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Comparison between bacampicillin and amoxycillin in treating genital and extragenital infection with *Neisseria gonorrhoeae* and pharyngeal infection with *Neisseria meningitidis*

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SUMMARY Sixty three patients presumed to have genital gonorrhoea who gave histories of extragenital sexual practices were randomly treated with amoxycillin 3 g or bacampicillin 4·8 g (equivalent to 3·5 g ampicillin) with probenecid 1 g to compare the efficacy of the drugs in treating gonorrhoea at all sites. Three patients were initially culture negative, and seven failed to return for follow up. Twenty seven of 28 patients receiving bacampicillin and all 25 receiving amoxycillin gave negative genital cultures for *Neisseria gonorrhoeae* five to nine days after treatment.

Twenty two of 60 patients had extragenital gonorrhoea. One failed to return, but all eight who had received amoxycillin and 12 of 13 who had received bacampicillin gave negative pharyngeal and anorectal cultures after treatment. *N meningitidis* was isolated from the pharynx in 17 of 60 patients on initial attendance. Three of 14 were still colonised with the meningococcus after treatment.

Two of 32 patients receiving amoxycillin and 12 of 31 receiving bacampicillin reported experiencing gastrointestinal side effects.

Introduction

We previously compared bacampicillin, a prodrug ester of ampicillin that is hydrolysed to ampicillin after absorption, in a dose of 1·6 g (equivalent to 1·12 g ampicillin) with 3·5 g ampicillin, both given with 1 g probenecid, in the treatment of uncomplicated gonorrhoea.[1] In that study we measured serum, urine, and salivary ampicillin concentrations two hours after administration of the antibiotics with probenecid, but were unable to detect any drug in the saliva with a microbiological assay sensitive to 0·01 mg/l. Combined data from four study groups showed treatment failure with 1·6 g bacampicillin in five of eight patients with pharyngeal gonorrhoea.[2] Other workers had found ampicillin and amoxycillin given with probenecid as a single dose to be inadequate for the treatment of gonorrhoea at this site.[3] DiCaprio *et al*, however, found ampicillin to be highly effective (96-99% cure rates for 77 patients with pharyngeal gonorrhoea) when using multiple doses (3·5 g ampicillin plus 1 g probenecid followed by ampicillin 500 mg every six hours for the succeeding two days).[4]

To find a more successful regimen for treating gonorrhoea of the genitalia, anorectum, and pharynx, we compared the efficacy of bacampicillin 4·8 g (equivalent to 3·36 g ampicillin) and 1 g probenecid with amoxycillin 3 g given with 1 g probenecid. Both these antibiotics are more completely absorbed and achieve better serum concentrations than ampicillin. The effect of probenecid given at the same time as opposed to half an hour before the antibiotics was not clear, particularly in relation to concentrations in saliva, so this was also studied.

Bacampicillin in a dose of 1·6 g gives no more gastrointestinal side effects than ampicillin in a dose of 3·5 g, but in one report gastrointestinal side effects were experienced by nearly half the patients receiving a dose of 2·4 g.[2] Accordingly, there was a need to see if increasing the dose to 4·8 g would confirm or refute this finding.

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Patients and methods

Informed consent was obtained from volunteers aged 18 or over who attended the sexually transmitted diseases (STD) clinic of the Winnebago County Public Health Department, Rockford, Illinois. Patients who were pregnant or nursing an infant, wished to donate blood during the study period, had clinical or serological evidence of syphilis, or both, were known or suspected to be allergic to any of the penicillins or cephalosporins, had clinical or laboratory evidence of hepatic or renal diseases, required concomitant antimicrobial treatment, had received systemic antimicrobial treatment in the previous 30 days, had infectious mononucleosis or impared immunological function, or had a urinary tract infection were excluded from the study. Patients were also excluded if there was evidence of trichomoniasis or non-specific vaginitis by properly performed Gram stains, saline mounts, and potassium hydroxide preparations. The procedures followed were in accordance with the ethical standards of the committees on human experimentation of the University of Illinois at the Medical Center.

Sixty three patients were assigned to receive either 12 tablets of bacampicillin 400 mg or six tablets of amoxycillin 500 mg according to a table of randomised numbers. The first half of the patients received 1 g probenecid 30 minutes before the antibiotic and the second half received it with the antibiotic.

At the initial visit urethral or endocervical specimens were obtained by calcium alginate swabs for Gram stained smear microscopy and culture. In addition, pharyngeal and anal cultures were obtained from all patients. All cultures were directly inoculated on to Martin-Lewis gonococcal (GC) medium (Granite Diagnostics, Burlington, North Carolina, United States of America) containing vancomycin, colistin, anisomycin, and trimethoprim and were incubated immediately at 35°C in 5-10% carbon dioxide. Cultures were then transported to the Rockford School of Medicine and held for up to 72 hours before being discarded. Colonies suspected of being *N gonorrhoeae* or *N meningitidis* were subcultured on to Gibco chocolate agar medium (No P2306, Gibco, Madison, Wisconsin) and subsequent sugar fermentations were performed according to the Minitek method.

