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Dose Ranging Study of Cefpimizole (U-63196E) for Treatment of Uncomplicated Gonorrhea in Men

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We conducted a two-center dose ranging study to evaluate the efficacy, tolerance, and toxicity of cefpimizole, a new cephalosporin, in the treatment of uncomplicated gonorrhea in 96 males. Twelve patients at each center were treated intramuscularly with single doses of 1.0, 0.5, 0.25, and 0.125 g of cefpimizole. All urethral infections were cured at the highest dose, but lower doses produced progressively decreasing cure rates of 90% (0.5 g), 83% (0.25 g), and 71% (0.125 g). Treatment failures of rectal and pharyngeal infections occurred at the highest dose level. Geometric mean MICs for cefpimizole for successfully and unsuccessfully treated volunteers were 0.088 and 0.282 μg/ml, respectively. A prominent adverse effect was clinically significant pain at the injection site, which occurred in 57 (59%) of 96 patients. Results of the study demonstrate that cefpimizole offers no advantage over currently available antibiotics in the treatment of uncomplicated gonorrhea in men.

Despite recent declines in the reported incidence of gonorrhea (1), consideration of new therapies for gonococcal infections is important from the standpoint of individual practitioners and public health officials. The primary impetus for investigation of new approaches to treatment has been the worldwide emergence of resistance to the antimicrobial agents commonly used for gonorrhea, including spectinomycin (4, 13). Additional problems in gonorrhea therapy include the variable efficacy of antibiotics at sites that are difficult to treat (e.g., the rectum and pharynx); coexisting chlamydial infection; and the need for improvement of antigonococcal treatment regimens in terms of tolerance, toxicity, and cost (13).

A number of recently developed β-lactam antibiotics have been evaluated as single-dose therapy of uncomplicated gonorrhea (5–9, 11, 14, 15, 18, 23). Cefpimizole (U-63196E) is another new broad-spectrum cephalosporin which demonstrates good in vitro activity against *Neisseria gonorrhoeae* (20). In this study we present data on a two-center, cooperative, dose ranging study of cefpimizole for the treatment of uncomplicated gonorrhea in men.

MATERIALS AND METHODS

Study population. Men 18 years of age and older were recruited in sexually transmitted disease clinics in Winston-Salem, N.C., and Seattle, Wash., between May and October 1984. Subjects were eligible for entry into the study if they had a gram-stained smear of urethral or rectal exudate showing polymorphonuclear leukocytes and gram-negative intracellular diplococci. Informed consent was obtained from all men who agreed to take part in the study. Exclusions to study entry included (i) a history of allergy to penicillin or cephalosporins, (ii) coexisting syphilis, (iii) epididymitis or disseminated gonococcal infection, (iv) antibiotic therapy during the preceding 14 days, or (v) active concurrent illness. Sexual orientation was recorded on the basis of sexual contacts within the preceding 2 months. If cultures obtained at the initial visit failed to yield *N. gonorrhoeae*, results were excluded from analysis of treatment efficacy but were included for the analysis of tolerance and toxicity.

Laboratory methods. Urethral specimens were obtained from all subjects by inserting a calcium alginate swab (Calgiswab; Inolex) 2 to 4 cm beyond the meatus. If indicated by the sexual history, pharyngeal and rectal specimens were collected with cotton-tipped swabs. Specimens were immediately inoculated onto modified Thayer-Martin medium and incubated at 36°C in candle extinction jars or an incubator with an atmosphere of 5% CO_2. *N. gonorrhoeae* was identified by standard techniques of colony morphology, Gram stain, and oxidase reactions (19). Isolated colonies were subcultured onto chocolate agar medium before they were stored at −70°C in 50% horse serum diluted in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.). MICs of cefpimizole, penicillin G, spectinomycin, tetracycline, and cefotaxime were determined by the agar dilution technique with a gonococcal agar base containing 1% hemoglobin and 1% IsoVitaleX (BBL). Production of β-lactamase was tested by the chromogenic cephalosporin technique in Winston-Salem (21) and by the acidometric method in Seattle (13). Urethral and rectal specimens for isolation of *Chlamydia trachomatis* were obtained from the subjects in Seattle and immediately placed in 0.2 M sucrose-phosphate buffer for transport. Within 24 h specimens were inoculated into tissue cultures, as described by Stamm et al. (25), with identification of chlamydial inclusions by fluorescein-labeled monoclonal antibodies (Microtrak; Syva Corp, Palo Alto, Calif.).

