

Double-blind trial of amoxycillin and ampicillin plus probenecid in the treatment of gonorrhoea in men

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SUMMARY In a double-blind study amoxycillin 3 g or ampicillin 3 g plus probenecid 1 g were randomly administered as a single oral dose to 160 men with uncomplicated gonococcal urethritis. The cure rate for each drug group was 98.6%. Tolerance to oral medication was good and no evidence of allergy or toxicity to either drug was shown. No case of post-gonococcal urethritis was observed over a 14-day follow-up period. Thus, both drug regimens proved very effective in treating uncomplicated gonococcal urethritis in men.

Introduction

Amoxycillin is an acid-stable, semisynthetic penicillin which is closely related to ampicillin having a similar antibacterial spectrum and level of activity (Sutherland and Rolinson, 1971; Sutherland *et al.*, 1972). When taken orally amoxycillin is better absorbed, and mean peak serum concentrations at two hours are twice those of an equivalent dose of ampicillin (Croydon and Sutherland, 1970). Amoxycillin is not converted into ampicillin in the body.

Several trials using both amoxycillin and ampicillin in the treatment of uncomplicated gonorrhoea have been reported (for example, Karney *et al.*, 1974). No such studies, however, have been reported from the Caribbean area. For this reason a double-blind study was conducted to compare the efficacy of ampicillin 3 g plus probenecid 1 g with amoxycillin 3 g, since the latter had been shown to give the best results.

Patients and methods

Men with uncomplicated gonorrhoea attending the sexually transmitted diseases section of the Comprehensive Health Centre during the period October to December 1977 were admitted to the study. A presumptive diagnosis was made by microscopical identification of typical Gram-

negative intracellular diplococci in smear specimens taken from the urethra. At the same time, material for culture was plated on Thayer-Martin (VCN) media and incubated immediately in candle-extinction jars at 37°C. These were examined for oxidase-positive colonies after 24 and 48 hours' incubation. Gram-stains from typical colonies were examined microscopically.

Patients were then each given a packet of medication containing six 500-mg capsules of either ampicillin plus probenecid or amoxycillin plus placebo tablets to take under direct supervision of a senior member of the clinic staff. The drugs had been coded in random order and prepacked by the manufacturers in identical white capsules, placebo probenecid tablets being used with the amoxycillin. The coding used was unknown to the clinic staff. Patients who were allergic to penicillin, or who were unlikely to attend for follow-up, were excluded from the trial.

Patients were advised to refrain from sexual intercourse and to return to the clinic three, seven, and 14 days after treatment. At each visit, they were questioned about symptoms and sexual contacts and the original instructions were repeated. Gram stains and cultures were also repeated as performed at the first visit.

Treatment was considered to have failed if presumptive gonococci were found in smears and cultures within 14 days in patients who denied further sexual intercourse. Patients were considered to be reinfected if gonococci were found and sexual intercourse admitted to during this follow-up period.

Post-gonococcal urethritis (PGU) was diagnosed if

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a urethral discharge containing at least 10 leucocytes per field on microscopy using a $\times 100$ objective was present.

Results

Eighty patients were treated with each regimen. Their age range was similar to that of patients with gonorrhoea seen routinely at the clinic (Table 1).

Table 1 Ages (in years) of the two treatment groups

Drug regimen	Mean	Median	Mode	Range
Amoxycillin	27.6	24.2	23	16-77
Ampicillin plus probenecid	26.2	24.2	20	16-48

They were all negroes in the lower socioeconomic class. Four patients in the group treated with amoxycillin and two in the group treated with ampicillin and probenecid were married; the remaining patients were single. The mean number of sexual partners in the preceding month was 1.5 and 1.7 in the former and latter groups respectively.

Of those patients treated with ampicillin 3 g plus probenecid 1 g, 71 (98.6%) of 72 patients who were followed up for 14 days were cured. Seven patients were reinfected and one defaulted in this group (Table 2).

