than in previous studies.

Introduction

Antibacterial drugs have been used for the treatment of gonorrhoea for 40 years, but the emergence of resistant strains of *Neisseria gonorrhoeae* has necessitated the continuous re-evaluation of treatment. Because of resistance, some formerly effective agents—such as the sulphonamides and streptomycin—can no longer be used. Penicillin and its derivatives are still generally effective, but the curative dosage has progressively increased and may before long, even with added probenecid, reach the limit of what is clinically practicable. This problem has been aggravated by the recent advent of the β -lactamase-producing gonococcus, which presents a continuing threat for the future. Sooner or later it will no longer be possible to use penicillin derivatives for the treatment of gonorrhoea, and it is prudent to plan for this eventuality, firstly by *in-vitro* studies of newer antibacterial agents and then by clinical trials.

In view of the importance of *Chlamydia trachomatis* in the aetiology of post-gonococcal urethritis (PGU) (Richmond *et al.*, 1972) and cervicitis (Oriel, 1977), any new antibiotic regimen

would ideally be active against both micro-organisms. The tetracyclines theoretically fulfil this criterion. Earlier studies of the effect of minocycline in gonorrhoea have produced variable results (Duncan *et al.*, 1971; Masterton and Schofield, 1976). We report in this paper a small trial of the effect of a single dose of 300 mg on both gonococcal urethritis in men and the incidence of PGU and the presence of *C. trachomatis*. The high failure rate in the treatment of gonorrhoea led to the curtailment of the clinical trial, but the obvious relationship between treatment failure and raised minimum inhibitory concentration (MIC) for the infecting strain of *N. gonorrhoeae* led us to investigate the current incidence of tetracycline resistance in this area. We also took the opportunity to determine the MIC of a number of newer antibiotics and to compare these with the drugs currently in use in this hospital, namely penicillin and spectinomycin. Erythromycin was included both because of its high activity against *C. trachomatis* and for comparison with rosamicin, which is a new macrolide.

Patients and methods

All the patients attended the Department of Genitourinary Medicine, University College Hospital, London, between October 1977 and January 1978. After local and general examination, a specimen of

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urethral discharge was taken and spread on a slide for Gram staining and microscopy. A second specimen was inoculated on to a culture medium for *N. gonorrhoeae*. A cottonwool-tipped wire endourethral swab was then inserted 4-5 cm into the urethra and the swab transferred to 2 ml transport medium for *C. trachomatis*. A first-catch urine specimen was examined for evidence of pyuria and serological tests for syphilis were performed.

A presumptive diagnosis of gonorrhoea was made on the basis of the presence of intracellular Gram-negative diplococci on the urethral smear, and patients were then treated with 3 × 100 mg tablets of minocycline given under supervision in the clinic in a single dose. The diagnosis of gonorrhoea was confirmed by culture in every case. Each patient was asked to return for follow-up examinations three, seven, and 14 days after therapy; there was some individual variation in follow-up attendance, but in many cases it was possible to keep patients under surveillance for longer periods. At each attendance symptoms were recorded and microscopy of urethral specimens, culture for *N. gonorrhoeae* and *C. trachomatis*, and examination of the urine for pyuria were repeated.

ASSESSMENT OF PGU

PGU was defined as the presence of ≥20 polymorphonuclear leucocytes (PMN) in at least three fields of a Gram-stained urethral smear examined at a magnification of ×900 (Oriel *et al.*, 1975), or of similar numbers of PMN in urinary sediment of first-catch urine specimens seven or more days after treatment, or of both.

LABORATORY METHODS

Gonococci were isolated from primary cultures on Thayer-Martin medium containing vancomycin, colistin, and trimethoprim. Pure cultures were then stored at -70°C until tested in batches. The first 57 strains were isolated from patients in the clinical trial but after this had been terminated all strains of *N. gonorrhoeae* isolated in the Department of Microbiology were included in the *in-vitro* studies.

MICs were determined by the plate-dilution method using Isosensitest agar (Oxoid) with 5% lysed horse blood added. The inoculum was prepared by growing the organism overnight on Columbia blood agar (Oxoid) and suspending the resulting growth in a small volume of broth until visibly turbid. The plates were inoculated with a multiple replicator using the suspensions diluted approximately 1/100.

All cultures were incubated overnight at 37°C in a CO₂ incubator. A pharmaceutical preparation of penicillin (Glaxo) was used and the remaining drugs were made available as follows: tetracycline,

minocycline, and piperacillin (Lederle Laboratories); sulphamethoxazole (Roche); spectinomycin (Upjohn Ltd); cefuroxime (Glaxo); cefotaxime (Roussel); rosamycin (Schering); erythromycin (Eli Lilly); and thiamphenicol (Infarzam).

Cell culture for *C. trachomatis* was by the method of Reeve *et al.*, (1975) using McCoy cells pretreated with idoxuridine.

