Comparative study of bacampicillin and ampicillin in the treatment of uncomplicated gonorrhoea*

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SUMMARY Bacampicillin hydrochloride, a pro-drug ester of ampicillin trihydrate which is hydrolysed to ampicillin after absorption, was used in a randomised comparative study of ampicillin 3.5 g and bacampicillin 1.6 g (each with probenecid 1 g) in the treatment of uncomplicated gonorrhoea. This dose of bacampicillin was selected because in serum it gives approximately the same peak concentration of ampicillin as 3.5 g of the parent drug. Genital, pharyngeal, and anal cultures were performed at the initial visit and at follow up 5-9 days after treatment. There was no statistically significant difference in the microbiological or clinical response of patients with genital gonorrhoea who were treated with ampicillin and those treated with bacampicillin. At 5-9 days after treatment, 93% of the ampicillin-treated patients and 89% of the bacampicillin-treated patients had negative genital, pharyngeal, and anal culture results; furthermore, 87% and 89% respectively had no symptoms of infection. Fewer gastrointestinal side effects were noted in the patients treated with bacampicillin.

Introduction

Oral antibiotic therapy has the advantages of greater patient co-operation and a lower rate of hypersensitivity reactions;^{1,2} moreover, there is a need for effective oral antibiotics which have the potential for eradicating gonorrhoea from the pharynx as well as from anogenital sites.

Several investigators have reported high pharyngeal colonisation rates, particularly in women and homosexual men. In studies by Wiesner *et al*³ and Bro-Jorgensen and Jensen⁴ of patients who had positive culture results for *Neisseria gonorrhoeae* at genital, rectal, or pharyngeal sites, pharyngeal colonisation rates ranged from 10-10.3% in women, 3.2-6% in male heterosexuals, and 20.9-25% in male homosexuals.^{3,4} In a population known to have infrequent orogenital sexual contact, Noble *et al*⁵ found that among patients with concurrent genital or rectal gonorrhoea 3.3% of the men and 1.9% of the women had gonococcal colonisation of the pharynx. In a recent study by Gartner and Edwards (paper presented at 79th Annual Meeting, American Society for Microbiology, Los Angeles-Honolulu, 1979)

multiple cultures were obtained from each potential site of infection—pharynx, anus, and genital tract—before treatment. Patients were selected for the study if they had either a positive result to a genital smear or a previous positive genital culture result. In this study 23.8% (10/42) of heterosexual women and 8.9% (4/45) of heterosexual men who were culture-positive at a genital or an anal site also had a positive result to a pharyngeal culture.

Bro-Jorgensen and Jensen⁴ and Karney *et al*⁶ demonstrated that *N gonorrhoeae* is difficult to eradicate from the pharynx with the multiple antibiotic regimens that they tried. The Centre for Disease Control in Atlanta, Georgia, does not recommend the use of the standard oral regimen for treating genital gonorrhoea (ampicillin 3.5 g with probenecid 1 g) for the treatment of pharyngeal gonorrhoea.⁷ However, in a recent study by Di Caprio⁸ success rates of 96.1-98.7% in the treatment of pharyngeal gonorrhoea were achieved with ampicillin trihydrate 3.5 g with probenecid 1 g initially, followed by 500 mg four times daily for two days, a total of 7.5 g of ampicillin.

In view of the need for oral antibiotics which can eradicate pharyngeal as well as genital gonorrhoea, we decided to study bacampicillin hydrochloride, an oral preparation which is a pro-drug ester of ampicillin trihydrate. Bacampicillin, after absorption, is hydrolysed to ampicillin and gives serum concentrations two to three times higher than an equimolar dose of ampicillin trihydrate.^{9,10}

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Patients and methods

STUDY POPULATION

Sixty-one men and 22 women with culture-positive uncomplicated gonorrhoea were randomly assigned to one of two oral treatment groups. One group was treated with ampicillin 3.5 g, the other with bacampicillin 1.6 g, a one-third equimolar dose. Probenecid 1 g was administered simultaneously with each drug.

The patients were volunteers aged 18 years or more, who attended the sexually transmitted diseases clinic at the Winnebago County Department of Public Health, Rockford, Illinois, USA. Those patients who were pregnant or nursing an infant, wished to donate blood during the study period, were known or suspected to be allergic to penicillin or cephalosporins, had hepatic disease or impaired renal function, required other concomitant antimicrobial therapy, had received systemic antimicrobial therapy within the previous month, or had infectious mononucleosis, impaired immunological function, syphilis, or chronic urinary tract infection were excluded from the study.

