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Comparison of Ciprofloxacin and Ceftriaxone as Single-Dose Therapy for Uncomplicated Gonorrhea in Women

EDWARD W. HOOK III,[1,2,3]* ROBERT B. JONES,[4] DAVID H. MARTIN,[5] GAIL A. BOLAN,[6] TOMASZ F. MROCZKOWSKI,[5] THERESA M. NEUMANN,[2,3] JO JEAN HAAG,[4] AND ROGER ECHOLS[7]

The University of Alabama, Birmingham, Alabama 35294-0006[1]; The Johns Hopkins University[2] and Baltimore City Health Department,[3] Baltimore, Maryland 21218; The Louisiana State University School of Medicine, New Orleans, Louisiana 70112[5]; The University of Indiana School of Medicine, Indianapolis, Indiana 46202[4]; The University of California at San Francisco and San Francisco Department of Public Health, San Francisco, California 94143[6]; and Miles Pharmaceuticals, West Haven, Connecticut 06516[7]*

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Although women bear the brunt of gonococcal infection-related morbidity, few large studies of gonorrhea treatment in women have been conducted. In a multicenter, double-blind, placebo-controlled trial, 181 evaluable women with uncomplicated gonorrhea were treated with ciprofloxacin (250 mg orally; 94 women) or ceftriaxone (250 mg intramuscularly; 87 women). Twenty-four percent of the participants were infected with antibiotic-resistant *Neisseria gonorrhoeae*. Cervical gonorrhea was cured in 100% (93 of 93) of the women treated with ciprofloxacin and 99% (83 of 84) receiving ceftriaxone. All pharyngeal (n = 5) or rectal (n = 20) infections treated with ciprofloxacin were cured, as were ceftriaxone-treated patients with pharyngeal (n = 6) or rectal (n = 21) infection. Geometric mean MICs (range) for 248 pretreatment isolates were: penicillin, 0.28 (0.015 to 8.0); tetracycline, 0.46 (0.06 to 4); ciprofloxacin, 0.003 (0.002 to 0.015); and ceftriaxone, 0.004 (0.001 to 0.125) μg/ml. Both drugs were well tolerated. Despite the high prevalence of antibiotic-resistant gonococci in these populations, 250 mg of oral ciprofloxacin was as effective as an injection of ceftriaxone.

Despite the more than 30% decline in gonorrhea cases reported in the decade of the 1980s, infections due to *Neisseria gonorrhoeae* continue to be the most common reportable bacterial disease in the United States (5). The proportion of isolates resistant to penicillin or tetracycline also has increased dramatically. Although not yet a major problem in the United States, development of resistance to alternative therapies such as spectinomycin or even the newer quinolones is a continuing concern (1, 5, 15). In addition, gonorrhea rates tend to be highest in Americans aged 15 to 24 years, but late consequences which disproportionately affect women (e.g., infertility, ectopic pregnancy) often do not become apparent until years after the acute infection. Paradoxically, while gonorrhea and its sequelae tend to most profoundly affect females, studies of gonorrhea therapy predominantly report data for men. To provide more data on the treatment of gonorrhea in women and on the utility of ciprofloxacin, a currently recommended alternative to ceftriaxone for gonorrhea treatment, we conducted a prospective, multicenter, randomized, double-blind, placebo-controlled trial comparing 250 mg of oral ciprofloxacin with 250 mg of intramuscular ceftriaxone for therapy of uncomplicated gonorrhea in women attending sexually transmitted disease (STD) clinics.

MATERIALS AND METHODS

Study design. The study was a prospectively conducted, randomized, double-blind, placebo-controlled trial in which all participants received both an injection and a single oral dose of medication. All medications were administered by a third party who had been instructed not to inform the study clinician of the therapeutic regimen utilized. Patients randomized to ciprofloxacin therapy received one 250-mg tablet of ciprofloxacin orally and an injection of sterile 0.9% sodium chloride, while patients assigned to the ceftriaxone treatment group received an intramuscular injection of 250 mg of ceftriaxone and a placebo tablet by mouth. Neither the patients nor the study clinicians were informed as to which regimen was received.

