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Clinical Comparison of Single-Oral-Dose Cefuroxime Axetil and Amoxicillin with Probenecid for Uncomplicated Gonococcal Infections in Women

LARRY M. BADDOUR,[1,2]* RONALD S. GIBBS,[3] GREGORY MERTZ,[4] DAVID M. COCCHETTO,[5] AND ROBERT C. NOBLE[6]

Division of Infectious Diseases, Department of Medicine, University of Missouri-Columbia, One Hospital Drive, Columbia, Missouri 65212[1]; Infectious Disease Section, Memphis and Shelby County Health Department, Memphis, Tennessee 38105[2]; Department of Obstetrics and Gynecology, University of Texas Health Science Center, San Antonio, Texas 78284[3]; Department of Medicine, Division of Infectious Diseases, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131[4]; Glaxo Inc., Research Triangle Park, North Carolina 27709[5]; and Division of Infectious Diseases, Department of Medicine, University of Kentucky College of Medicine, Lexington, Kentucky 40536[6]*

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Four hundred sixty-six female patients were enrolled in a randomized study that compared the clinical efficacies of single oral doses of cefuroxime axetil and amoxicillin with probenecid in the treatment of uncomplicated gonorrhea. Two hundred ninety-five patients had culture-positive gonococcal infections and completed the investigation. Cure rates for the patients treated with cefuroxime axetil and those treated with amoxicillin with probenecid were high (>95%) for genitorectal infections. Pharyngeal infections, however, were not uniformly eradicated by either cefuroxime axetil (60%) or amoxicillin with probenecid (64%). Approximately 13% of each patient group suffered adverse events, which were gastrointestinal in the majority and were transient. Compared with amoxicillin plus probenecid, cefuroxime axetil in a single oral dose was an equally safe and effective drug for the treatment of uncomplicated gonorrhea in women caused by penicillin-susceptible strains.

Earlier studies (3, 4, 8–10, 12, 14, 16) examining the treatment of uncomplicated gonorrhea with a single dose of parenteral cefuroxime with and without oral probenecid demonstrated that this regimen was efficacious and well tolerated. Cefuroxime axetil, the ester prodrug of cefuroxime, was also shown to be effective (2, 5, 13, 18) in the treatment of uncomplicated gonorrhea when administered in a single oral dose, with and without probenecid. Although these investigations with cefuroxime axetil provided much information on the treatment of urethral infections in men, the studies enrolled relatively few women. We therefore examined the efficacy of single-dose cefuroxime axetil in a large number of women with uncomplicated gonorrhea who were seen at sexually transmitted disease clinics of four different city or county health departments.

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MATERIALS AND METHODS

Women were enrolled in the study from September 1986 through November 1987 if they had had sexual contact with a partner with culture-proven gonococcal infection. Patients were either asymptomatic or had signs and symptoms consistent with uncomplicated gonorrhea (e.g., dysuria, cervicitis, menorrhagia). The numbers (n) of patients enrolled from the sexually transmitted disease clinics were as follows: Memphis and Shelby County Health Department Clinic, Memphis, Tenn. (n = 125); Lexington-Fayette County Health Department Clinic, Lexington, Ky. (n = 40); San Antonio Metropolitan Health District Clinic, San Antonio, Tex. (n = 80); and Bernalillo County Health Department Clinic, Albuquerque, N.Mex. (n = 50). Patients were excluded from the trial if they had a positive pretreatment pregnancy test; evidence of concurrent syphilis; evidence of disseminated gonorrhea; a historical allergy to cephalosporins, penicillins, or probenecid; or a gastrointestinal disorder that could diminish antibiotic absorption or if they were unwilling to comply with follow-up visits. The study protocol was approved by the local institutional review board at each center, and informed consent was obtained from all patients.

After enrollment, medical and sexual histories and oropharyngeal and genitourinary examinations were performed. During the physical examination, swabs were taken for *Neisseria gonorrhoeae* cultures from the cervix, urethra, rectum, and pharynx of each patient. In addition, swabs were obtained for chlamydia cultures from the cervix and urethra.

N. gonorrhoeae was identified from specimens as oxidase-positive colonies of gram-negative diplococci on either modified Thayer-Martin, Martin-Lewis, chocolate, or NYC agar. Sugar fermentation was performed for verification of species. Tests of susceptibility to penicillin G, ampicillin, and cefuroxime and the nitrocefin method to detect penicillinase production were done. Urethral and cervical specimens were cultured for *Chlamydia trachomatis* by a McCoy cell culture method that included the use of fluorescein-conju-

* Corresponding author.