COLLECTION OF SPECIMENS

At the initial visit, urethral and endocervical specimens were obtained by calcium alginate swabs from men and women respectively for Gram stain and culture. Pharyngeal and anal specimens were obtained for culture from all patients. To monitor adverse drug reactions, total blood counts, urine analyses, and serum analyses for hepatic and renal function (bilirubin, alkaline phosphatase, creatinine, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and urea nitrogen) were performed. Routine serological Venereal Disease Research Laboratory (VDRL) tests for syphilis were performed; patients with reactive VDRL test results were excluded from the study. Gram stains, freshly centrifuged urine sediment specimens, and saline-diluted wet-mount preparations of vaginal secretions were examined microscopically for yeast forms and trichomonads. Patients with apparent candidosis or trichomoniasis were not included in the study. Two hours after treatment, specimens of urine, blood, and saliva were collected for determination of ampicillin concentrations.

Follow-up visits took place 5-9 days after treatment, at which time patients were questioned about symptoms and possible drug-related reactions. Gram stains, cultures, wet-mount preparations, urine analyses, and tests to monitor for adverse drug reactions were repeated as for the initial visit. The procedures followed were in accordance with the ethical standards of the committees on human experimentation of the University of Illinois.

DIAGNOSIS

All cultures were inoculated directly on to modified Thayer-Martin medium (Baltimore Biological Laboratories, Cockeysville, Maryland) containing vancomycin, colistin, nystatin, and trimethoprim¹¹ and were incubated immediately at 35°C in 5-10% carbon dioxide. Cultures were transported to the Rockford School of Medicine laboratories where standard procedures for isolation and identification of *N gonorrhoeae* were followed with confirmation of pharyngeal and anal isolates by sugar fermentation tests.¹²

ANTIBIOTIC SENSITIVITIES

Minimum inhibitory concentrations (MICs) of ampicillin for *N gonorrhoeae* isolates were determined by the agar dilution technique.¹³ A suspension of 10⁵ organisms per ml in Mueller-Hinton broth supplemented by 1% IsoVitaleX (Baltimore Biological Laboratories, Cockeysville, Maryland) was delivered by automatic inoculator to the surface of each agar plate with antibiotic concentrations from 0.049 to 100.0 µg/ml. The ampicillin-containing agar plates were prepared just before use in GC medium base (Difco Laboratories, Detroit, Michigan) with 1% IsoVitaleX. The MIC was defined as the dilution with no visible growth after 48 hours of incubation.

MICs of penicillin were not determined.

β-LACTAMASE PRODUCTION

Fresh subcultures of *N gonorrhoeae* on chocolate agar were tested for β-lactamase production using the chromogenic cephalosporin method.¹⁴

FIG 1 Correlation of ampicillin concentrations in serum and urine specimens from 37 patients two hours after administration of ampicillin 3.5 g with probenecid 1 g.

ANTIMICROBIAL ASSAY FOR AMPICILLIN CONCENTRATIONS

Specimens of urine, blood, and saliva were frozen immediately and transported to the Rockford School of Medicine laboratories, where they were stored at -20°C . Specimens were tested for drug concentrations within 72 hours of collection by agar-well bioassay¹⁵ using *Bacillus subtilis* as the indicator organism.

STATISTICAL METHODS

χ^2 analysis with Yates's correction was used for statistical comparisons of proportions and Student's *t* test for unpaired data (one-tailed) for comparisons of means. Correlation analyses (figs 1 and 2) were computed by Pearson product-moment correlation coefficients using the one-tailed Student's *t* test for unpaired data to determine levels of significance.

Results

PATIENT POPULATION

Of the 83 patients treated, 57 (69%) returned for a follow-up visit. The treatment groups were statistically similar with regard to sex, race, history of previous infection, and age (table I).

The study population differed from our regular clinic population in that it was predominantly male whereas the latter was equally divided between men and women. More men than women volunteered for the study, and women who were possibly pregnant were excluded. Racial distribution was representative of the regular clinic population; both the study group and the regular clinic population were approximately 50% white and 50% non-white.

FIG 2 Correlation of ampicillin concentrations in serum and urine specimens from 38 patients two hours after administration of bacampicillin 1.6 g with probenecid 1 g.

TABLE I Characteristics of patients treated for gonorrhoea with ampicillin and bacampicillin

Characteristics	Treatment group	
	Ampicillin (n = 30)	Bacampicillin (n = 27)
Sex		
Male	21	22
Female	9	5
Race		
White	14	11
Non-white	16	16
Previous gonococcal infection	14	15
Mean age (years)	24.1	23.9

Two men in the study group stated that they were homosexuals and one stated that he was bisexual; the rest of the patients claimed to be practising heterosexuals.