Patients. The patients enrolled in this study were recruited from public STD clinics in Baltimore, Indianapolis, New Orleans, and San Francisco. Women aged 18 to 50 years were eligible for enrollment if they gave a history of sexual exposure to a man with urethral gonorrhea, if they had a gram-stained endocervical smear showing gram-negative diplococci within polymorphonuclear leukocytes, or if they had a history of an untreated culture positive for *N. gonorrhoeae*. Isolation of *N. gonorrhoeae* at the enrollment visit was required for participants to be considered evaluable for analysis of treatment efficacy. Patients were excluded from study participation if they were pregnant or nursing, had been previously enrolled in the study, gave a history of allergy to carboxyquinolone or cephalosporin antibiotics, had signs or symptoms of complicated gonococcal infection (pelvic inflammatory disease), had a chronic or acute intercurrent illness which would compromise treatment evaluation, had evidence of other acute STDs requiring treatment at the time of initial evaluation, or had received systemic antimicrobial therapy with an agent known to be active against *N. gonorrhoeae* during the 2 weeks prior to study enrollment.

Patient evaluation. At the time of study enrollment, all patients underwent the screening physical examination and a thorough genitourinary examination. All women had endocervical, rectal, and pharyngeal specimens obtained for

* Corresponding author.

TABLE 1. Selected demographic characteristics of 258 women treated with ciprofloxacin or ceftriaxone for uncomplicated gonorrhea

Treatment	No. enrolled	No. (%) evaluable for efficacy	Mean age ± SD (yr)	No. (%) of women:		
				Black	White	Other
250 mg of oral ciprofloxacin	130	94 (72)	24 ± 4.9	80 (85)	13 (14)	1 (1)
250 mg of intramuscular ceftriaxone	128	87 (68)	24 ± 5.0	76 (86)	12 (14)	

TABLE 2. Eradication of *N. gonorrhoeae* by 250 mg of oral ciprofloxacin and 250 mg of intramuscular ceftriaxone by site of infection

Site of infection	Patients cured/patients evaluated (%)	
	Ciprofloxacin	Ceftriaxone
Cervix	93/93 (100)	83/84 (98.8)
Rectum[a]	20/20 (100)	21/21 (100)
Throat	5/5 (100)	6/6 (100)
Overall[b]	94/94 (100)	86/87 (98.9)

[a] Four participants (one in the ciprofloxacin group, three in the ceftriaxone group) were culture positive for *N. gonorrhoeae* only at the rectum.
[b] Values describe eradication of *N. gonorrhoeae* from all sites of infection. In some patients, multiple mucosal sites were culture positive.

culture of *N. gonorrhoeae*. In addition, all patients had an endocervical culture for *Chlamydia trachomatis*.

Treatment efficacy was evaluated in patients returning for follow-up examination and *N. gonorrhoeae* culture 5 to 9 days after study enrollment. At the time of the follow-up visit, repeat specimens for culture of *N. gonorrhoeae* and *C. trachomatis* testing were obtained from all anatomical sites cultured at enrollment. Efficacy was assessed on the basis of posttreatment culture results without regard to the presence of signs, symptoms, or history of sexual reexposure. Patients from whom *C. trachomatis* was isolated were treated at the time of their follow-up visit.

Laboratory procedures. Specimens for *N. gonorrhoeae* isolation were inoculated directly onto selective media and promptly incubated at 35°C in carbon dioxide-rich environments. Presumptive *N. gonorrhoeae* isolates were confirmed at local laboratories according to their standard protocols. All gonococcal isolates were saved in Trypticase soy broth containing 15% glycerol and were frozen at −70°C. All isolates were shipped to the Baltimore laboratory, where their identity was confirmed with monoclonal antibodies to *N. gonorrhoeae* protein (6). β-Lactamase production was determined by the chromogenic cephalosporin method (9). The MICs of ciprofloxacin, ceftriaxone, penicillin, and tetracycline hydrochloride were determined by agar dilution in GC Agar Base (Becton Dickinson, Baltimore, Md.) supplemented by 1% IsoVitaleX and doubling dilutions of antibiotic as previously described (13). Plasmid-mediated tetracycline resistance was defined presumptively on the basis of a tetracycline MIC of ≥16 mg/liter. Isolates were considered to have chromosomally mediated resistance on the basis of MICs of tetracycline of 2.0 to 8.0 mg/liter or, if the isolate did not produce β-lactamase, MICs of penicillin of ≥2.0 mg/liter. Each laboratory utilized its standard cell culture system to isolate and identify *C. trachomatis*.

