

Comparison of Single-Dose Cefuroxime Axetil with Ciprofloxacin in Treatment of Uncomplicated Gonorrhea Caused by Penicillinase-Producing and Non-Penicillinase-Producing *Neisseria gonorrhoeae* Strains

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A randomized, multicenter, investigator-blind trial was conducted to compare the efficacies of cefuroxime axetil and ciprofloxacin for treatment of patients with uncomplicated gonorrhea caused by penicillinase-producing *Neisseria gonorrhoeae* (PPNG). A total of 832 patients (434 females and 398 males) received a single oral dose of cefuroxime axetil (1,000 mg [417 patients]) or ciprofloxacin (500 mg [415 patients]). *N. gonorrhoeae* was eradicated from the cervix in 114 of 118 (97%) and 118 of 119 (99%) bacteriologically evaluable females treated with cefuroxime axetil and ciprofloxacin, respectively ($P = 0.213$; difference, -2%; 95% confidence interval, -6 to 1%), and from the urethra in 154 of 166 (93%) and 171 of 171 (100%) bacteriologically evaluable male patients treated with cefuroxime axetil and ciprofloxacin, respectively ($P < 0.001$; difference, -7%; 95% confidence interval, -11 to -3%). Both treatments were effective in eradicating *N. gonorrhoeae* in females with rectal infections (cefuroxime axetil, 29 of 30 [97%]; ciprofloxacin, 25 of 25 [100%]; $P = 1.00$). In small numbers of patients, cefuroxime axetil was less effective than ciprofloxacin in treating males with pharyngeal infections (eradication in 4 of 10 and in 8 of 8 patients, respectively; $P = 0.013$). PPNG was eradicated from the cervix in 22 of 23 (96%) and 32 of 32 (100%) bacteriologically evaluable female patients treated with cefuroxime axetil and ciprofloxacin, respectively ($P = 0.418$; difference, -4%; 95% confidence interval, -13 to 4%), and from the urethra in 35 of 36 (97%) and 34 of 34 (100%) bacteriologically evaluable male patients treated with cefuroxime axetil and ciprofloxacin, respectively ($P = 1.00$; difference, -3%; 95% confidence interval, -8 to 3%). The incidences of drug-related adverse events were similar for the two study drugs. In summary, treatment with a single oral dose of cefuroxime axetil is as effective as treatment with a single oral dose of ciprofloxacin in eradicating PPNG from males and females with uncomplicated gonorrhea (urethral and endocervical), and both regimens are well-tolerated. However, in the present study, cefuroxime axetil was less effective than ciprofloxacin in treating urethral gonococcal infections in male patients, although both study drugs were highly effective in treating cervical gonococcal infections in female patients.

The proportion of *Neisseria gonorrhoeae* isolates in the United States demonstrating plasmid-mediated resistance to penicillin has increased steadily in the 1980s and now approaches 10% nationwide (4). The increased incidence of gonorrhea caused by penicillinase-producing *N. gonorrhoeae* (PPNG) strains has led the Centers for Disease Control and Prevention (CDC) to recommend the use of broad-spectrum cephalosporins or fluoroquinolones as primary therapy for uncomplicated gonorrhea (2, 3). More recently, concerns have been raised as to the emergence of strains with decreased susceptibility to quinolones in certain geographic areas of the United States (11, 12, 21), some of which have been associated with treatment failures (5).

Although the CDC has recommended intramuscular ceftriaxone and oral ciprofloxacin, ofloxacin, and cefixime as the single-dose regimens of choice in the treatment of uncomplicated gonorrhea (3, 13), there is a need for additional single-dose oral cephalosporin regimens. Cefuroxime axetil is the oral

ester prodrug of cefuroxime, a parenterally administered expanded-spectrum cephalosporin characterized by stability to bacterially-produced beta-lactamases and broad-spectrum activity against gram-positive and gram-negative bacteria, including *N. gonorrhoeae* (8, 18). Previous studies have shown that a single 1,000-mg oral dose of cefuroxime axetil, either with or without probenecid, is effective in the treatment of uncomplicated gonorrhea in men and women (1, 9).