Treatment and study design. Subjects were assigned to one of four dosage groups (1.0, 0.5, 0.25, or 0.125 g); at each treatment center a minimum of 12 entries were required in the higher dose category before therapy with the next lower dose was begun. Before treatment a directed history and

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TABLE 1. Efficacy of cefpimizole for eradication of *N. gonorrhoeae* by site and dose

Dose (g)	No. cured/no. returned for follow-up (% cured) for the following isolate sites:		
	Urethra	Rectum	Pharynx
1	22/22 (100)	1/2 (50)	0/1 (0)
0.5	19/21 (90)	3/3 (100)	0/1 (0)
0.25	20/24 (83)	0/0	0/0
0.125	17/24 (71)	0/1 (0)	1/2 (50)

physical examination were performed; appropriate bacteriologic specimens were obtained; urine was obtained for urinalysis; and blood was obtained for complete blood count, platelet count, direct Coombs test, prothrombin time, blood urea nitrogen, creatinine, creatinine phosphokinase, Venereal Disease Research Laboratory serology, alkaline phosphatase, lactic dehydrogenase, aspartate transferase, and alanine transferase. Cefpimizole was supplied in vials as 1 g of the monosodium salt which was reconstituted with 3.2 ml of sterile water to a concentration of 0.25 g/ml. Patients in the 1-g group received 0.5 g (2.0 ml) intramuscularly in each buttock; patients treated with lower doses received single gluteal injections. Injection site pain was characterized as none, mild, moderate, or severe. Subjects were scheduled to return 3 to 7 days after therapy for repeat laboratory tests and to assess the efficacy of therapy and the possible occurrence of adverse drug experiences. Patients were instructed to abstain from sexual contact until after the follow-up visit. All initial treatment failures were given further appropriate therapy.

Statistical methods. Statistical analysis was performed by the chi-square test for trend and by Student's *t* test.

RESULTS

Patient characteristics. A total of 113 subjects were enrolled in the study. Seventeen were excluded from full evaluation, including eight from whom *N. gonorrhoeae* was not isolated at the initial visit and nine who failed to return for follow-up. A total of 48 evaluable patients (12 in each dose tier) were entered at each participating center. The age range of the study population was 18 to 44 years, with a mean of 26. Self-reported sexual preference was 75 of 95 (79%) heterosexual and 20 of 95 (21%) bisexual or homosexual.

Efficacy in uncomplicated gonorrhea. In Table 1 is shown the details of treatment response by site of infection and cefpimizole dose. All urethral infections treated with the highest dosage regimen of 1 g were cured, but further reductions in dosage were accompanied by a significant linear decrease in response rate of 9.5% per group ($P = 0.004$ by chi-square for trend). Four of five anorectal infections were cured with either the 1- or 0.5-g dose; the single failure occurred in a man who received the highest (1.0-g) dose. Only one of four pharyngeal isolates was eradicated, even at the higher dose levels. There was no statistically significant difference in results between the two centers.

Antimicrobial susceptibility of *N. gonorrhoeae*. All infections except one were caused by non β-lactamase-producing strains of *N. gonorrhoeae*. The single urethral isolate which was β-lactamase positive was eliminated by 0.125 g of cefpimizole (MIC, 0.25 μg/ml). In addition, a single patient with urethritis caused by a spectinomycin-resistant strain (spectinomycin MIC, >256 μg/ml) was cured with the 1-g dose of cefpimizole (cefpimizole MIC, 0.25 μg/ml). In Table 2 is shown the antimicrobial susceptibility of the gonococcal strains isolated from the subjects in Seattle. Pretreatment gonococcal isolates from 35 subjects cured by cefpimizole were more susceptible to cefpimizole (geometric mean MIC, 0.088 μg/ml) than were pretreatment isolates from 11 subjects who failed therapy (geometric mean MIC, 0.282 μg/ml; $P = 0.001$ by Student's *t* test). In two patients with persistent infection following treatment, posttreatment isolates demonstrated increased MICs of ≥2 dilutions for at least one of the antibiotics tested when compared with those of pretreatment isolates. In one of these, the MIC of penicillin increased from 0.06 to 0.25 μg/ml, unaccompanied by any change in sensitivity to the other drugs (including cefpimizole) that were tested. The other positive follow-up culture in a patient treated with 0.125 g yielded two isolates, one identical to the pretreatment organism and another with the following pre- to posttreatment MIC increases: cefpimizole, 0.25 to 4 μg/ml; cefotaxime, <0.008 to 0.06 μg/ml; tetracycline, 1 to > 32 μg/ml.

