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Comparative Therapeutic and Pharmacological Evaluation of Amoxicillin and Ampicillin Plus Probenecid for the Treatment of Gonorrhea

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Single doses of 3.5 g of ampicillin with 1.0 g of probenecid or of 3.0 g of amoxicillin alone were administered orally to 58 males and 56 females with uncomplicated gonococcal infection. The failure rate for genital or anal infection, or both, was 1.7% for ampicillin plus probenecid and 4.2% for amoxicillin alone. However, patients with oropharyngeal infection responded poorly. Seventy-five isolates of *Neisseria gonorrhoeae* recovered from patients in this study were all inhibited by 1.0 μg or less of ampicillin or amoxicillin per ml; penicillin G, ampicillin, and amoxicillin had similar activity in vitro against these isolates. Serum concentrations of amoxicillin in 10 volunteers remained above the minimal inhibitory concentration for most strains of *N. gonorrhoeae* for periods up to 10 h after a 3.0-g oral dose. After 2.0 g of ampicillin was given with probenecid, the serum levels during the 5- to 12-h period approached those achieved with 3.5 g of ampicillin plus probenecid, and actually exceeded levels attained during the same interval with 3.0 g of amoxicillin administered alone.

Single oral doses of 2.0 to 3.5 g of ampicillin have given variable results in the treatment of uncomplicated gonorrhea. Johnson et al. reported a 100% cure rate in Filipino women given 3.5 g for asymptomatic infection (9). However, 29% of men with gonorrhea acquired in the Philippines were not cured with 3.5 g of ampicillin (10), and approximately 20% of Swedish men and women infected with strains of *N. gonorrhoeae* resistant to 0.1 μg of ampicillin per ml were not cured with a single 2.0-g oral dose of ampicillin (5). The use of 1.0 g of probenecid with 2.0 to 3.5 g of ampicillin has consistently resulted in cure rates greater than 95% (5, 8–10, 14) in both men and women. The U.S. Public Health Service currently recommends 1.0 g of probenecid plus 3.5 g of ampicillin orally for the treatment of uncomplicated gonorrhea, although the efficacy of lower doses of ampicillin given with probenecid has not been studied in this country.

The new semisynthetic penicillin, amoxicillin (α-amino-*p*-hydroxybenzyl penicillin), is synthesized by hydroxylation of the phenyl side chain of ampicillin. This modification does not alter antibacterial activity or serum half-life, but results in better absorption yielding higher serum concentrations of antibiotic (2, 12, 13) which might render amoxicillin effective without probenecid for single dose oral treatment of gonorrhea. In a recent report from England (17), single oral doses of 0.5, 1.0, and 2.0 g of amoxicillin cured 82, 88, and 91% of men with gonorrhea, respectively. Deal (Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 12th, Atlantic City, abstr. no. 125, 1972) recently reported that single oral doses of 1.5 and 3.0 g cured 72 and 94%, respectively, of men with gonorrhea in a study in Florida.

In the present study, the serum concentrations of antibiotic attained after graded oral doses of ampicillin given together with 1.0 g of probenecid were compared with those attained after graded dosage increments of amoxicillin given without probenecid to provide a guide for selection of dosage schedules likely to be effective clinically. The efficacy of a single 3.0-g oral dose of amoxicillin without probenecid was then compared with that of 3.5 g of ampicillin plus 1.0 g of probenecid for the treatment of uncomplicated gonorrhea in men and women, and the activities of penicillin G, ampicillin, amoxicil-

lin, and carbenicillin against strains of *N. gonorrhoeae* recovered during this study were compared in vitro.

MATERIALS AND METHODS

Clinical pharmacology of ampicillin plus probenecid and of amoxicillin. In order to assess the potential efficacy of treatment regimens containing varying doses of amoxicillin, or ampicillin plus 1.0 g of probenecid given simultaneously, 10 male volunteers each participated in eight separate experiments. At 1-week intervals, increasing oral doses of amoxicillin, and then of ampicillin plus probenecid, were administered to each volunteer, who remained in a fasting state through the 1st 4 h after ingestion of antibiotic. Blood specimens were obtained hourly during each experiment through the 1st 6 h and at 8, 10, and 12 h. Sera were stored at −20 C for subsequent testing, and serum concentrations of ampicillin and of amoxicillin were determined according to the technique described by Bennett et al. (1) by using *Bacillus subtilis* as the assay organism. The serum half-life was determined by the formula $t_{\frac{1}{2}} = ln\ 2/Ke$, where $ln\ 2$ is the natural logarithm of 2. Ke, the rate constant of drug elimination in percentage per hour, was determined by the method of least squares from the slope of the line obtained from at least four separate concentrations measured during the logarithmic phase of elimination.