While cefuroxime axetil is approved for the treatment of uncomplicated gonorrhea (urethral and endocervical) caused by non-PPNG strains, insufficient data were available from previous studies to allow an assessment of its efficacy in patients with uncomplicated gonorrhea caused by PPNG strains. The present study was designed to compare the efficacy and safety of single-dose oral treatments with cefuroxime axetil versus ciprofloxacin in patients with uncomplicated gonorrhea caused by PPNG strains.

MATERIALS AND METHODS

Patients. Patients were enrolled into this randomized, investigator-blind, multicenter trial between April 1992 and March 1994 at 10 public sexually transmitted disease clinics located throughout the United States and Puerto Rico (Indi-

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anapolis, Ind.; Denver, Colo.; Birmingham, Ala.; Akron, Ohio; Brooklyn, N.Y.; San Juan, Puerto Rico; Baltimore, Md.; Chicago, Ill.; Memphis, Tenn.; and Boston, Mass.). Outpatients between the ages of 18 and 65 with uncomplicated gonorrhea, whether symptomatic or asymptomatic, as well as sexual contacts of individuals with known gonorrhea, were candidates for study enrollment. Isolation of *N. gonorrhoeae* at enrollment from at least one of the three body sites cultured was required to evaluate the efficacy of treatment. The targeted enrollment of 750 patients was selected to ensure the inclusion of a sufficient number of evaluable PPNG cases for meaningful analyses to be performed.

Patients were excluded if they were pregnant or lactating, if they had a history of an immediate or delayed hypersensitivity to any cephalosporin, penicillin, or quinolone, if they had taken any systemic antibiotic within 3 days prior to enrollment, if they had gastrointestinal disorders that would interfere with the absorption of orally administered antibiotics, if they had signs or symptoms of complicated gonorrhea or syphilis, if they were immunocompromised or receiving systemic steroids, or if they had concomitant underlying conditions compromising their ability to respond to infections. The study protocol was approved by the institutional review board at each center, and written informed consent was obtained from all patients.

Diagnostic tests. Specimens for the isolation of *N. gonorrhoeae* were obtained from the urethra, pharynx, and, when possible, from the rectum for male patients and from the endocervix, pharynx, and rectum for female patients. Specimens for *Chlamydia trachomatis* culture or antigen detection were obtained from the urethra in men and from the cervix in women. A serologic test for syphilis was done with a pretreatment serum sample by using either the Venereal Disease Research Laboratory or the Rapid Plasma Reagin test. All women of childbearing potential were required to have a negative urine pregnancy test at the pretreatment visit prior to being enrolled in the study.

Treatment and study design. Patients were randomly assigned to receive either a single 1,000-mg oral dose of cefuroxime axetil (Ceftin; Glaxo Wellcome Inc., Research Triangle Park, N.C.) or a single 500-mg oral dose of ciprofloxacin (Cipro; Miles, Inc., West Haven, Conn.), according to a computer-generated randomization scheme. To maintain investigator blinding, medication was dispensed by the study coordinator or other clinic staff, and patients were instructed not to discuss their study medication with the investigator conducting the clinical evaluation.

The primary efficacy endpoint was bacteriological outcome, which was based on eradication of *N. gonorrhoeae* from body sites which were positive pretreatment. The study was prospectively designed so that patients were bacteriologically evaluable if at least one body site was culture positive for *N. gonorrhoeae* at enrollment, if all pretreatment *N. gonorrhoeae* isolates were susceptible in vitro to both study drugs, and if they returned for follow-up examination and culture for *N. gonorrhoeae* 4 to 8 days after treatment. At follow-up, specimens were obtained for culture of *N. gonorrhoeae* from all body sites tested at enrollment. Patients whose pretreatment test was positive for *C. trachomatis*, whose pretreatment syphilis serology indicated active infection, or who had symptoms of postgonococcal urethritis at the follow-up visit received appropriate therapy and additional follow-up according to local protocol.