Specimens of urine, blood, and saliva were obtained one hour after administration of the antibiotics, frozen, and immediately transported to Rockford School of Medicine where they were stored at −70°C and analysed weekly for antibiotic content by an agar well microbiological assay using Antibiotic Medium (No 1, Difco 0263-02, Detroit, Michigan, USA) and *Micrococcus lutea* (ATCC 9341) as the indicator organism (lower limits of assay 0·01 mg/l). Complete blood counts, rapid plasma reagin tests, urine analyses, and 25 separate serological tests including those denoting hepatic and renal functions were performed.

Patients were re-evaluated after five to nine days for clinical symptoms, test-of-cure cultures, and repeat laboratory tests. Cultures positive for *N gonorrhoeae* were tested for production of β-lactamase. Postgonococcal urethritis (PGU) was diagnosed if a man had persisting urethral symptoms and >5 polymorphonuclear leucocytes/high power field on urethral Gram stain at follow up.

Statistical tests included the χ^2 test and Student's two tailed *t* test for paired data as indicated.

Results

Three patients entered into the study on the basis of known exposure to gonorrhoea were subsequently evaluated only for drug variables when their cultures were found to be negative for *N gonorrhoeae*. Table I shows the sites of isolation of *N gonorrhoeae* and *N meningitidis* in the remaining 60 patients. Seven patients did not return for follow up. Of the 53 evaluable patients, nine women and 19 men were treated with bacampicillin and seven women and 18 men with ampicillin. Anorectal gonorrhoea was found in 13 (21·7%) of the patients and pharyngeal gonorrhoea in the same number.

TABLE I *Sites of isolation of Neisseria gonorrhoeae and N meningitidis in 60 patients with gonorrhoea*

Site of isolate	*Neisseria spp isolated*	*Men*	*Women*	*Total*
Genitalia	*N gonorrhoeae*	39	21	60
Anorectum	*N gonorrhoeae*	5	8	13
Pharynx	*N gonorrhoeae*	6	7	13
	N meningitidis	15	2	17

N.B. *N meningitidis* was not isolated from genitalia or anorectum or with *N gonorrhoeae*.

Table II shows that the time of administration of probenecid appreciably affected serum and saliva concentrations of amoxycillin, but not of bacampicillin. Patients who vomited or chewed their tablets were excluded from this analysis. Three patients treated with bacampicillin who vomited and another patient who chewed his bacampicillin tablets had very high saliva concentrations, but serum and urine concentrations were not appreciably different from those of patients treated with bacampicillin who did not vomit or chew their tablets.

TABLE II *Effect on concentrations of antibiotics of time of administering probenecid*

Probenecid administered	*Amoxycillin (mg/l) in:*			*Bacampicillin (mg/l) in:*		
	Saliva	*Serum*	*Urine*	*Saliva*	*Serum*	*Urine*
30 min before antibiotic	0·36*	34·6†	864	0·25	36·8	1500
With antibiotic	0·12	23·5	1246	0·21	32·4	3246

*Significantly ($t = 3·71$; $p<0·001$) more amoxycillin in saliva when probenecid administered before the antibiotic.
†Significantly ($t = 2·88$; $p<0·01$) more amoxycillin in serum when probenecid administered before the antibiotic.
(Differences in urine concentration of amoxycillin and saliva, serum, and urine concentrations of bacampicillin not significant.)

Table III shows the results of treatment. All patients who received amoxycillin and all but one who received bacampicillin were cured of anogenital gonorrhoea. The treatment failure occurred in a prostitute who had unprotected sexual re-exposure before return for follow up. Of 11 patients with pharyngeal gonorrhoea, 10 responded to treatment. Of 17 patients yielding positive pharyngeal cultures for *N meningitidis,* 15 were men (table I). No anogenital cultures yielded this organism and it was never isolated at the same site as *N gonorrhoeae.* In 14 patients who had pharyngeal cultures taken at follow up, the organism was eradicated from the pharynx of 11 (table III).

TABLE III *Cure with amoxycillin or bacampicillin of genital and extragenital infection with Neisseria gonorrhoeae or N meningitidis*

Site of Infection	*Infecting Neisseria spp*	*No cured/No treated with:*	
		Amoxycillin	*Bacampicillin*
Genitalia	*N gonorrhoeae*	25/25	27/28
Anorectum	*N gonorrhoeae*	7/7	6/6
Pharynx	*N gonorrhoeae*	2/2	8/9
	N meningitidis	6/8	5/6

Postgonococcal urethritis (PGU) occurred in 14 of 37 men, and there was no appreciable difference in incidence between those treated with amoxycillin (six of 18) and bacampicillin (eight of 19).