RESULTS

Study population. Of 258 women enrolled in this study, 181 (70%) had a positive *N. gonorrhoeae* culture and returned for follow-up. Among patients not evaluable for efficacy, 63 had negative gonorrhea cultures at enrollment and 14 failed to return for follow-up. There were no significant differences noted between the two treatment groups with regard to age, race, coinfections, or proportion evaluable for efficacy (Table 1). Coinfections were common in study participants. Among ciprofloxacin-treated participants, 17% (16 patients) had *C. trachomatis* and 15% (14 patients) had *Trichomonas vaginalis* infections while 14% (12 patients) of evaluable ceftriaxone-treated women were coinfected with each pathogen.

Efficacy of therapy. Each regimen was a highly effective treatment for uncomplicated gonococcal infection (Table 2). Endocervical infection was eradicated in 100% (93 of 93) of ciprofloxacin recipients and 98.8% (83 of 84) of ceftriaxone-treated women. Similarly, each drug cured extragenital infection in all participants. Twenty women with rectal infection and 5 with pharyngeal infection were cured with 250 mg of ciprofloxacin by mouth, as were 21 and 6 ceftriaxone-treated women with rectal and pharyngeal infections, respectively.

Neither therapy was highly effective for eradication of *chlamydia* coinfections. At the time of follow-up evaluation, *C. trachomatis* cultures were positive in 20 (21.5%) and 22 (26.2%) participants treated with ciprofloxacin and ceftriaxone, respectively.

Safety and tolerance. Both therapeutic regimens were well tolerated by participants. Pain at the site of injection was reported by 2% (two patients) of patients receiving ceftriaxone and no patients who received placebo injection. Of 244 participants (126 treated with ciprofloxacin, 118 who received ceftriaxone) who returned and could be evaluated for safety and tolerance, 9% (11 patients) of ciprofloxacin-treated participants and 6% (7 patients) in the ceftriaxone groups reported adverse events. All adverse events were mild and well tolerated. Of participants receiving ciprofloxacin, vaginitis (4%), vaginal pruritus (2%), and headache (2%) were most common. In the ceftriaxone group, no adverse experience was reported by more than a single participant. Problems reported included irritability, nausea, diarrhea, abdominal discomfort, vaginitis, and vaginal pruritus.

Antimicrobial susceptibility of *N. gonorrhoeae*. Two hundred forty-eight pretreatment isolates of *N. gonorrhoeae* from study participants were available for antimicrobial susceptibility testing (Table 3). Overall, 58 (23%) isolates displayed at least one form of clinically significant antibiotic resistance; 17 (7%) produced β-lactamase (penicillinase-producing *N. gonorrhoeae*), 5 (2%) had plasmid-mediated tetracycline resistance (tetracycline-resistant *N. gonorrhoeae*), 2 (1%) were penicillinase-producing and tetracycline-resistant *N. gonorrhoeae*, and 34 (14%) were chromosomally resistant to penicillin or tetracycline. The MICs for isolates from this study were in the expected range. No isolate was resistant (MIC of >0.06 μg/ml) to ciprofloxacin, and all had MICs of ceftriaxone in the susceptible range (≤0.25 mg/liter—two isolates had MICs of 0.125 mg/liter).

TABLE 3. Susceptibility of 248 pretreatment isolates of *N. gonorrhoeae* to antimicrobial agents

Antimicrobial agent	MIC[a]			
	Geometric mean	MIC_{50}	MIC_{90}	Range
Ciprofloxacin	0.003	0.004	0.004	0.002–0.015
Ceftriaxone	0.004	0.004	0.015	0.001–0.125
Penicillin G[b]	0.282	0.25	1	0.015–8
Tetracycline[c]	0.457	0.5	1	0.06–4

[a] MIC_{50} and MIC_{90} describe the MICs for 50 and 90% of isolates, respectively.
[b] Excludes 19 isolates which produced β-lactamase.
[c] Excludes seven isolates with high-level, plasmid-mediated resistance to tetracycline.