Design of treatment study. During the period July 1972 through November 1972, 58 men and 56 women with uncomplicated gonorrhea, who were seen at the Harborview Medical Center, Seattle-King County Venereal Disease Clinic, were treated either with 3.0 g of amoxicillin or with 3.5 g of ampicillin given simultaneously with 1.0 g of probenecid, which were administered orally according to a randomized, double-blind study protocol. Patients gave written consent and were paid to return within 2 weeks for follow-up examination. Patients with a history of allergy to the penicillins were excluded. All patients treated were questioned regarding appearance of rash or other possible allergic reactions which might have resulted from the study drugs.

Urethral specimens were obtained for culture from men before and after treatment with a calcium alginate swab, and rectal and cervical cultures were obtained with a cotton-tipped applicator from each woman before and after treatment. Throat and rectal cultures were obtained from all male homosexuals, and throat cultures were obtained from women who admitted to orogenital sexual contact.

Isolation, identification, and antimicrobial susceptibility testing of N. gonorrhoeae. Specimens were immediately inoculated onto Thayer-Martin medium and incubated at 37 C in 3% CO_2. Typical oxidase-positive colonies of gram-negative diplococci were identified as *N. gonorrhoeae* by sugar fermentations. Isolates of *N. gonorrhoeae* were then stored at −70 C in 50% Trypticase soy broth (BBL) and 50% horse serum for subsequent susceptibility testing. The minimal inhibitory concentrations of penicillin G, amoxicillin, ampicillin, and carbenicillin were determined by a method described previously (15) for all isolates recovered after storage. Serial $\log_2$ dilutions of each antibiotic were prepared in concentrations ranging from 0.031 to 2.0 μg/ml in chocolate agar.

RESULTS

Pharmacological studies. The mean serum concentrations attained up to 12 h after increasing single oral doses of each drug are plotted in Fig. 1. The peak concentrations of amoxicillin were reached 1 h sooner than the peak for ampicillin plus probenecid, and the serum concentrations of amoxicillin also fell more rapidly. For each patient given 3.0 g of amoxicillin or 3.5 g of ampicillin plus probenecid, a plot on semilogarithmic paper of at least four separate concentrations obtained during the logarithmic phase of elimination gave an essentially straight line (correlation coefficient ≥ 0.958 for each). In 10 subjects, the mean serum half-life (±1 standard deviation) for 3.0 g of amoxicillin was 66.3 min (±4.6), and the corresponding value for 3.5 g of ampicillin plus 1.0 g of probenecid was 98.1 min (±13.8). After the 3.0-g dose of amoxicillin, the serum concentration of amoxicillin equalled or exceeded the minimal inhibitory concentration of amoxicillin for the most resistant strains of *N. gonorrhoeae* encountered in this study (1.0 μg/ml) from 1 through 6 h in all subjects. Mean serum concentrations of ampicillin were not strikingly increased from 4 through 12 h by increasing the dose of ampicillin administered with probenecid from 2.0 to 3.5 g; and the mean serum concentrations attained after 2.0 g of ampicillin plus 1.0 g of probenecid were higher at every interval from 5 to 12 h than those reached at the same intervals after 3.0 g of amoxicillin.

Results of treatment. The results of treatment are summarized in Table 1. Of 114 infected men and women who were treated, 108 returned for follow-up examination within 14 days after treatment. Twenty-four of 25 men and 22 of 23 women with anal or genital gonococcal infection, or both, who were treated with 3.0 g of oral amoxicillin had negative cultures when reexamined 3 to 14 days after treatment. Of the six patients given amoxicillin who were not given follow-up examinations within 14 days, five were reexamined from 15 to 33 days after treatment, and none remained infected. Twenty-nine of 30 men and all 30 women given 1.0 g of probenecid plus 3.5 g of ampicillin were cured of anal or genital infection, or both.