Of those patients treated with amoxycillin 3 g, 71 (98.6%) of 72 patients who were followed up for 14 days were cured. Six patients were reinfected and two defaulted (Table 2).

Of the 13 patients with reinfections all had negative results to tests for gonococci on the third day (Table 3). On the seventh day, eight patients had positive results, four results remained negative, and one patient defaulted. By the 14th day, the four patients who had had negative results and the one who had failed to attend previously all had positive culture results. All admitted to re-exposure to infection.

By contrast, both patients in whom treatment failed had positive results to investigations taken on the third day. The results of one patient remained positive on the seventh day when he was removed from the study. The other patient who did not attend

for follow up on the seventh day had a positive result when he attended on the 14th day. Both these patients had minimal symptoms (Table 3).

No case of PGU was identified during the 14-day follow-up period.

Table 3 Follow-up results in 15 cases of failure/reinfection

Results	Follow-up period (days)		
	3	7	14
Positive	2	9*	6*
Negative	13	4	0
Removed from study	0	0	9*
Defaulted from visit	0	2*	0
Total	15	15	15

*One treatment failure

Discussion

Although, for technical reasons, it was not possible to perform antibiotic sensitivity tests on gonococcal strains isolated in this study, the cure rate of 98.6% with either regimen is very satisfactory when it is remembered that in 1971 74% of strains isolated at this clinic gave minimum inhibitory concentrations of penicillin of 0.1 unit/ml and over (Fleming *et al.*, 1974). These results are comparable to some obtained from areas with a much lower incidence of less sensitive strains. Alergant (1973) reported a cure rate of 94.2% with amoxycillin 1 g plus probenecid 1 g in Liverpool; Willcox (1974), in London, obtained a cure rate of 98.8% using amoxycillin 3 g in two oral doses five hours apart; Karney *et al.* (1974) had a cure rate of 95% with amoxycillin 3 g and of 98% with ampicillin 3.5 g plus probenecid 1 g in Seattle; Deal *et al.* (1974), in Florida, reported a 97% cure rate with amoxycillin 3 g; Gurwith *et al.* (1974) using amoxycillin 3 g and 2 g plus probenecid 0.5 g obtained cure rates of 95.4% and 89.5% respectively in Manitoba; Roberts (1974) obtained rates of 84% and 95% using amoxycillin 1 g and 3 g respectively in Tennessee; and Wolk (1974), in California, claimed a cure rate of 94% in men using amoxycillin 3 g.

Lassus *et al.* (1975), in Helsinki, had a cure rate of 100% with amoxycillin 3 g if the two possible reinfections are excluded. In London, Price and Fluker (1975) using amoxycillin 3 g obtained a cure

Table 2 Results of the two treatment regimens in patients followed up for 14 days

Drug regimen	Cure		Failure		Reinfection		Defaulted		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Amoxycillin 3g	71	98.6	1	1.4	6		2		80	100
Ampicillin 3g plus probenecid 1g	71	98.6	1	1.4	7		1		80	100

rate of 99% in men and 95% in women assessed at the first follow-up three days later. Thin *et al.* (1977), in London, in the only double-blind study in this series, claimed cure rates of 86% and 94% using amoxycillin 1 g and 3 g respectively (both given with probenecid). In all of these studies cure rates were assessed within 14 days of treatment.

The early (upward) part of the blood concentration curve following administration of amoxycillin 3 g has been shown by Neu (1974) to approximate that following ampicillin 3.5 g plus probenecid 1 g, but disappearance was faster with amoxycillin. Kvale *et al.* (1971) claimed a cure rate of 96% in men treated with ampicillin 3.5 g plus probenecid 1 g for acute gonococcal urethritis in the Philippines, an area with a high incidence of strains insensitive to penicillin. Their result is similar to that found by Karney *et al.* (1974) and to that of the present trial. Whereas Kvale *et al.* (1971) found a 47.9% incidence of PGU during a 21-day follow-up period, however, no cases of PGU with either regimen were seen in this trial at 14 days.

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