

Cefuroxime, thiamphenicol, spectinomycin, and penicillin G in uncomplicated infections due to penicillinase-producing strains of *Neisseria gonorrhoeae*

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SUMMARY The use of cefuroxime and thiamphenicol in uncomplicated gonococcal infection was studied in 562 women confined to a clinic to preclude reinfection before cultural confirmation of cure. Cefuroxime was as effective as spectinomycin in the treatment of infections due to penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) and was significantly more effective than 4.8 units of aqueous procaine penicillin G with probenecid among non-penicillinase-producing (non-PPNG) strains. Thiamphenicol was highly effective against PPNG, but the failure rate in infections with non-PPNG was high and appeared to be related to the minimum inhibitory concentrations of thiamphenicol. This rate was not, however, significantly higher than that for PPNG strains. Thiamphenicol might therefore be used as an alternative for infections due to PPNG strains. If, however, thiamphenicol is used widely, selection of more resistant strains and thus an increasing proportion of failures may be expected.

Introduction

The progressive increase in the penicillin resistance of *Neisseria gonorrhoeae* and the appearance of penicillinase-producing (PPNG) strains in particular has created an urgent need to reevaluate the treatment of gonococcal infection and find effective alternative treatment regimens. Among the drugs used in the treatment of infection with PPNG strains spectinomycin showed good results with failure rates of 0.3-7% with a 2 g dose and no failure with a 4 g dose.^{1,2} The unusually high failure rates of 32-54.4% with tetracycline preclude its use in infections due to PPNG strains.^{1,2} β -lactam antibiotics, including cefuroxime and cefoxitin, are highly active against PPNG strains *in vitro*,^{3,4} and cefoxitin is clinically efficacious.⁵ Thiamphenicol, a methyl-sulphone derivative of chloramphenicol, was effective in uncontrolled studies on patients with uncomplicated

gonococcal infection due to non-PPNG strains,⁶ but has not been tested against PPNG strains.

We report the results of a controlled study of the effectiveness of a single dose of either cefuroxime or thiamphenicol in the treatment of uncomplicated gonococcal infection in women due to PPNG and non-PPNG strains. Treatment responses were compared with those with currently recommended standard regimens of spectinomycin and penicillin for PPNG and non-PPNG strains respectively. Treatment failures were correlated with the minimum inhibitory concentration (MIC) of the drug used against the infecting strain.

Patients and methods

The study was undertaken at the Social Hygiene Clinic in Balibago, Angeles City, Pampanga, Philippines. Cultures from the endocervix and the urethra of registered "hospitality girls" were screened weekly and processed at the Clark Air Force Base laboratory. Patients with positive culture results for *N gonorrhoeae* were enrolled in the study after the study protocol had been explained and written

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consent obtained. The patients were stratified into two groups based on the production or non-production of penicillinase by the infecting strain and randomly assigned to a treatment regimen.

TREATMENT REGIMENS

Infections due to PPNG were treated with (a) 2 g spectinomycin intramuscularly; (b) 1.5 g cefuroxime intramuscularly with 1 g probenecid orally; or (c) 2.5 g thiamphenicol orally. Infections due to non-PPNG strains were treated with (a) 4.8 mega units of aqueous procaine penicillin G intramuscularly with 1 g probenecid orally; (b) 1.5 g cefuroxime intramuscularly with 1 g probenecid orally; or (c) 2.5 g thiamphenicol orally. All drugs were given in a single dose.

A culture specimen was obtained from the endocervix, urethra, rectum, and pharynx before treatment to confirm gonococcal infection. Only cases with confirmed gonococcal infections based on a positive pretreatment culture result were evaluated. To exclude possible reinfection before the test-of-cure culture all the patients were confined in the clinic for three days after treatment. A test-of-cure culture sample was obtained from the same sites on the third day after treatment, based on the finding that 96% of failures were detectable within the first three days after treatment.⁷ Treatment was considered a failure if *N gonorrhoeae* was grown in the posttreatment culture.

LABORATORY STUDIES

Isolation, identification, and determination of penicillinase production by *N gonorrhoeae* were performed according to standard procedures.⁸ The minimum inhibitory concentrations (MICs) of cefuroxime, thiamphenicol, penicillin, and spectinomycin for the isolates from patients treated with these drugs were determined by the standard agar dilution method using chocolate Mueller-Hinton medium enriched with Isovitalex and an improvised replicator which delivers an inoculum containing 10^{-3} ml of a standardised suspension in trypticase soy broth calibrated to contain approximately 10^7 cfu/ml.⁹ The plates were incubated overnight in 5% CO₂ in a candle jar at 35°C and the MIC determined as the lowest concentration of the antibiotic inhibiting the growth of the test organism.