Results

EFFECT OF MINOCYCLINE ON GONOCOCCAL URETHRITIS

A group of 72 men with gonococcal urethritis confirmed by culture were treated with a single dose of minocycline 300 mg. Of these men, 59 were heterosexual and 13 homosexual. The drug was well tolerated and no side effects were seen in any of the men. Three patients were reinfected with gonorrhoea during the follow-up period and were removed from the trial, thus leaving a study group of 69 (56 heterosexual and 13 homosexual). Of these, 60 (87%) were cured; 11 were followed up for up to one week (with one negative post-treatment culture result), 27 for up to two weeks (two negative culture results), 14 for up to three weeks (three negative culture results), and eight for up to four weeks (four negative culture results). Nine (13%) of the 69 men had a relapse; all denied further sexual intercourse since treatment. Positive culture results for *N. gonorrhoeae* were obtained from eight of these men on their first follow-up examination seven days after treatment and from one man on the second follow-up examination nine days after treatment, the first post-treatment culture result having been negative.

There was a marked correlation between the clinical results and the MIC estimations for the infecting strains of *N. gonorrhoeae*. Of the eight isolates available for study from men who had a relapse, an MIC of 0.5 µg/ml was found for six, the mean MIC being 0.67 µg/ml; there was no change in MIC for the organisms reisolated from four of these patients. Of the 41 isolates available from men who had been cured, an MIC of 0.5 µg/ml was found for only two, the mean MIC being 0.14 µg/ml.

MIC DETERMINATIONS

The results of the MIC determinations for *N. gonorrhoeae* are presented in the Figure as cumulative percentages of strains inhibited by increasing concentrations. A total of 171 strains were tested against each drug except for piperacillin, cefotaxime, and cefuroxime, for which only 65 strains were tested.

Although minocycline was four times more active than tetracycline against sensitive strains, strains

Figure Sensitivity of 171 strains of *N. gonorrhoeae* to (a) penicillin, minocycline, and tetracycline; (b) spectinomycin and sulphamethoxazole; (c) rosamicin, erythromycin, and thiamphenicol; and of 65 strains to (d) piperacillin, cefotaxime, and cefuroxime. Graphs show cumulative percentages of strains inhibited by increasing concentrations of each drug.

resistant to the latter showed a similar or even greater relative increase in the MIC of tetracycline (Figure, a). The curve for penicillin has been included in each graph for comparison and it is obvious that the curves for not only the tetracycline but also for piperacillin, cefotaxime, cefuroxime, sulphamethoxazole, erythromycin, and thiamphenicol all run nearly parallel to this and that for rosamicin is similar but the increase in resistance is less. In contrast, the line for spectinomycin is almost vertical; no resistance was seen and all strains were inhibited by 16 µg/ml.

EFFECT OF MINOCYCLINE ON *C. TRACHOMATIS*
Isolates of *C. trachomatis* were obtained from 10 (17%) of 58 heterosexual men with gonorrhoea but from none of 13 homosexual men. One specimen (from a heterosexual man) was contaminated. None of the three men removed from the trial because of reinfection by *N. gonorrhoeae* yielded chlamydiae before treatment. Of the 10 men who had chlamydia-positive isolates before minocycline therapy, nine had negative results subsequently, the follow-up periods being three days for one man (one negative culture result) eight days for one man (one

negative culture result), nine days for one man (two negative culture results), 14 days for one man (two negative culture results), and 17 days for two men (three negative culture results). *C. trachomatis* was reisolated from one man 14 days after treatment, cell culture having given a negative result after eight days. One other man, chlamydia-negative before treatment, yielded chlamydiae 19 days later; both these men denied sexual intercourse since treatment.

EFFECT OF MINOCYCLINE ON PGU

Of the 72 men with gonorrhoea treated with minocycline, 45 were followed for seven or more days; 36 were heterosexual, of whom six were chlamydia-positive before but not after treatment, one chlamydia-positive both before and after treatment, and one, chlamydia-negative before treatment, yielded chlamydiae subsequently. Nine men were homosexual and were chlamydia-negative throughout. Of the 45 men, eight (18%) developed PGU, including the two who yielded chlamydiae after treatment. None of the five men who were chlamydia-positive before but not after treatment developed PGU.

Discussion

In vitro, minocycline shows considerable activity against *N. gonorrhoeae*; an MIC of ≥ 0.5 $\mu\text{g/ml}$ was found for only 8% of 171 strains. Although minocycline was four times as active as tetracycline against sensitive strains, those resistant to the latter showed a similar, or greater, relative increase in the MIC of minocycline. The parallel patterns of resistance of *N. gonorrhoeae* to tetracycline, minocycline, erythromycin, rosamicin, and thiamphenicol is interesting and suggests the possibility of difficulties in the use of these antibiotics in the event of treatment failure with penicillin. The lack of such a pattern with spectinomycin confirms the value of this drug in the therapy of penicillin-resistant gonorrhoea.

Minocycline is highly active against the gonococcus but it is clear that treatment with a single dose of 300 mg is unlikely to be successful if the infecting strain shows increased resistance to tetracycline. A failure rate of 13% indicated to us that minocycline in this dosage has only a limited place in the treatment of gonorrhoea. Other workers in Britain have obtained better clinical results, probably because of local variations in the prevalence of tetracycline-resistant strains.