Follow-up throat cultures were obtained dur-

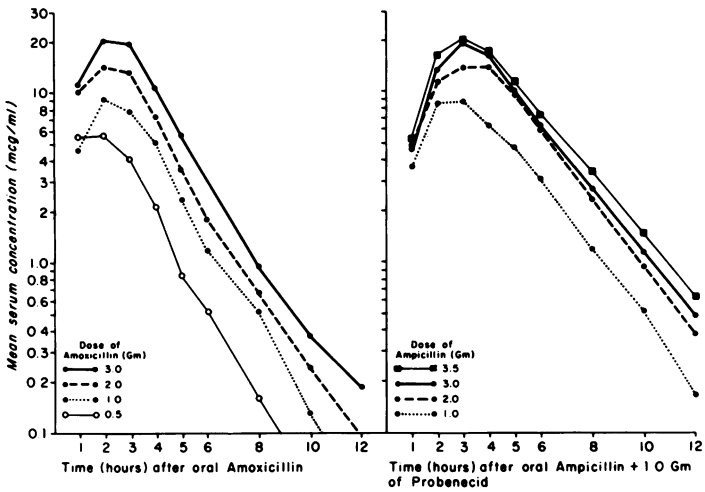

FIG. 1. *Mean serum concentrations of antibiotic during 12 h after graded oral doses of ampicillin, plus 1.0 g probenecid, and of amoxicillin in 10 male volunteers.*

TABLE 1. *Results of treatment of anogenital and oropharyngeal gonococcal infection with amoxicillin or with ampicillin plus probenecid*

Antibiotic	Anogenital		Oropharyngeal	
	No. treated	No. failed per no. examined by 3-14 days[a]	No. treated	No. failed per total no. examined by 7-43 days[b]
Amoxicillin, 3.0 g				
Males	28	1/25	1	0:0
Females	26	1/23 >4.2%	2	0:1
Ampicillin, 3.5 g, + 1.0 g of probenecid				
Males	30	1/30	2	2:2
Females	30	0/30 >1.7%	2	2:2

[a] Reexposure was admitted by all three patients who failed treatment.

[b] Reexposure was admitted by one female who failed treatment.

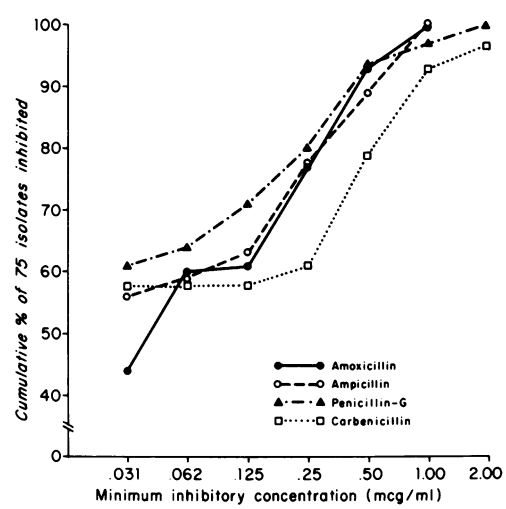

FIG. 2. *Cumulative percentage of isolates of N. gonorrhoeae inhibited by increasing concentrations of amoxicillin, ampicillin, penicillin G, and carbenicillin.*

ing reexamination from five of seven patients who had oropharyngeal infection documented prior to treatment. *N. gonorrhoeae* persisted in the oropharynx of all four patients given ampicillin plus probenecid, although three of these patients had concomitant anogenital infection which was cured by this treatment.

One additional heterosexual man with gonococcal urethritis was treated with ampicillin and probenecid, and throat cultures were not obtained at the initial visit. Eight days after treatment, he was hospitalized with classical manifestations of disseminated gonococcal infection, and *N. gonorrhoeae* was recovered from the throat, but not from the urethra. He denied interim sexual reexposure. He was retreated successfully for his disseminated gonococcal infection with a loading dose of 3.5 g of ampicillin plus 1.0 g of probenecid orally, followed by 2.0 g of ampicillin in four divided daily oral doses for 10 days. *N. gonorrhoeae* was eradicated from his pharynx with this regimen.

The only side effects noted in this study were

vomiting in two patients given amoxicillin and transient diarrhea in two patients given amoxicillin and in two given ampicillin plus probenecid.

In vitro susceptibility testing. Figure 2 shows the cumulative percentage of 75 isolates of *N. gonorrhoeae* which were inhibited by increasing concentrations of penicillin G, amoxicillin, ampicillin, and carbenicillin. Ampicillin and amoxicillin had comparable activity in vitro. The most sensitive strains of *N. gonorrheae* were often inhibited by slightly lower concentrations of penicillin G than of ampicillin (or amoxicillin), whereas relatively resistant strains were slightly more sensitive to ampicillin or amoxicillin than to penicillin G. The relatively greater activity of ampicillin against penicillin-resistant strains has been noted previously by others (8), and amoxicillin appears to be similar in this respect. Carbenicillin was the least effective drug in vitro, with 21% of the *N. gonorrhoeae* strains not inhibited by 0.5 μg of antibiotic per ml.