Results

STUDY POPULATION

There were 715 infections (224 due to PPNG and 491 due to non-PPNG strains) among the 544 patients enrolled in the study. One hundred and forty six of

the 715 screening cultures initially positive for *N gonorrhoeae* (55 for PPNG and 91 for non-PPNG strains) were negative before treatment and thus unsuitable for analysis. Seven patients randomly allocated to treatment with penicillin because of negative preliminary test results for penicillinase production were later found to harbour PPNG strains and so were excluded from the analysis. Thus among 428 patients with confirmed gonococcal infection only 562 infections were based on a positive pretreatment culture result. Of these 428 patients, 98 were treated more than once because of reinfections, which were common in the women studied. The age range of the patients was 13-30 years with a median age of 21 years. Of the 562 cases studied, only 336 (59.8%) of the total were accompanied by symptoms, which have been reported separately.¹⁰

TREATMENT

The bacteriological response in 169 infections due to PPNG and 393 infections due to non-PPNG strains is shown in table I; the overall treatment failure rates were 1.2% and 5.9% respectively. Among the PPNG infections, no treatment failures occurred with spectinomycin while the failure rate with cefuroxime and thiamphenicol was 1.7% with each drug. Treatment with penicillin failed in all seven patients with PPNG infections who were previously thought to be infected with non-PPNG strains and were excluded from the analysis. In infections due to non-PPNG strains treatment with the standard regimen of penicillin failed in 11 of 127 (8.7%) cases including one of orogenital infection. In contrast, the treatment failure rates with cefuroxime and thiamphenicol were 1.5% and 7.5% respectively.

The overall treatment failure in patients with PPNG infections was significantly lower compared with those with non-PPNG infections ($t=2.39$, $p<0.05$) owing to the significant difference in failure rates with the standard regimens of spectinomycin

TABLE I Bacteriological response after single-dose treatment of "hospitality girls" with uncomplicated gonorrhoea

Antimicrobial	Total No of cases	Treatment failures	
		No	%
PPNG strains:			
Spectinomycin	52	0	
Cefuroxime	59	1	1.7
Thiamphenicol	58	1	1.7
Total	169	2	1.2
Non-PPNG strains:			
Aqueous procaine penicillin G	127	11	8.7
Cefuroxime	133	2	1.5
Thiamphenicol	133	10	7.5
Total	393	23	5.9

PPNG = penicillinase-producing *Neisseria gonorrhoeae*

for the first and penicillin for the last ($t=2.20$, $p<0.05$). No difference was noted in the two groups of patients treated with either cefuroxime ($t=0$, $p>0.05$) or thiamphenicol ($t=1.61$, $p>0.05$).

No differences in treatment response were noted among the different regimens in patients with PPNG infections ($\chi^2=0.899$, $p>0.05$). In contrast, there was a significant difference in the response among the treatment regimens in patients with non-PPNG infections ($\chi^2=7.05$, $p<0.05$) where a significantly lower treatment failure rate occurred with cefuroxime than with penicillin ($t=2.66$, $p<0.05$) and with thiamphenicol ($t=2.25$, $p<0.05$). No difference was observed between treatment with penicillin and with thiamphenicol ($t=0.35$, $p>0.05$).

CORRELATION OF MICs AND TREATMENT FAILURES

The relationship of treatment failures with the MICs of spectinomycin, penicillin, thiamphenicol, and cefuroxime for the isolates from patients treated with these drugs is shown in table II. Treatment with cefuroxime failed in one case with a PPNG infection (MIC of $\leq 0.1 \mu\text{g/ml}$) and in two with non-PPNG infections (MICs of 0.5 and $1.0 \mu\text{g/ml}$). The failures in the cefuroxime treatment group were too few for valid correlation with the MICs.

One patient with a PPNG infection had an MIC of $1.0 \mu\text{g/ml}$ of thiamphenicol and failed to respond to treatment with this drug. In non-PPNG infections the treatment failure rate with thiamphenicol was significantly higher ($t=2.46$, $p<0.05$) when the infecting strains had MICs of $\geq 2.0 \mu\text{g/ml}$ (eight out of 47) than when the MICs were $\leq 1.0 \mu\text{g/ml}$ (one out of 47).