Laboratory procedures. Specimens for the isolation of *N. gonorrhoeae* were inoculated directly onto selective (modified Thayer Martin or Martin Lewis) and/or nonselective (chocolate agar) media and promptly incubated at 35 to 37°C in a 5% CO₂ environment. Gram staining was performed on colonies with characteristic morphology to demonstrate the presence of typical gram-negative diplococci. Presumptive *N. gonorrhoeae* isolates (i.e., oxidase-positive colonies present on selective media) were confirmed by sugar utilization or fluorescent monoclonal antibody confirmation tests. Beta-lactamase (penicillinase) production was determined by the chromogenic cephalosporin method with a nitrocephin substrate (17). The MICs of cefuroxime, ciprofloxacin, penicillin G, and tetracycline were determined by the agar dilution methodology recommended by the National Committee for Clinical Laboratory Standards. *N. gonorrhoeae* isolates were classified as susceptible, moderately susceptible, or resistant according to the breakpoint criteria established by NCCLS for cefuroxime, penicillin, and tetracycline (14) and a susceptibility breakpoint of ≤ 0.06 µg/ml for ciprofloxacin (7).

Specimens for *C. trachomatis* culture were inoculated onto cyclohexamide-treated McCoy cells, and these were incubated at 37°C. *C. trachomatis* was identified by the presence of inclusion bodies on staining. For laboratories in which chlamydia was not routinely identified by culture, acceptable alternative procedures used were direct fluorescent antibody or enzyme immunoassay techniques. Syphilis serology results by either the Venereal Disease Research Laboratory or the Rapid Plasma Reagin test were expressed as nonreactive, weakly reactive, or reactive.

Safety assessment. The safety of the study drugs was assessed by recording adverse events. The investigator evaluated the severities of all adverse events and judged whether an event was related to the study drug.

Statistical analyses. The two treatments were compared with respect to bacteriological outcomes (i.e., eradication of *N. gonorrhoeae*) at each body site and for each sex by using a Pearson chi-square test or a two-sided Fisher exact test (6), as appropriate.

Demographic characteristics of sex and ethnic origin were compared by a Pearson chi-square test, while the age comparison was done by the Wilcoxon rank sum test. Incidence rates for adverse events were compared between treat-

TABLE 1. Summary of demographic characteristics of study patients

Characteristic	Cefuroxime axetil (%)	Ciprofloxacin (%)	<i>P</i> value ^a
No. of patients	417	415	
Sex			
Female	220 (52.8)	214 (51.6)	0.731
Male	197 (47.2)	201 (48.4)	
Ethnic origin			
Black	381 (91.4)	391 (94.2)	0.112
Caucasian	23 (5.5)	10 (2.4)	
Hispanic	13 (3.1)	13 (3.1)	
Unknown	0 (0.0)	1 (0.2)	
Age (yrs)			
Mean (± SEM)	26.1 (±0.4)	26.0 (±0.4)	0.866
Range	17–64	17–54	
Chlamydia coinfection			
Females	28 (12.7)	33 (15.4)	
Males	10 (5.1)	18 (9.0)	
Total	38 (9.1)	51 (12.3)	0.141

^a Sex, ethnic origin, and chlamydia coinfection were compared by a Pearson chi-square statistic (test for ethnic origin comparing black versus all other groups). Age was compared by the Wilcoxon rank sum statistic.

ment groups for all adverse events and for those deemed by the investigator to be drug related. To define incidence, an adverse event in a patient experiencing the same event more than once was counted only once. Analysis was done by a two-sided Fisher exact test for each type of event, grouped by body system and over all body systems. In all cases, a *P* value of less than or equal to 0.05 was considered an indication of statistical significance.

RESULTS

A total of 832 patients were enrolled in the study, of whom 417 and 415 were treated with cefuroxime axetil and ciprofloxacin, respectively. There were no significant differences between treatment groups with respect to all demographic characteristics (Table 1). Slightly more than half of the patients in each treatment group were female, and >90% of the patients in each treatment group were black. One patient in each group was below the minimum age of 18 and was considered unevaluable because of this enrollment violation.

