

Single dose oral amoxycillin 3 g with either 125 mg or 250 mg clavulanic acid to treat uncomplicated anogenital gonorrhoea

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SUMMARY A single supervised oral dose of amoxycillin 3 g combined with clavulanic acid 125 mg as a suspension (Augmentin 3.125G) plus probenecid 1 g, cured 97 of 100 assessable patients who had uncomplicated anogenital gonorrhoea. Thirteen of the 100 patients were infected with penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG) and 11 (85%) of these patients were cured, including one infected with a PPNG strain that was also resistant to spectinomycin.

Another group of 93 assessable patients was treated with ampicillin 3 g plus probenecid 1 g, and only 85 (91%) patients were cured. Of the eight treatment failures in this group, five were found to be infected with PPNG strains.

In a second study 144 assessable patients were treated with amoxycillin 3 g combined with clavulanic acid 250 mg, (Augmentin 3.250G) plus probenecid 1 g, and a 97% cure rate was again obtained. Five of seven (71%) patients infected with PPNG strains were cured.

Although both Augmentin regimens were effective for treating gonorrhoea caused by PPNG and non-PPNG strains, side effects were noted in more patients treated with 250 mg clavulanic acid (24%) than with 125 mg clavulanic acid (5%). In addition, a similar cure rate was obtained in the three primary sites of infection, the urethra, cervix, and rectum.

Introduction

The addition of clavulanic acid to amoxycillin is effective in restoring the antibacterial activity of amoxycillin against penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG).¹ PPNG strains have become more prevalent in many countries including Britain during the past few years, and parenteral drugs, such as spectinomycin or certain cephalosporins,² have been recommended for treating gonorrhoea caused by these strains. Resistance to spectinomycin has, however, been recently recognised in some PPNG strains,^{3,4} and in many third world countries supervised oral rather than parenteral drug treatment is preferred as it is less expensive.⁵⁻⁸ We therefore decided to compare the efficacy of and tolerance to a single oral dose of Augmentin (amoxycillin 3 g combined with either

125 mg or 250 mg clavulanic acid) plus probenecid 1 g with the current first line drug regimen used in this hospital, ampicillin 3 g plus probenecid 1 g, for treating uncomplicated gonorrhoea.

Patients and method

STUDY POPULATION

Men and women patients with uncomplicated gonorrhoea, which was subsequently confirmed by isolation of gonococci from urethral, cervical, or rectal sites, were included in the trial studies, after giving informed consent. Patients were excluded from the trial if they had allergy to penicillins; suspected coexisting syphilis; had complications related to gonococcal infections, such as pelvic inflammatory disease; suspected pregnancy; or were unable to attend for the follow up assessments. Of the 348 patients investigated, 257 were men and 91 women. About two thirds of the men were homosexual.

In the first study, conducted in 1982-3, patients were randomly given either oral ampicillin 3 g plus

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probenecid 1 g, or oral Augmentin powder, consisting of amoxycillin 3 g plus clavulanic acid 125 mg, dissolved immediately before use in 50 ml of water, plus probenecid 1 g under supervision. Follow up assessments of efficacy and acceptability were carried out on days 2, 7, and 10 after treatment. No other antibiotics were given during this time. If the patient was still found to have gonorrhoea at the final assessment on day 10, an injection of either spectinomycin 2 g or a cephalosporin was given and the patient followed up further.

In a second study, in 1983, 150 consecutive patients were treated with amoxycillin 3 g plus clavulanic acid 250 mg (Augmentin 3.250G) with probenecid 1 g, and were similarly followed up.

BACTERIOLOGICAL TECHNIQUES

Swabs from the urethra, cervix, and rectum were plated direct on to the gonococcal selective medium (Oxoid gonococcal (GC) agar base, CM 367, plus supplements) containing haemoglobin, isovitalax, vancomycin, colistin, nystatin, and trimethoprim. The plates were immediately incubated in a humidified atmosphere rich in carbon dioxide at 37°C for up to 48 hours. *N gonorrhoeae* was identified according to standard procedures using carbohydrate fermentation tests, the *N gonorrhoeae* fluorescent antibody test and the Phadabact gonococcus test (Pharmacia, Hounslow, Middlesex,

England). Every patient was serologically tested for syphilis.