No treatment failures occurred with spectinomycin in 52 infections due to PPNG strains despite the fact that this drug was relatively less active in vitro than the others. Treatment failures with penicillin occurred only in those patients whose isolates had

penicillin MICs of $\geq 1.0 \mu\text{g/ml}$; the failure rate was progressively higher with increasing MICs of penicillin ranging from two out of 16 (12.5%) to three out of six (50%), with an overall failure rate of 11 out of 52 (21.1%) for these patients. Regression analysis showed a significant positive correlation between failure rate and MIC of penicillin at this level ($r=0.91$, $p<0.05$, $Y=16.914 + 12.792 \log_e X$ where X is the MIC value and Y the failure rate).

SIDE EFFECTS

Side effects of treatment were noted in 23 of 562 (4.1%) cases, the lowest rate of 1.1% occurring with thiamphenicol and the highest of 6.3% with penicillin compared with 5.8% for spectinomycin and 5.2% for cefuroxime. The side effects of penicillin and cefuroxime were similar, presenting most frequently as headache, pruritus, rash, and fever. Three patients had headache, one had dizziness, and another had malaise with spectinomycin, while one patient had pruritus and another had dizziness with thiamphenicol.

Discussion

Treatment with cefuroxime plus probenecid was highly effective against infection due to PPNG strains and was superior to that with penicillin against non-PPNG strains. The reported failure rates in this study of 1.7% and 1.5% for PPNG and non-PPNG infections respectively were similar to those reported previously in women infected with non-PPNG strains¹¹ and are comparable with those with spectinomycin. This result may be attributed to the excellent in vitro activity of cefuroxime against *N gonorrhoeae*. More than half of the isolates had an MIC of $\leq 0.1 \mu\text{g/ml}$ cefuroxime/ml, and this was true for both PPNG (31 out of 42) and non-PPNG (55 out of 95) isolates.

TABLE II *Minimum inhibitory concentration (MIC) of drugs against penicillinase-producing and non-penicillinase-producing strains of N gonorrhoeae (PPNG and non-PPNG) correlated with treatment failures. (Values are number of isolates; number of treatment failures are given in parentheses)*

MIC ($\mu\text{g/ml}$)	Cefuroxime		Thiamphenicol		Spectinomycin	Penicillin
	PPNG	Non-PPNG	PPNG	Non-PPNG	PPNG	Non-PPNG
≤ 0.1	31 (1)	55				10
0.2	5	23	3	6		13
0.5	4	8 (1)	8	9		10
1.0	0	5 (1)	12 (1)	32 (1)		23 (3)
2.0	2	4	12	32 (6)	3	16 (2)
4.0			1	12 (2)	5	7 (3)
8.0			1	3	15	6 (3)
16.0					13	
32.0					3	
Not tested	17	28	21	39 (1)	13	42
Total	59 (1)	133 (2)	58 (1)	133 (9)	52	127 (11)

Thiamphenicol appears to be highly effective against PPNG strains but not significantly better than penicillin against non-PPNG strains. While the failure rate with non-PPNG infections was high and appeared to be related to the MIC of thiamphenicol for these infecting strains, this was, however, not significantly greater than the failure rate with thiamphenicol for PPNG strains. These results indicate that thiamphenicol might be used as an alternative drug particularly for PPNG infections. As thiamphenicol resistant strains may be selected out with a more extensive use of the drug in the community an increasing proportion of failures may be expected.

Unlike chloramphenicol thiamphenicol does not undergo glucuronidation in the liver.¹² For this reason it has a longer half life and correspondingly longer in vivo activity, which explains the clinical efficacy of a single dose in the treatment of uncomplicated gonorrhoea. Current data from uncontrolled clinical studies have shown that only the reversible dose-related suppression of erythropoiesis is associated with thiamphenicol.¹³ Bone marrow aplasia, which is attributed to the inhibition of DNA synthesis, is unlikely to occur with thiamphenicol since it has very little effect on DNA synthesis in contrast with chloramphenicol, which in high concentrations inhibits DNA synthesis in vitro.¹⁴ More importantly, no haematological changes occurred in patients receiving single dose treatment for gonococcal infection.⁶

The failure rate of 8.7% with penicillin in the treatment of non-PPNG infections is disturbingly high and correlates with the high MICs of penicillin among these strains. In this series, 61.2% of non-PPNG strains from patients treated with penicillin had MICs of 1.8 µg/ml penicillin, and all failures occurred in this group only. The overall failure rate of 21.1% in this group was higher than 13.5% previously reported for organisms with MICs of ≥ 1.0 µg/ml penicillin.¹⁵ With such a high level of penicillin resistance in the population, penicillin may not be appropriate in the dose currently recommended as primary treatment for gonococcal infection even when it is due to non-PPNG strains. Furthermore, in a community such as this, where the incidence of PPNG strains is approximately 40%,⁸ the routine use of penicillin cannot be recommended unless penicillinase production can first be excluded by an appropriate screening test.

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