Of the 398 males, only one lacked clinical signs and symptoms of uncomplicated gonorrhea at the pretreatment visit (data not shown); this patient was a contact of an individual known to have gonorrhea. In the case of the 434 females enrolled in the study, 15% (64 of 434) lacked clinical signs and symptoms of uncomplicated gonorrhea at the pretreatment visit. Of these, 78% (50 of 64) were contacts of an individual known to have gonorrhea, with the remaining 14 females enrolled because of a recent screening cervical culture which had been positive for *N. gonorrhoeae* or because of intracellular gram-negative diplococci on Gram staining of an endocervical specimen.

Bacteriological outcome. Although three body sites were cultured in male and female patients, the primary bacteriological efficacy assessment focused on the principal body sites, the urethra in males and the cervix in females.

(i) Females. Of the 434 females, 237 (55%) were bacteriologically evaluable (Table 2). This low evaluability rate primarily reflects the considerable number of female patients who yielded no pretreatment cervical *N. gonorrhoeae* isolate. Three-fourths (154 of 197) of the unevaluable female patients failed to yield a pretreatment cervical *N. gonorrhoeae* isolate, while 9% (17 of 197) yielded an isolate which was not tested for in vitro susceptibility because of loss of viability, and 8% (15 of 197) failed to return for the follow-up visit. The remaining 11

TABLE 2. Bacteriological efficacy by culture source in female patients with uncomplicated gonorrhoea treated with cefuroxime axetil or ciprofloxacin^a

Treatment and group	Source of culture	No. eradicated (% ^b)	No. that persisted (% ^b)	Total no. of evaluable patients	No. of unevaluable patients	Total no. of patients
All female patients						
Cefuroxime axetil (1,000 mg)	Cervix	114 (96.6)	4 (3.4)	118	102	220
	Rectum	29 (96.7)	1 (3.3)	30	12	42
	Pharynx	9 (75.0)	3 (25.0)	12	6	18
Ciprofloxacin (500 mg)	Cervix	118 (99.2)	1 (0.8)	119	95	214
	Rectum	25 (100)	0 (0.0)	25	7	32
	Pharynx	13 (100)	0 (0.0)	13	3	16
Female PPNG patients only						
Cefuroxime axetil (1,000 mg)	Cervix	22 (95.7)	1 (4.3)	23	6	29
	Rectum	2 (100)	0 (0.0)	2	3	5
	Pharynx	2 (100)	0 (0.0)	2	0	2
Ciprofloxacin (500 mg)	Cervix	32 (100)	0 (0.0)	32	3	35
	Rectum	7 (100)	0 (0.0)	7	1	8
	Pharynx	3 (100)	0 (0.0)	3	0	11

^a Comparison of eradication rates between treatment groups was performed by the Fisher exact test. For cefuroxime axetil versus ciprofloxacin, *P* values for all female patients were as follows: cervix, 0.213; rectum, 1.000; pharynx, 0.096. For female PPNG patients only, *P* values were as follows: cervix, 0.418; rectum and pharynx, not done.

^b Percentage of evaluable patients.

patients, none of whom both yielded a cefuroxime-resistant gonococcal isolate and were randomized to cefuroxime axetil, were unevaluable for a variety of other miscellaneous reasons.

N. gonorrhoeae was eradicated from the cervixes of 114 of 118 (97%) and 118 of 119 (99%) of bacteriologically evaluable females treated with cefuroxime axetil or ciprofloxacin, respectively (*P* = 0.213; difference, -2%; 95% confidence interval [CI], -6 to 1%; Table 2). Two of five (40%) female treatment failures (both in the cefuroxime axetil group) reported that they failed to refrain from sexual activity while in the study, thus raising the possibility of reinfection of these patients. Consistent with this possibility was the finding that a lower proportion of successfully treated female patients (17%; 40 of 232; *P* = 0.22) reported being sexually active while in the study.