TABLE 1. Demographic characteristics of patients in each treatment group

Characteristic	Cefuroxime axetil	Amoxicillin plus probenecid
No. of women	235	231
Mean age (yr) (range)	24 (18–47)	25 (18–52)
% of patients with symptoms or signs at presentation	60	66
No. of pretreatment cultures for *N. gonorrhoeae*		
No site infected	65	69
1 site infected	51	59
2–4 sites infected	119	103
No. of patients with positive cultures not lost to follow-up/total (%)	152/170 (89.4)	143/162 (88.3)

gated monoclonal antibodies to identify chlamydial inclusions (1).

Women were randomly allocated to receive a single oral dose of cefuroxime axetil (1 g) or of amoxicillin (3 g) with 1 g of probenecid. Patients were counseled regarding the need to remain sexually abstinent while participating in the investigation. For several reasons, the study was not conducted in double-blind manner. First, placebo amoxicillin and probenecid were not available from the drugs' manufacturers. Second, there were practical limitations to the number of tablets (active plus placebo) that each patient could be asked to ingest in a double-blind, double-dummy design. Third, the test of cure cultures provided an objective measure of the microbiologic response to the antimicrobial agents.

After 4 to 7 days, the patients with positive gonococcal cultures returned to the clinics for reexamination. All four sites were again swabbed for *N. gonorrhoeae* cultures. At this time, chlamydia culture results were available, and women with positive cultures were given tetracycline (500 mg) to be taken orally four times daily for 7 days.

At 12 to 14 days after the initial visit, patients with positive chlamydia cultures were contacted for follow-up evaluation. Chi-square tests were used for comparison in the evaluation of therapeutic efficacy and drug toxicity.

RESULTS

The demographic features, microbiologic findings, and therapeutic efficacy rates of enrollees at the four study sites were similar; 466 women were randomized in this multicenter study, with 235 (50.4%) patients receiving cefuroxime axetil and 231 patients receiving amoxicillin with probenecid. Of the cefuroxime axetil-treated patients, 72.3% had one or more sites culture positive for *N. gonorrhoeae* compared with 70.1% (162 of 231) of the patients who received amoxicillin with probenecid (Table 1). Of those patients with documented gonococcal infections, 119 (70%) of the cefuroxime axetil recipients and 103 (64%) of the amoxicillin-probenecid-treated patients had multiple positive site cultures for *N. gonorrhoeae* (Table 1). The two groups were similar in age. Sixty percent of patients treated with cefuroxime axetil showed signs and/or symptoms of possible gonococcal infection, whereas two-thirds of the amoxicillin with probenecid-treated patients had clinical evidence of infection at initial presentation to the clinic.

Ninety-three percent of evaluable women who received treatment with cefuroxime axetil had cervical cultures positive as compared with 91% of culture-positive women treated with amoxicillin-probenecid. Approximately two-thirds of patients in both groups had urethral infections. In contrast, rectal and pharyngeal infections were proven in less than 40% of patients in each group. One-third of the women in both treatment groups had *C. trachomatis* isolated from pretreatment cultures. No follow-up chlamydial cultures were obtained after treatment with tetracycline.

Evaluation of efficacy showed that the two treatment regimens were similar. Overall, 136 (89.5%) of 152 of the cefuroxime-treated patients and 132 (92.3%) women who received amoxicillin with probenecid were cured (Table 2). Cure rates for both treatments decreased as the number of infected sites increased. When examined by site of infection, the data indicate that both regimens were efficacious, clearing gonococcal infections in over 95% of cervical, urethral, and rectal sites (Table 2). In contrast, both regimens fared less well in the treatment of pharyngeal gonococcal infections, with approximately two-thirds of pharyngeal sites infected with *N. gonorrhoeae* cured. The pharyngeal site accounted for 10 (62.5%) of 16 and 8 (72.7%) of 11 patients who failed the regimen of cefuroxime axetil and the regimen of amoxicillin with probenecid, respectively.

None of the gonococcal isolates that accounted for the microbiologic failures in patients treated with either of the two drug regimens was resistant to penicillin, ampicillin, or cefuroxime in in vitro susceptibility testing with disk diffusion. Three of the gonococcal isolates from patients who were microbiologically cured with either cefuroxime axetil ($n = 2$) or amoxicillin with probenecid ($n = 1$) demonstrated penicillinase production, whereas no chromosomally mediated penicillin resistance was found among the gonococcal isolates.

The drugs were well tolerated, with approximately 13% of patients in each treatment group reporting adverse events (Table 3). Various gastrointestinal reactions, such as nausea, vomiting, diarrhea, upset stomach, and abdominal pain, accounted for more than three-quarters of these complaints. Other events in both treatment groups included vaginitis, rash or pruritis, shortness of breath, dizziness, sleepiness or fatigue, headache, and fainting.