DISCUSSION

In this double-blind, randomized trial, 250 mg of ciprofloxacin administered by mouth was as effective for therapy of uncomplicated gonorrhea at genital and extragenital sites in women as 250 mg of ceftriaxone, intramuscularly, which is the current therapeutic regimen of choice recommended by the Centers for Disease Control and Prevention (2). Both drugs were effective in eradicating nearly 100% of infections, over 20% of which were caused by *N. gonorrhoeae* with clinically significant antimicrobial resistance. Women participating in these studies were recruited from STD clinics in four different geographic locations, thereby extending the applicability of these observations. It is also noteworthy that these results were obtained with half of the ciprofloxacin dose currently recommended by the Centers for Disease Control and Prevention for therapy of uncomplicated gonorrhea. Thus, like ceftriaxone (10), the currently recommended dose of ciprofloxacin provides a margin of safety which, theoretically, might reduce the likelihood of development of antimicrobial resistance to the drug.

Ciprofloxacin compares well with ceftriaxone for therapy of gonorrhea. Unlike ceftriaxone, which must be administered parenterally, ciprofloxacin may be administered by mouth, thereby obviating the need for patients to receive unwanted injections and reducing the risk of health care workers for needle stick injuries. In addition, at the present time while a single 250-mg dose of ceftriaxone costs $9.61, the average wholesale price of ciprofloxacin in doses of 250 and 500 mg is considerably cheaper, costing $2.14 and $2.46, respectively. At a time when an increasing proportion of patients with gonorrhea are treated in publicly funded clinics, the cost savings may be an important consideration for severely stressed public health budgets.

Concerns have been voiced about the propensity of the newer quinolone antibiotics for inducing development of antimicrobial resistance. These concerns are based in large part on reports of high levels of quinolone resistance occurring among patients attending sexually transmitted disease clinics in the Philippines (5a). Since that time, several published reports from the same area suggest that while clinically significant quinolone resistance is present in that area, the proportion of isolates displaying this form of resistance is relatively low (3, 4). There have been few reports of high-level quinolone resistance in North Americans who have not traveled to areas of southeast Asia where quinolone resistance is more common. In one of the cities participating in this study (Baltimore), ciprofloxacin (500 mg) has been the drug of choice for treatment of uncomplicated gonorrhea since November 1988. In this setting, despite widespread use, clinically significant quinolone resistance has yet to be described (11). Taken in combination, these data, as well as prior reports of treatment efficacy for males (7, 12, 14) suggest that ciprofloxacin, like other quinolone antibiotics proven effective for treatment of uncomplicated gonorrhea, may be able to make an important contribution to the therapeutic armamentarium for patients, particularly when cost is considered. Nonetheless, given the tendency of *N. gonorrhoeae* to develop resistance, prospective monitoring of gonococcal susceptibilities, as is currently performed by the Centers for Disease Control and Prevention (13), is warranted for ciprofloxacin as it is for other frequently used agents.

Twenty-three percent (42 of 181) of evaluable patients in this study had *C. trachomatis* coinfection demonstrable at pre- or posttest evaluation, a proportion that is somewhat lower than the 40% coinfection rate commonly cited (2). Both gonorrhea and chlamydia infections tend to be most common in younger patients (5, 8), thus this lower prevalence of chlamydia may reflect the older mean age of participants in this study. As observed in prior studies, more patients were culture positive for *C. trachomatis* at follow-up than at enrollment. Neither single doses of ciprofloxacin nor ceftriaxone were curative for an acceptable proportion of patients infected with *C. trachomatis*. Thus, as is currently recommended (2), cotherapy with agents effective against *C. trachomatis* (doxycycline, tetracycline, erythromycin, or azithromycin) should be administered to patients with uncomplicated gonococcal infections. In addition to being effective therapy for chlamydia, use of these agents as cotherapy for patients with gonorrhea may also help to prevent selection of antibiotic-resistant *N. gonorrhoeae.*

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