When eradication of *N. gonorrhoeae* at secondary body sites was examined, there were too few evaluable female patients with pharyngeal infections to allow meaningful analyses (Table 2). However, both study drugs were highly effective in eradicating rectal gonorrhoea in females in that 29 of 30 (97%) and 25 of 25 (100%) bacteriologically evaluable patients treated with cefuroxime axetil or ciprofloxacin, respectively, were assessed as bacteriological cures. Both study drugs were also effective in eradicating both cervical and rectal gonorrhoea in females infected at these two body sites; all 18 such patients treated with ciprofloxacin who were bacteriologically evaluable had their infections at both body sites eradicated, while eradication of both infections was obtained in 24 of 27 (89%) such patients treated with cefuroxime axetil. The three cefuroxime axetil-treated female patients with an unsuccessful bacteriological outcome at one of the body sites included one patient whose cervical infection was eradicated but whose rectal infection persisted and two patients with the opposite outcome.

(ii) **Female PPNG.** Of the 434 females enrolled in the study, 64 (15%) had cervical infections caused by PPNG strains. Fifty-five of the 237 (23%) bacteriologically evaluable females had PPNG cervical infections. Nine women with PPNG infections were unevaluable either because they failed to return for the follow-up visit (6 patients) or because their isolates were nonviable for in vitro testing (3 patients). Cervical PPNG was eradicated from 22 of 23 (96%) and 32 of 32 (100%) of bacteriologically evaluable females treated with cefuroxime axetil

or ciprofloxacin, respectively (*P* = 0.418; difference, -4%; 95% CI, -13 to 4%; Table 2). The single bacteriological failure denied being sexually active while on study. While the number of female patients with PPNG infections at the two secondary body sites was too small to allow meaningful analysis, both study drugs eradicated all treated PPNG rectal and pharyngeal infections (cefuroxime axetil, 4 [2 + 2]; ciprofloxacin, 10 [7 + 3]).

(iii) **Males.** Of the 398 males enrolled in the study, 337 (85%) were bacteriologically evaluable (Table 3). Half (31 of 61) of the unevaluable patients failed to return for the follow-up visit, and for one-sixth (10 of 61), either no pretreatment urethral *N. gonorrhoeae* isolate was yielded or the isolate obtained was not tested for in vitro susceptibility because of loss of viability. The remaining 10 patients, none of whom both yielded a cefuroxime-resistant gonococcal isolate and were randomized to cefuroxime axetil, were unevaluable for a variety of other miscellaneous reasons.

N. gonorrhoeae was eradicated from the urethras of 154 of 166 (93%) and 171 of 171 (100%) of bacteriologically evaluable males treated with cefuroxime axetil or ciprofloxacin, respectively (*P* < 0.001; difference, -7%; 95% CI, -11 to -3%; Table 3). As in the case of treatment failures among females, a higher proportion of unsuccessfully treated males (25%; 3 of 12) reported being sexually active while in the study than did male patients with cured urethral gonococcal infections (12%; 39 of 325; *P* = 0.18), once again raising the possibility of reinfection in these patients. However, the percentages of sexually active males in the cefuroxime axetil and ciprofloxacin groups were identical (12%), despite the higher rate of treatment failures in the former group.

When eradication of *N. gonorrhoeae* at secondary body sites was examined, there were too few evaluable male patients with rectal infections to allow meaningful analyses (Table 3). Although the number of cases was small, the cure rate for pharyngeal gonorrhoea with cefuroxime axetil (40%; 4 of 10) was significantly lower than that seen with ciprofloxacin (100%; 8 of 8 [*P* = 0.01]).

(iv) **Male PPNG.** Of the 398 males enrolled in the study, 78 (20%) had urethral infections caused by PPNG strains. Seventy of the 337 (21%) bacteriologically evaluable males had PPNG

TABLE 3. Bacteriological efficacy by culture source in male patients with uncomplicated gonorrhoea treated with cefuroxime axetil or ciprofloxacin^a