No abnormal laboratory findings could be associated with either antibiotic. No allergic rashes were noted. Table IV shows that 38·7% of the patients treated with bacampicillin experienced gastrointestinal side effects (six vomited (one also had five to six loose stools for one day) and six had nausea or one to two loose stools). There was a noticeable difference between patients who had food in their stomach during the previous one to three hours and those who took the medication on an empty stomach or with a small amount of food. The presence or absence of food in the stomach made no appreciable difference in those treated with amoxycillin.

No β-lactamase producing *N gonorrhoeae* were found in cultures that were positive on follow up.

TABLE IV *Effect of presence or absence of food in the stomach on gastrointestinal side effects of amoxycillin and bacampicillin*

Food	*No (%) with side effects after taking:*	
	Amoxycillin	*Bacampicillin*
Present	0/7 (0)	1/13 (7·7)
Absent	2/25 (8)	11/18 (61·1)
Total	2/32 (6·3)	12/31 (38·7)

Significant difference between amoxycillin and bacampicillin ($\chi^2 = 9·6$; $p<0·01$).
Significant effect of food in patients taking bacampicillin ($\chi^2 = 9·0$; $p<0·01$).

Discussion

In our previous study we did not find ampicillin in the saliva two hours after administration of 1·6 g bacampicillin or 3·5 g ampicillin, each given simultaneously with 1 g probenecid.[1] In this study a dose of 4·8 g bacampicillin given with 1 g probenecid gave mean saliva concentrations of more than 0·17 mg/l, the mean minimum inhibitory concentration (MIC) for *N gonorrhoeae* recorded for isolates in our previous study.[1]

Other workers found high (43-60%) treatment failure rates for pharyngeal gonorrhoea with 3·5 g ampicillin, 1·6 g and 2·4 g bacampicillin, and 3 g amoxycillin (all given with 1 g probenecid).[2-5] In 11 of our patients with pharyngeal gonorrhoea, eight of nine given 4·8 g bacampicillin and both patients given 3 g amoxycillin (all given with 1 g probenecid) had *N gonorrhoeae* eradicated from the pharynx, although the small number of patients treated and followed up obscures the relevance of these findings.

Some workers have suggested that pharyngeal gonorrhoea is not important from either an epidemiological or clinical viewpoint as the natural history of pharyngeal *N gonorrhoeae* in 17 asymptomatic patients showed no evidence of disease in untreated patients during three months.[6] Counterbalanced against this is the observation that some patients have had symptoms of pharyngitis and over a dozen cases of gonococcaemia have been reported in which the pharynx was the sole site of isolation of *N gonorrhoeae* other than the blood.[7] Recent information

also indicates that gonorrhoea may be spread from the pharynx to the genitals.[7-9] In this study, the demonstrable saliva concentrations of antibiotics correlated with the eradication of pharyngeal *N gonorrhoeae* in 10 of 11 patients and pharyngeal *N meningitidis* in 11 of 14 patients (table III).

Earlier studies have suggested that bacampicillin may produce more gastrointestinal side effects than ampicillin.[2] The presence of food already in the stomach (but not given simultaneously with the bacampicillin) was protective, but this is not convenient in most outpatient departments as the patients may have to wait an hour or so before the administration of antibiotics. The role of the larger number of bacampicillin tablets is subject to conjecture. In this study amoxycillin had appreciably fewer gastrointestinal side effects than bacampicillin whether given on an empty or full stomach. We therefore believe further study is indicated using oral antibiotics that have the potential for eradicating pharyngeal *N gonorrhoeae* and *N meningitidis*. On the basis of this study, although bacampicillin is effective at the dose used, it is limited by the high incidence of gastrointestinal side effects.

References

1. Spengler PJ, Edwards LD. Comparative study of bacampicillin and ampicillin in the treatment of uncomplicated gonorrhoea. *Br J Vener Dis* 1980;**56**:151-5.
2. Wagner KF, Counts G, Holmes KK, Sparling PF, Gentry LO, Edwards LD. Clinical evaluation of single-dose oral bacampicillin or ampicillin in therapy of uncomplicated gonorrhea. *Rev Infect Dis* 1981;**3**:166-9.
3. Washington AE. Experience with various antibiotics for treatment of anorectal gonorrhea. *Sex Transm Dis* 1979;**6** suppl: 148-51.
4. DiCaprio JM, Reynolds J, Frank G, Carbone J, Nishimura R. Ampicillin therapy for pharyngeal gonorrhea. *JAMA* 1978; **239**:1631-3.
5. Kraus SJ. Incidence and therapy of gonococcal pharyngitis. *Sex Transm Dis* 1979;**6** suppl: 143-7.
6. Wallin J, Seigel MS. Pharyngeal *Neisseria gonorrhoeae:* coloniser or pathogen? *Br Med J* 1979; i: 1462-3.
7. Tice AW, Rodriguez VL. Pharyngeal gonorrhea. *JAMA* 1981; **246**:2717-9.
8. Harrison WC. Pharyngeal gonorrhea [editorial]. *JAMA* 1981; **246**:2726-7.
9. Soendjojo A. Gonococcal urethritis due to fellatio. *Sex Transm Dis* 1983;**10**:41-2.