Isolation of *C. trachomatis*. *C. trachomatis* was isolated from 9 of 48 (19%) patients on entry into the study in Seattle. Eight isolates were urethral and one was rectal. Among the four patients with symptoms of urethral infection at follow-up, two had urethral cultures that were positive for *C. trachomatis*.

Adverse effects. Pain or cramping at the injection site was experienced by 57 of 96 (59%) subjects. Of 24 patients receiving bilateral gluteal injections (the 1-g dose), 8 (33%) had pain or cramping. All other patients received single injections; pain or cramping occurred in 18 of 24 (75%) receiving 0.5 g, 17 of 24 (71%) receiving 0.25 g, and 14 of 24 (58%) receiving 0.125 g. The subjective description of pain was often moderate or severe, resulting in impaired muscle function. No other clinical problems occurred, except for one case of diarrhea not related to *Clostridium difficile* infection. Hematologically 5 of 48 (10.4%) of the patients in Winston-Salem experienced transient mild leukopenia, and 1 patient had eosinophilia 3 days after treatment; among the subjects in Seattle 4 of 48 (8.3%) developed a mild increase in lymphocyte count. Mild elevations of hepatic enzymes were documented in 9 of 48 (18.75%) of the patients in the Winston-Salem treatment group. One patient had an unexplained transient rise in serum creatinine posttherapy. Elevated creatinine phosphokinase levels were documented in 24 of 96 (25%) following the intramuscular injection. None of these laboratory abnormalities was persistent or clinically significant.

DISCUSSION

Results of this study suggest that cefpimizole offers no advantage over the many other cephalosporins available for treatment of uncomplicated gonorrhea in men. The dose-

TABLE 2. Geometric mean MICs

Drug	Mean MIC (μg/ml)		
	Successfully treated (35[a])	Treatment failure (11)	Range
Penicillin	0.079	0.282	0.015–2.0
Cefpimizole	0.088	0.282	0.015–1.0
Tetracycline	0.69	0.78	40.06–4.0
Cefotaxime	0.005	0.01	0.0005–0.06
Spectinomycin	23.4	20.01	12–32

[a] Number of isolates tested are given in parentheses.

response data indicate that the 1-g dose (administered as two intramuscular injections) would be necessary for acceptable efficacy of gonococcal urethritis. As with other cephalosporins not diluted in lidocaine, postinjection pain was common (2, 9, 10).

Rectal or pharyngeal gonococcal infections are often more difficult to cure than urethral or cervical gonorrhea, with few agents approaching the efficacy (≥95%) of standard aqueous procaine penicillin G-probenecid therapy at both sites (9, 16). Although too few extragenital infections were documented in the present study to fully evaluate the efficacy of cefpimizole at these sites, failures occurred with the highest dose for both rectal and pharyngeal gonorrhea.

The level of coinfection with *Chlamydia trachomatis* in this study (19%) was comparable to that which has been found previously (12). If not adequately treated along with gonorrhea, chlamydial infection may persist, cause postgonococcal urethritis in men, and be transmitted to women in whom significant morbidity from salpingitis may occur (24). Although no in vitro data are available on chlamydial sensitivity to cefpimizole, cephalosporins as a class lack significant in vitro activity against *C. trachomatis* (22) and have not performed well clinically. The incidence of postgonococcal urethritis (3) was not determined in our study because of the length of follow-up; however, two patients had positive urethral cultures for *C. trachomatis* 3 to 7 days after treatment with cefpimizole.

Patient intolerance to intramuscular injections of cefpimizole was significant (59% overall) and was reported more often with single injections, possibly because the difference in pain and cramping was more striking if only one gluteal group was impaired.

Although leukopenia has been reported following the use of a number of β-lactam antibiotics (17), the 10.4% incidence following treatment with single doses of cefpimizole was unexpected and bothersome if confirmed by other clinical studies, especially when multiple days of therapy with cefpimizole may be required. In addition, mild elevations in hepatic enzymes (18.75%) and one case of an unexplained rise in serum creatinine in this study suggest that these parameters of potential toxicity need to be explored more fully, particularly for patients receiving multiple doses.

Within the treatment failure group, the demonstration of an increased MIC of cefpimizole in one posttreatment isolate suggests the possibility of the emergence of resistance in vivo when cefpimizole is used, particularly at a low dose.

In conclusion, drug tolerance problems coupled with decreased clinical efficacy with lower dose regimens limit the usefulness of cefpimizole as single-dose treatment of uncomplicated gonococcal infections in men.

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