Treatment	Source of culture	No. eradicated (% ^b)	No. that persisted (% ^b)	Total no. of evaluable patients	No. of unevaluable patients	Total no. of patients
All male patients						
Cefuroxime axetil (1,000 mg)	Urethra	154 (92.8)	12 (7.2)	166	31	197
	Rectum	1 (100)	0 (0.0)	1	1	2
	Pharynx	4 (40.0)	6 (60.0)	10	2	12
Ciprofloxacin (500 mg)	Urethra	171 (100)	0 (0.0)	171	30	201
	Rectum	1 (100)	0 (0.0)	1	1	2
	Pharynx	8 (100)	0 (0.0)	8	3	11
Male PPNG patients only						
Cefuroxime axetil (1,000 mg)	Urethra	35 (97.2)	1 (2.8)	36	4	40
	Rectum	0 (0.0)	0 (0.0)	0	0	0
	Pharynx	1 (50.0)	1 (50.0)	2	0	2
Ciprofloxacin (500 mg)	Urethra	34 (100)	0 (0.0)	34	4	38
	Rectum	0 (0.0)	0 (0.0)	0	0	0
	Pharynx	2 (100)	0 (0.0)	2	0	2

^a Comparison of eradication rates between treatment groups was performed by a Pearson chi-square test (all male patients) or Fisher exact test (male PPNG patients only). For cefuroxime axetil versus ciprofloxacin, *P* values for all male patients were as follows: urethra, <0.001; rectum, not done; pharynx, 0.013. For male PPNG patients only, *P* values were as follows: urethra, 1.000; rectum, not applicable; pharynx, not done.

^b Percentage of evaluable patients.

urethral infections. Of the 8 men with PPNG infections who were unevaluable, 5 failed to return for the follow-up visit, 2 had major protocol violations, and 1 yielded an isolate which was not tested for in vitro susceptibility because of loss of viability. Urethral PPNG was eradicated from 35 of 36 (97%) and 34 of 34 (100%) of bacteriologically evaluable males treated with cefuroxime axetil or ciprofloxacin, respectively (*P* = 1.00; difference, -3%; 95% CI, -8 to 3%; Table 3). The single bacteriological failure reported being sexually active while in the study and thus may have been reinfected. No male patients had a PPNG infection at the rectal site, and one of the two cefuroxime axetil-treated male patients with pharyngeal PPNG infections failed treatment.

Antimicrobial susceptibility of *N. gonorrhoeae*. A total of 756 pretreatment *N. gonorrhoeae* isolates from all body sites examined survived storage and were tested for in vitro susceptibility to cefuroxime, ciprofloxacin, penicillin G, and tetracycline, of which 648 represented single isolates obtained from individual patients (Table 4). The MICs of the four antibiotics tested were in the expected ranges, with the geometric mean MICs of cefuroxime and ciprofloxacin, the two study drugs, being 0.064 and 0.004 µg/ml, respectively. It is interesting to note that when strains producing beta-lactamase and/or demonstrating plasmid-mediated resistance to tetracycline are excluded, both

the MICs at which 50% of the isolates are inhibited (MIC₅₀s) and MIC₉₀s for penicillin G and tetracycline are very similar to those reported previously (10) against *N. gonorrhoeae* isolates obtained from patients enrolled in a study comparing single-dose treatment with cefixime and ceftriaxone.

Of the *N. gonorrhoeae* isolates collected in the present study, one-fourth (166 of 646) were resistant to penicillin G, most of which (139) produced beta-lactamase. When the role of chromosomally mediated penicillin resistance in determining bacteriological outcome was examined, 147 of 567 (26%) patients whose gonococcal infections were eradicated yielded penicillin-resistant isolates versus 3 of 18 (17%) patients who were not cured (*P* = 0.58). In addition, nearly one-third (203 of 648) of the isolates were resistant to tetracycline, reflecting plasmid-mediated resistance in 38% (77) of these strains. Only two isolates were resistant to cefuroxime (MIC, 4.0 µg/ml), both of which also demonstrated chromosomally mediated resistance to penicillin G and tetracycline, while none of the isolates were resistant to ciprofloxacin. One of the patients with a resistant strain was a bacteriological cure following treatment with cefuroxime axetil, while the other patient was randomized to ciprofloxacin. Three patients had isolates which were moderately susceptible to cefuroxime, two of whom were successfully