GRAM STAINS AND CULTURES

At the time of the initial visit, intracellular Gram-negative diplococci typical of *N gonorrhoeae* were identified on Gram stains of urethral exudate of all 43 men and on Gram stains of endocervical exudate of 11 (79%) of the 14 women. Three women who entered the study as named contacts of men with confirmed gonococcal urethritis had negative Gram stains and positive endocervical culture results.

Initially, all patients had positive genital culture results and negative pharyngeal culture results. Only one patient, female, had a positive result to an anal culture.

MICs

MICs for all 58 isolates taken at the initial visit are shown in table II. There was no significant difference in the distribution of MICs between the group treated with ampicillin and that treated with bacampicillin ($\chi^2 = 3.63$, $P \leq 0.46$).

TABLE II Minimum inhibitory concentrations of ampicillin for 58 isolates of *Neisseria gonorrhoeae* obtained at patients' initial visits

MICs (µg/ml)	Isolates from patient-groups					
	Ampicillin (n = 31)		Bacampicillin (n = 27)		Total	
	No	%	No	%	No	%
0.049	10	32.2	12	44.4	22	37.9
0.098	8	25.8	6	22.2	14	24.1
0.195	3	9.7	5	18.5	8	13.8
0.390	9	29.0	4	14.8	13	22.4
0.780	1	3.2	0	0	1	1.7
Mean	0.104		0.086		0.170	
Median	0.198		0.137		0.098	

β -LACTAMASE PRODUCTION
No isolates produced β -lactamase.

DRUG CONCENTRATIONS

For 37 patients treated with ampicillin (fig 1), the serum ampicillin concentrations at two hours ranged from 5.8-58.0 $\mu\text{g/ml}$ with a median value of 18.3 $\mu\text{g/ml}$ and a mean value of 21.1 $\mu\text{g/ml}$; urine concentrations ranged from 370.0-15 400 $\mu\text{g/ml}$ with median and mean values of 2595 and 3364.6 $\mu\text{g/ml}$ respectively.

For 38 patients treated with bacampicillin (fig 2), the serum ampicillin concentrations at two hours ranged from 4.7-28 $\mu\text{g/ml}$ with median and mean values of 13.6 $\mu\text{g/ml}$; urine concentrations ranged from 700-85 000 $\mu\text{g/ml}$ with median and mean values of 5220 $\mu\text{g/ml}$ and 8292.5 $\mu\text{g/ml}$ respectively.

No ampicillin was detected in saliva specimens from patients in either treatment group.

There was a strong positive correlation between serum and urine concentrations in the ampicillin-treated patients ($r=0.72$, $P<0.001$). Concentrations of ampicillin in the serum and urine of bacampicillin-treated patients showed no significant correlation ($r=0.18$, $P\geq 0.14$).

Serum drug concentrations at two hours in the ampicillin-treated patients were significantly higher than those in the bacampicillin-treated group ($t=3.70$, $P<0.001$) and urine concentrations were significantly lower ($t=-2.10$, $P<0.025$).

MICROBIOLOGICAL RESPONSE

The microbiological response was similar in the two groups ($\chi^2=0.02$, $P\geq 0.9$). Ninety-three per cent (28/31) of the ampicillin-treated patients and 89% (24/27) of the bacampicillin-treated patients had negative culture results at follow up, including the female patient whose initial anal culture gave a positive result. Five heterosexual patients, four male and one female, who were initially culture-positive at genital sites, were culture-positive 5-9 days after treatment. Four had positive results at genital sites; one male patient had a positive pharyngeal culture result after treatment although his initial pharyngeal culture had a negative result. On examination and interview during the follow-up visit, all five of these patients were asymptomatic.

For the five patients who were culture-positive after treatment, no significant difference was noted between MICs on initial and post-treatment isolates (table III).

The four men, including the one with a positive pharyngeal culture result, admitted to further contact during the study period and may represent reinfections rather than treatment failures.