A relationship between treatment failure with single-dose regimens of tetracyclines and the susceptibility of the infecting strains has been described for methacycline and doxycycline by

Wiesner *et al.*, (1973). These, and our own, results show that the clinician who is contemplating a single-dose regimen of a tetracycline for the treatment of gonorrhoea should be aware of the pattern of gonococcal resistance in his own area and keep this under constant review. Whether there has been a general increase in the resistance of *N. gonorrhoeae* to tetracyclines in Britain is not known, but this has undoubtedly occurred in other countries. It seems unlikely that single-dose treatment of gonorrhoea with any tetracycline will prove a satisfactory alternative to present remedies if, and when, these can no longer be used.

The incidence of PGU after minocycline therapy (18%) was markedly lower than we have observed in comparable studies using single-dose ampicillin (37%) or spectinomycin (40%) (Oriel *et al.*, 1976; Oriel *et al.*, 1977). This is probably largely due to the activity of minocycline against *C. trachomatis*, the major cause of PGU. In the present study, chlamydiae were reisolated from only one of eight men after treatment. The periods of follow-up, however, were short, and possibly longer periods of observation would have shown more recurrences; there is evidence from *in-vitro* studies which would support this idea (Ridgway *et al.*, 1978). Nevertheless, from our results chlamydial genital infections might possibly be successfully treated with shorter courses of therapy with minocycline than those presently in use.

Further studies of single-dose treatment of synchronous genital infections with *N. gonorrhoeae* and *C. trachomatis* are desirable, and any new antibacterial agent developed for the treatment of gonorrhoea should be evaluated in this way, with the object of reducing the incidence of PGU and of persistent chlamydial genital infection in women. Rosamicin is highly active against *C. trachomatis*, with an MIC of 0.015 $\mu\text{g/ml}$, and might be considered for this purpose if the drug is clinically effective in gonorrhoea. Conversely, thiamphenicol, with an MIC for *C. trachomatis* of 0.5 $\mu\text{g/ml}$, would not be expected to be an effective treatment in this respect.

The high activity of piperacillin (a carbenicillin) and cefotaxime (a cephalosporin) against the gonococcus must be regarded as primarily of academic interest; the place of these antibiotics is more likely to be in the treatment of serious infections with Gram-negative bacilli.

References

- Duncan, N. C., Glicksman, J. M., Knox, J. M., and Holder, W. R., (1971). Treatment of gonorrhoea with a single oral dose of minocycline. *British Journal of Venereal Diseases*, 47, 364-366.

- Masterton, G. and Schofield, C. B. S. (1976). Minocycline hydrochloride (Minocin) as a single-dose oral treatment of uncomplicated gonorrhoea in men. *British Journal of Venereal Diseases*, **52**, 43-45.
- Oriel, J. D. (1977). In *Non-gonococcal Urethritis and Related Infections*, p. 230. Edited by D. Hobson and K. K. Holmes. American Society for Microbiology: Washington DC.
- Oriel, J. D., Reeve, P., Thomas, B. J., and Nicol, C. S. (1975). Infection with *Chlamydia* group A in men with urethritis due to *Neisseria gonorrhoeae*. *Journal of Infectious Diseases*, **131**, 376-382.
- Oriel, J. D., Ridgway, G. L., Reeve, P., Beckingham, D. C., and Owen, J. (1976). The lack of effect of ampicillin plus probenecid given for genital infections with *Neisseria gonorrhoeae* on associated infection with *Chlamydia trachomatis*. *Journal of Infectious Diseases*, **133**, 568-571.
- Oriel, J. D., Ridgway, G. L., Tchamouloff, S., and Owen, J. (1977). Spectinomycin hydrochloride in the treatment of gonorrhoea: its effect on associated *Chlamydia trachomatis* infections. *British Journal of Venereal Diseases*, **53**, 226-229.
- Reeve, P., Owen, J., and Oriel, J. D. (1975). Laboratory procedure for the isolation of *Chlamydia trachomatis* from the human genital tract. *Journal of Clinical Pathology*, **28**, 910-914.
- Richmond, S. J., Hilton, A. L., and Clarke, S. K. R. (1972). Chlamydial infection. Role of *Chlamydia* sub group A in non-gonococcal and postgonococcal urethritis. *British Journal of Venereal Diseases*, **48**, 437-444.
- Ridgway, G. L., Owen, J., and Oriel, J. D. (1978). The antimicrobial susceptibility of *Chlamydia trachomatis* in cell culture. *British Journal of Venereal Diseases*, **54**, 103-106.
- Wiesner, P. J., Holmes, K. K., Sparling, P. F., Maness, M. J., Bear, D. M., Gutman, L. T., and Karney, L. L. (1973). Single doses of methacycline and doxycycline for gonorrhoea: a co-operative study of the frequency and cause of treatment failure. *Journal of Infectious Diseases*, **127**, 461-466.