TABLE 4. Antimicrobial susceptibilities of pretreatment isolates of *N. gonorrhoeae*^a

Antimicrobial agent	MIC (µg/ml)							
	All isolates (<i>n</i> = 648)				PPNG isolates only (<i>n</i> = 139)			
	Geometric mean	MIC ₅₀	MIC ₉₀	Range	Geometric mean	MIC ₅₀	MIC ₉₀	Range
Cefuroxime	0.064	0.060	0.25	≤0.002–4.0	0.048	0.060	0.25	0.002–1.0
Ciprofloxacin	0.004	0.004	0.015	≤0.001–0.060	0.003	0.004	0.015	≤0.001–0.015
Penicillin G	0.429	0.25	32	0.008–128	12.4	32	32	0.030–128
Penicillin G ^b	0.171	0.125	1.0	0.008–16				
Tetracycline	0.921	0.50	16	≤0.015–>32	1.97	2.0	16	≤0.060–32
Tetracycline ^c	0.608	0.50	4.0	≤0.015–8.0				

^a Only one *N. gonorrhoeae* isolate per patient is included; in cases in which more than one pretreatment isolate was obtained from an individual patient, a single isolate was included in this data analysis in the following order of preference of body sites: genital > rectum > pharynx.

^b Excludes 139 beta-lactamase-producing strains.

^c Excludes 77 strains with plasmid-mediated resistance to tetracycline (i.e., tetracycline with a MIC of ≥16 µg/ml).

treated with cefuroxime axetil while the other received ciprofloxacin.

Adverse events. One or more adverse events judged by the investigator to be drug related were reported by 15% of cefuroxime axetil-treated patients and 13% of ciprofloxacin-treated patients ($P = 0.42$). The most common drug-related adverse events in both treatment groups were associated with the gastrointestinal system (10 versus 7%, respectively), particularly nausea and diarrhea. No patients in either group withdrew from the study because of adverse events.

DISCUSSION

Successful control of sexually transmitted diseases is facilitated by the ability to administer effective therapy in a single oral dose. Single-dose therapy resolves problems of patient compliance, and oral medications tend to be less expensive, easier to administer, and preferred by patients.

Prior to the late 1970s, single-oral-dose therapy for gonorrhea was achieved with the use of ampicillin and probenicid. Spread of PPNG and other types of antimicrobial resistance in the United States has necessitated discontinuation of this regimen and has resulted in injectable ceftriaxone becoming the therapy of choice. Currently, PPNG accounts for more than 10% of gonococcal isolates nationwide (4), underscoring the appropriateness of using beta-lactamase-resistant antimicrobial agents for treating all patients with uncomplicated gonorrhea. Although ceftriaxone, cefixime, ciprofloxacin, and ofloxacin continue to be recommended by the CDC as first-line therapy against gonorrhea, alternative oral-single-dose regimens are available which are equally effective. These therapies include drugs from the quinolone and cephalosporin classes of antibiotics.

Cefuroxime axetil was initially evaluated for the treatment of uncomplicated gonorrhea in the mid-1980s. A single 1,000-mg oral dose was found to be 98 to 100% efficacious; however, too few PPNG infections were initially studied for the drug to be recommended against PPNG (15). On the basis of its *in vitro* activity against PPNG as well as non-PPNG strains and the continuing need for additional single-dose oral agents for the treatment of gonorrhea, it was decided to reevaluate cefuroxime axetil's performance in patient populations with high PPNG prevalence.

The present study compared cefuroxime axetil with ciprofloxacin for the treatment of uncomplicated gonorrhea in a population with a PPNG rate of 17% (142 of 832). Microbiological efficacy rates of 96 and 97% in females and males, respectively, were demonstrated among individuals with PPNG infections. The overall efficacies of cefuroxime axetil against all strains of gonorrhea were 97% for females and 93% for males, while ciprofloxacin was 100% effective in eradicating PPNG and non-PPNG strains from the genital site in males and >99% effective in females. The efficacy of the two drugs did not differ significantly for females, but did in males ($P < 0.001$). Rectal infections in females were eradicated successfully by both drugs. There were insufficient numbers of rectal infections in men to satisfactorily judge the performance of cefuroxime axetil. While the number of patients of either sex with pharyngeal infections was relatively small, the results indicated that cefuroxime axetil was less effective than ciprofloxacin in treating males with pharyngeal infections ($P = 0.013$).