Minimum inhibitory concentrations (MICs) of penicillin, amoxycillin, and amoxycillin plus clavulanic acid in a 2:1 ratio, were measured for all strains using the plate incorporated method and a Denley multipoint inoculator (inoculum size about 10³ colony forming units (cfu). Diagnostic sensitivity test medium (Oxoid) with lysed blood but without isovitalax, was used in measuring the MICs. Every strain was tested for the production of penicillinase by the Intralactam test system (Diamed Diagnostics, Liverpool, England). Penicillin resistant strains were also tested by disc antibiotic sensitivity methods for sensitivity to spectinomycin (100 µg disc) and cefuroxime (30 µg disc). Penicillinase producing strains were sent to the Venereal Disease Reference Laboratory, London, who carried out plasmid analysis.

Results

Table I shows the site of primary infection and presence or not of PPNG strains before treatment in the 348 patients (337 of whom were assessed both clinically and microbiologically for cure) including the 15 who did not respond to treatment. No PPNG strains were isolated from the rectum of any man or woman in the three treatment groups of patients.

TABLE I No of strains of *Neisseria gonorrhoeae* isolated before treatment and No of treatment failures related to sites of infection

	No of strains of <i>N gonorrhoeae</i> isolated from:					
	Urethra		Cervix		Rectum	
	PPNG	Non-PPNG	PPNG	Non-PPNG	PPNG	Non-PPNG
Group 1 (97 patients before treatment with ampicillin 3 g + probenecid 1 g)	3	58	2	15	0	19
Treatment failures	3 (men)	1 (man)	2 (women)	0	0	2 (men)
Group 2 (101 patients before treatment with amoxycillin 3 g clavulanic acid 125 mg + probenecid 1 g)	6	44	7	22	0	22
Treatment failures	2 (men)	1 (man)	0	0	0	0
Group 3 (150 patients before treatment with amoxycillin 3 g, clavulanic acid 250 mg + probenecid 1 g)	2	80	5	38	0	25
Treatment failures	1 (man)	2 (men)	1 (woman)	0	0	0

PPNG = Penicillinase producing strains of *N gonorrhoeae*.

GROUP 1

Of the 97 patients treated with ampicillin 3 g plus probenecid 1 g, 79 were men and 18 women; and of the 93 assessable at follow up, 85 (91%) were cured. Of the eight treatment failures, five were infected with PPNG strains and three with ampicillin sensitive strains. No PPNG strain was cured in this group.

GROUP 2

Of the 101 patients (72 men and 29 women) treated with amoxycillin 3 g plus clavulanic acid 125 mg and probenecid 1 g, 100 were assessable at follow up, and 97 (97%) were cured. Of 13 patients in this group infected with PPNG strains, 11 (85%) were cured.

GROUP 3

In this group of 150 patients treated with amoxycillin 3 g plus clavulanic acid 250 mg and probenecid 1 g, 106 were men and 44 women. Of the 144 assessable at follow up, 140 (97%) were cured. Seven were infected with PPNG strains, five (71%) of whom were cured.

SENSITIVITY TO ANTIBIOTICS OF GONOCOCCI ISOLATED

A total of 27 (8%) patients had gonorrhoea caused by PPNG strains, but two defaulted without any follow up. The PPNG strains were all sensitive to

amoxycillin combined with clavulanic acid (in a ratio of 2:1), and table II shows that the MICs of Augmentin for all strains were ≤ 3 mg/l. The non-PPNG strains isolated were all sensitive to ampicillin and amoxycillin, and 98% had a MIC of amoxycillin of < 1 mg/l. One PPNG strain isolated from the cervix was resistant to spectinomycin, and was eradicated by Augmentin 3.125G. All the gonococci were sensitive to cefuroxime. No PPNG strains were isolated from homosexual patients.