The minimal inhibitory concentration of ampicillin was 0.031 μg/ml for the cervical, rectal, and pharyngeal pretreatment isolates from a female patient with persistent pharyngeal gonococcal infection, who admitted to reexposure, was 0.25 and 0.5 μg/ml for the pretreatment pharyngeal isolates from two patients with persistent pharyngeal infection who denied reexposure, and was 0.5 μg/ml for the pretreatment urethral isolate from a male patient with persistent urethral infection who admitted reexposure. Pretreatment isolates from other patients with persistent infection were not saved for susceptibility testing.

DISCUSSION

Amoxicillin and ampicillin have comparable activity against *N. gonorrhoeae* in vitro. In this study, the efficacy of a single 3.0-g oral dose of amoxicillin alone in treating uncomplicated gonococcal infection of the urethra, endocervix, and anal canal was not significantly different from that of a single 3.5-g oral dose of ampicillin with 1.0 g of probenecid, one of the treatment regimens currently recommended by the U.S. Public Health Service. The efficacy of a single 3.0-g dose of amoxicillin should be evaluated in a larger number of patients, because the use of a single-drug regimen may be preferable to the use of two potentially allergenic drugs, ampicillin and probenecid, together for gonorrhea.

The failure of the single-dose ampicillin-probenecid regimen to cure oropharyngeal gonococcal infection has not previously been noted. Single intramuscular doses of 2.0 to 4.0 g of spectinomycin have also been very effective for anogenital gonococcal infection, but ineffective for pharyngeal infection (16). The high efficacy reported for other currently recommended treatment regimens for pharyngeal gonococcal infection (16) requires confirmation.

Eriksson (4) has suggested that the outcome of treatment of gonorrhea with varying dosage schedules of ampicillin is determined less by the peak concentration of ampicillin attained in the serum than by the total duration of time that the serum concentration exceeds that concentration which kills gonococci at the maximum rate. Similarly, Eagle's studies indicated that maximal rates of killing of pneumococci, streptococci, and *Treponema pallidum* could be achieved in vitro by critical concentrations of penicillin G, and higher concentrations of penicillin G did not produce more rapid killing (3). Although the concentration of ampicillin necessary for the maximal rate of killing of *N. gonorrhoeae* is unknown, the minimum bactericidal concentration of ampicillin closely approximates the minimal inhibitory concentration for most strains of *N. gonorrhoeae* (11).

The beneficial effect of increasing dosage of ampicillin, of giving a second dose of ampicillin after several hours, or of giving probenecid with ampicillin may, therefore, be due to prolongation of the time that the serum concentration remains above a certain critical level, throughout the minimal effective duration necessary to effect cure of gonorrhea (4). In this regard, Gibaldi and Schwartz (6) have suggested that the enhanced serum levels of ampicillin attained with probenecid are not attributable to the diminished tubular secretion of ampicillin, but are principally due to a significant decrease in the apparent volume of distribution of ampicillin. Probenecid has been a useful adjunct for the single-dose treatment of gonorrhea with ampicillin, but it is not clear whether this is primarily because probenecid produces a redistribution of ampicillin into the central body compartment or because it prolongs the serum half-life of penicillin by inhibiting renal tubular secretion.

The calculated serum half-life after 3.0 g of amoxicillin (66.3 ± 4.6 min) was close to the values obtained by Gordon et al. after 0.5 g of amoxicillin (61.3 ± 5.6 min) and 0.5 g of ampicillin (60.3 ± 3.3 min) (7). The serum half-life of ampicillin was shown to be increased to 98.1 ± 13.8 min when ampicillin was given together with 1.0 g of probenecid. The serum half-life of amoxicillin and of ampicillin given with probenecid did not appear to be dose-dependent in this study.

The minimal effective duration of amoxicillin for cure of gonorrhea is probably no more than 12 h, because the serum concentration of amoxicillin at 12 h was less than 0.25 μg/ml (the minimal inhibitory concentration of 22% of gonococcal isolates) in 7 of 10 volunteers given 3.0 g of amoxicillin by mouth. It seems likely that amoxicillin, if given with probenecid or in two divided doses separated by a 4- to 5-h interval, should be even more effective than comparable doses of ampicillin.

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