While there was no significant difference in cure rates between females treated with cefuroxime axetil and ciprofloxacin, males treated with cefuroxime axetil had cure rates lower than those expected. The higher-than-expected failure rate of cefu-

roxime axetil in treating male urethral infections deserves further comment. The two major reasons for therapeutic failures in this setting are reinfection and antimicrobial resistance. Since comparable studies of cefuroxime axetil showed efficacy rates of 96 to 99% in males with urethral gonorrhea (1, 9, 15, 16, 20), it is possible, although difficult to prove, that reinfection was a contributor to the relatively poor performance of cefuroxime axetil in males in the present study. In agreement with a role for reinfection, twice as many males assigned to the cefuroxime axetil group in whom *N. gonorrhoeae* was not eradicated admitted to continued sexual activity between the enrollment and follow-up visits as did cefuroxime axetil-treated males in whom the gonococcal infection was cured. However, similar rates of sexual activity were found in male patients in the ciprofloxacin group.

If antimicrobial resistance was an important contributor to the present findings, it would have been expected to also influence the response to treatment in female patients. Further arguing against the explanation of antimicrobial resistance was the observation that, with the exception of two strains which exhibited *in vitro* resistance to cefuroxime, one of which was obtained from a patient successfully treated with cefuroxime axetil and the other of which was obtained from an unevaluable ciprofloxacin-treated patient, the antimicrobial susceptibility profiles indicated good susceptibility to this agent, with the geometric mean MIC being 0.064 $\mu\text{g/ml}$. It should also be noted that the MIC₉₀ for cefuroxime with the gonococcal isolates obtained from patients enrolled in the present study (0.25 $\mu\text{g/ml}$) is identical to that reported nearly 20 years ago for 862 gonococcal isolates, 110 of which were penicillinase producing (19), suggesting that gonococcal resistance to cefuroxime has not increased markedly over the past 2 decades. Not unexpectedly, inclusion of the small numbers of patients whose gonococcal isolates were not tested for susceptibility to the study drugs (17 females and 10 males) into the evaluable patient population had no effect on the overall findings or conclusions.

When gonococcal strains from cefuroxime axetil-treated male patients who failed therapy for urethral gonorrhea were compared with those from male patients who were successfully treated with cefuroxime axetil, there was no meaningful difference in the proportion of isolates classified as chromosomally resistant (i.e., MIC for penicillin G or tetracycline of ≥ 2.0 $\mu\text{g/ml}$; 6 of 12 [50%] versus 66 of 154 [43%], respectively; $P = 0.63$). Although comparison of the geometric mean MICs for cefuroxime for these two groups of gonococcal strains indicated that the mean MIC for isolates obtained from the treatment failures was higher than that for isolates obtained from successfully treated male patients, this difference was not statistically significant (0.117 versus 0.050 $\mu\text{g/ml}$, respectively; $P = 0.20$). Interestingly, there were no similar differences in the geometric mean MICs for penicillin G or tetracycline when these two groups of gonococcal strains were compared.

In summary, cefuroxime axetil at a single dose of 1,000 mg, which is currently approved for the treatment of uncomplicated gonorrhea (urethral and cervical) due to non-PPNG strains, is also an acceptable oral agent for the treatment of uncomplicated gonorrhea caused by PPNG strains. Further studies will be needed to determine whether the lower-than-expected efficacy seen in the present study for cefuroxime axetil in treating urethral gonorrhea in male patients is an anomaly or reflects an actual decrease in effectiveness of this antibiotic in patients with gonococcal infections. However, test-of-cure cultures for patients with genital or rectal gonorrhea who are treated with this agent are not necessary, although local sexually transmitted disease control programs which choose to use this or any other agent as their primary

therapy should continuously monitor susceptibility trends among a portion of their isolates.

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