ADVERSE DRUG REACTIONS

No patient developed serious reactions to the drugs. Only two (2%) of the 93 assessable patients in group 1 complained of side effects, one with diarrhoea and the other with headache. Five (5%) of the 100 assessable patients in group 2 developed mild side effects compared with 34 (24%) of the 144 assessable patients in group 3, who were treated with the same drug combination but using 250 mg rather than 125 mg clavulanic acid. The most common side effects, nausea and diarrhoea, occurred in patients with rectal infection. Two of the patients treated with the higher dose of clavulanic acid vomited. One patient developed a drug rash. The Augmentin powder was easily dissolved in a beaker of water (50 ml) and its taste and ease of swallowing was quite acceptable to the patients.

TABLE II *Plasmid types and MICs of Augmentin for 25 PPNG strains isolated from 337 assessable patients*

Source of isolate	Case No	Type of plasmid	MIC (mg/l) of:		Result of treatment
			Penicillin	Augmentin	
Group 1 (patients treated with ampicillin)	1	African	>4	1.5	Failed
	2	Asian	>4	1.5	Failed
	3	Asian	>4	1.5	Failed
	4	Asian	>4	1.5	Failed
	5	NA	>4	1.5	Failed
Group 2 (patients treated with amoxycillin + clavulanic acid 125 mg)	6	Asian	>4	3.0	Failed
	7	Asian	>4	1.5	
	8	NA	>4	1.5	
	9	African	>4	NA	
	10	Asian	>4	1.5	
	11	Asian	>4	0.75	
	12	African	>4	3.0	
	13	Asian	>4	0.75	
	14	Asian	>4	1.5	
	15	African	>4	3.0	Failed
	16	NA	>4	1.5	
17	NA	>4	1.5		
18	NA	>4	NA		
Group 3 (patients treated with amoxycillin + clavulanic acid 250 mg)	19	NA	>4	1.5	Failed
	20	NA	>4	3.0	
	21	NA	>4	3.0	
	22	NA	>4	1.5	
	23*	NA	>4	1.5	
	24	African	>4	1.5	Failed
	25	African	>4	1.5	

NA = Not available.

*Strain from this patient was also resistant to spectinomycin.

Discussion

In many genitourinary clinics a supervised single dose of oral ampicillin 2 or 3 g, with probenecid, is used to treat uncomplicated gonorrhoea. Recently American workers have recommended an oral dose of ampicillin 3.25 g with probenecid 1 g, and cure rates of 92-96% have been reported. During the first part of our study, in 1982, when we used ampicillin 3 g and probenecid 1 g, a cure rate of 91% was observed and treatment failed, as expected, in all five patients infected with PPNG strains. In contrast, when clavulanic acid 125 mg was given with amoxicillin 3 g plus probenecid 1 g a cure rate of 97% was obtained including 11 (85%) of 13 patients infected with PPNG strains. Only 5% of patients treated with this clavulanic acid combination (Augmentin 3.125G) complained of side effects, which were mild. We therefore concluded that this oral treatment was well tolerated and reasonably effective for treating gonorrhoea caused by both PPNG and non-PPNG strains.

Patients in the second study received 250 mg clavulanic acid with amoxicillin (Augmentin 3.250G), and the overall cure rate was also 97%. In this second study, however, five (71%) of seven patients infected with PPNG strains were cured, and the MICs of Augmentin for the strains from treatment failures were 1.5 to 3 mg/l. There were not enough patients with gonorrhoea caused by PPNG strains to allow the two regimens with different doses of clavulanic acid to be compared statistically. Two treatment failures in each Augmentin study were, however, associated with infections caused by PPNG strains. We therefore think that there is probably no obvious advantage in using the higher dose of clavulanic acid in a single dose regimen. Indeed, this dosage was associated with a higher incidence of mild gastrointestinal side effects.

Primary infections of the rectum had the same cure rate (96% overall gonococcal clearance) as those in which the urethra or cervix were the primary sites of infection.

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