TABLE 2. Biological efficacy by site of infection

Treatment (n)	No. of patients cured/total (%) with infection as follows:					
	Cervix	Urethra	Rectum	Combination[a]	Pharynx	Total
Cefuroxime axetil (152)	138/141 (97.9)	98/102 (96.1)	53/54 (98.1)	136/142 (95.8)[b]	15/25 (60.0)	136/152 (89.5)[b]
Amoxicillin-probenecid (143)	129/130 (99.2)	87/89 (97.8)	41/42 (97.6)	132/135 (97.8)[b]	14/22 (63.6)	132/143 (92.3)[b]

[a] Any combination of genital and/or rectal infections.
[b] No significant difference ($P > 0.05$, chi-square test).

TABLE 3. Number of patients reporting adverse events among all patients treated with single-dose therapies[a]

Adverse event	No. of patients reporting event after treatment with:	
	Cefuroxime axetil (n = 235)	Amoxicillin plus probenecid (n = 231)
Nausea	9	5
Vomiting	8	2
Diarrhea	3	8
Upset stomach	2	5
Abdominal pain or cramps	3	5
Vaginitis	7	5
Rash or pruritis	2	2
Shortness of breath	0	1
Dizziness	2	2
Sleepiness or fatigue	1	3
Headache	1	0
Fainting	0	1

[a] Some patients reported more than one event: 32 of 235 (13.6%) women receiving cefuroxime axetil and 31 of 231 (13.4%) women receiving amoxacillin plus probenecid.

DISCUSSION

After previous investigators (3, 4, 8–10, 12, 14, 16) demonstrated the efficacy of parenteral cefuroxime in the treatment of uncomplicated gonorrhea, Reichman and colleagues (13) used a single oral dose of cefuroxime axetil with and without probenecid in a randomized study of 184 patients with uncomplicated gonorrhea. They employed three treatment regimens which included (i) cefuroxime axetil (1 g), (ii) cefuroxime axetil (1 g) with probenecid, and (iii) amoxicillin (3 g) with probenecid. Cure rates in the treatment groups were 98, 98, and 96%, respectively. Only 2% of patients who received cefuroxime axetil alone complained of nausea, as compared with 11% of those who received either regimen that contained probenecid ($P < 0.05$). With only 29 women enrolled in the study, the efficacy of oral cefuroxime axetil in the therapy of uncomplicated gonorrhea in women was not as well established as that for men.

Three different studies (2, 5, 18) published 1 year later supported the clinical impression that cefuroxime axetil was as efficacious and as safe as standard therapy with either ampicillin or amoxicillin with probenecid. However, only 40 (11.6%) of the 346 patients examined in the three drug trials were women. Moreover, one of the investigations (5) included men exclusively.

Before the present survey, only a small number of patients treated in the four published cefuroxime axetil comparison trials (2, 5, 13, 18) manifested rectal gonococcal infections. One study (2) entered no patients with rectal infections, and another survey (18) did not distinguish numbers of patients with either rectal or pharyngeal infections. Since only 8 of 129 patients in the latter study (18) harbored infections at sites other than the cervix or urethra, recommendations with regard to the treatment of gonococcal infections of the rectum and pharynx were precluded. Only 13 patients with rectal infections were evaluated in the two remaining studies (5, 13). Five of seven patients given cefuroxime axetil alone were cured, whereas all six patients treated with both cefuroxime axetil and probenecid were successfully treated.

Of 54 women with rectal gonococcal infections treated with cefuroxime axetil, 53 (98.2%) were cured. In addition, over 97% of patients treated with the amoxicillin-probenecid regimen had rectal infection eliminated.

As seen in the present investigation, pharyngeal gonococcal infections are usually more difficult to eradicate as compared with genitorectal infections (6). To control the spread of *N. gonorrhoeae*, identifying therapeutic regimens effective in eradicating gonococci from the oropharynx seems appropriate (6). At the same time, pharyngeal infections are usually asymptomatic (6, 17, 20), undergo spontaneous cure (6, 17), and are considered by some as unusual sources of transmission of *N. gonorrhoeae* (17, 19).

Several statements seem appropriate concerning the use of cefuroxime axetil for the treatment of uncomplicated gonorrhea. First, cefuroxime axetil is as effective and safe as amoxicillin with probenecid for the therapy of cervical, urethral, and rectal infections in women. Second, cefuroxime axetil, like amoxicillin with probenecid, is much less efficacious for the treatment of gonococcal pharyngeal infections. Third, the role of cefuroxime axetil in the treatment of infections caused by penicillinase-producing *N. gonorrhoeae* remains to be established, since only three women in this study were infected with penicillinase-producing strains. At the same time, in vitro susceptibility data (7, 11, 15), reports of small numbers of successfully treated cases (18) (including the two women in the present series treated with cefuroxime axetil), and previously demonstrated efficacy of parenteral cefuroxime therapy suggest that cefuroxime axetil may be effective against infections due to penicillinase-producing *N. gonorrhoeae* and deserves further evaluation.

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