Gram stains gave positive results for the three men

TABLE III MICs of ampicillin for *N gonorrhoeae* isolates from five patients at initial visit and at follow up (before and after treatment)

Patient No	Sex	Drug	MIC ($\mu\text{g/ml}$)	
			Initial visit	Follow-up visit
1	M	Bacampicillin	0.390	0.780
2	M	Ampicillin	0.195	0.390
3	M	Bacampicillin	0.049	0.049
4	F	Ampicillin	0.098	0.390
5	M	Bacampicillin	0.390	0.390*

*Pharyngeal isolate

with positive urethral culture results after treatment. These three patients, two initially treated with bacampicillin and one treated with ampicillin, and the man with a positive pharyngeal culture result, who was initially treated with bacampicillin, responded satisfactorily to retreatment with intramuscular spectinomycin or aqueous procaine penicillin G. The culture-positive female patient had a negative Gram-stain result and therefore was not immediately retreated. After culture results were known, we were unable to locate this patient.

CLINICAL RESPONSE

There was no statistical difference between the treatment groups in clinical response at 5-9 days ($\chi^2=0.02$, $P\geq 0.9$). Eighty-seven per cent (26/30) of the patients treated with ampicillin and 89% (24/27) of those treated with bacampicillin had no symptoms at follow up. Seven patients (13.3% of those treated with ampicillin and 11.1% of those treated with bacampicillin) had symptoms after treatment, all of whom were culture-negative. Of these, four were women who complained of vaginal discharge; one had candidosis, one trichomoniasis, and two unexplained vaginal discharge. Three men had either dysuria, discharge, or frequency of micturition.

ADVERSE REACTIONS

Adverse reactions occurred more commonly in the ampicillin group (23.3%; 7/30) than in the bacampicillin group (3.7%; 1/27) ($\chi^2=3.06$, $P\geq 0.08$). Five patients had diarrhoea with four to six stools per day for one or two days; two had mild nausea or epigastric discomfort. One patient treated with ampicillin experienced globus hystericus. Haematological tests, urine analyses, and tests for renal and hepatic function showed no drug-related abnormalities.

Discussion

Studies have shown that a one-third equimolar dose of bacampicillin (1.6 g) results in approximately the

same peak serum concentrations as ampicillin 3.5 g and that peak ampicillin concentrations are obtained approximately 30 minutes earlier with bacampicillin than with ampicillin.^{9 10} Unpublished information supplied by the pharmaceutical company (Pfizer Inc., New York, NY) indicated that peak serum concentrations of ampicillin would be obtained at 1.5 hours with bacampicillin and 2.2 hours with ampicillin when these drugs are administered without probenecid. We were limited to collecting single specimens for drug assays in this outpatient clinic and all our patients received probenecid; thus we chose to collect specimens at two hours. The significantly lower serum concentrations and higher urine concentrations obtained in the bacampicillin-treated group suggest that peak serum concentrations occurred earlier in the bacampicillin group than in the ampicillin group.

There was no statistical difference in microbiological response or clinical response between the two treatment groups. Bacampicillin in the dosage used was as effective as the standard regimen of treatment with ampicillin.

The persistence of symptoms in 13% (7/52) of patients who were culture-negative for *N gonorrhoeae* after treatment suggests that they were initially infected with multiple micro-organisms. Although we did not perform cultures for *Chlamydia trachomatis*, Bowie *et al*¹⁶ and Holmes *et al*¹⁷ isolated *C trachomatis* from 18% and 19% respectively of men with urethral gonorrhoea, all of whom developed postgonococcal urethritis.

Other micro-organisms have also been implicated as causative agents of nongonococcal urethritis, cervicitis, and vaginitis. In two of the four women with persistent symptoms, candidosis and trichomoniasis were diagnosed at 5-9 days although the presence of yeasts or trichomonads was not noted before treatment.

With the doses used in this study, we were unable to detect ampicillin in the saliva of patients from either treatment group. We could not evaluate the efficacy of bacampicillin in the treatment of pharyngeal gonorrhoea since our study population mainly comprised male heterosexuals, none of whom had pharyngeal colonisation before treatment. The administration of bacampicillin 1.6 g with probenecid 1 g, however, was tolerated with minimal gastrointestinal side effects and was as effective as the standard oral regimen of ampicillin trihydrate for anogenital gonococcal infection.

Since Di Caprio *et al*⁸ found ampicillin to be effective in treating pharyngeal gonorrhoea when using a dose of 3.5 g with probenecid 1 g followed by 500 mg four times daily for two days and we found bacampicillin 1.6 g to be as effective as the single

dose ampicillin-probenecid regimen in genital gonorrhoea, we believe that bacampicillin should be studied at higher doses in a population with a high frequency of orogenital sexual practices to see if adequate salivary concentrations can be obtained and correlated with eradication of *N gonorrhoeae* in the pharynx.

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