NOTES

Single-Dose Oral Cefixime versus Amoxicillin plus Probencid for the Treatment of Uncomplicated Gonorrhea in Men

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In this randomized study, a single 800-mg oral dose of cefixime cured 96 of 97 men with uncomplicated gonococcal urethritis, compared with 44 cures of 46 men who received standard therapy with amoxicillin (3 g) plus probencid (1 g). Both regimens were ineffective against coexistent infection with Chlamydia trachomatis and Ureaplasma urealyticum. Cefixime was well tolerated, and all side effects were mild and self-limited.

Cefixime is a novel oral cephalosporin with β-lactamase stability and in vitro activity similar to that of many of the broad-spectrum cephalosporins (5, 6). Previous studies have revealed that Neisseria gonorrhoeae is highly susceptible to cefixime in vitro (2, 5, 6). MICs for 90% of isolates of penicillin-susceptible strains as well as for those strains demonstrating penicillinase production and chromosomally mediated resistance have been ≤0.05 μg/ml. Furthermore, it has been shown that a single 400-mg oral dose of cefixime in healthy volunteers results in mean levels in serum of 3.85 μg/ml at 4.3 h (peak) and 1.13 μg/ml at 12 h following administration (4). Thus, we wished to compare the clinical efficacy and tolerability of a single dose of cefixime (in this case, 800 mg) with those of an established regimen, namely amoxicillin and probenecid, in the treatment of uncomplicated gonorrhea in men.

Males aged 18 years and older with positive cultures for N. gonorrhoeae from any site or with gram-negative intracellular diplococci from endourethral or rectal swabs were eligible for study. Patients receiving antimicrobial therapy in the preceding 2 weeks were excluded from the study, as were persons with a history of hypersensitivity to penicillins or cephalosporins and those with serious underlying disorders. All participants provided informed, written consent.

At the initial visit, all patients were questioned about symptoms, prior medications, and sexual history and underwent examination of the external genitilia. Endourethral swabs for Gram stain and culture for N. gonorrhoeae, Chlamydia trachomatis, and Ureaplasma urealyticum were collected. Pharyngeal swabs for N. gonorrhoeae culture were obtained from all patients, but rectal swabs were performed only on homosexual and bisexual men. Patients were then randomized in a 2:1 ratio to receive either cefixime (800 mg in four 200-mg capsules) as a single oral dose (without probenecid) or amoxicillin (3.0 g) and probenecid (1.0 g) orally. All men were provided with a diary card to record subsequent side effects, symptoms, and sexual contact, if any.

Patients were requested to return for follow-up 6 to 9 days after treatment, and men whose cultures were initially C. trachomatis positive and those with persistent symptoms or signs of infection following therapy were encouraged to return 3 and 6 weeks posttreatment. At each follow-up visit, patients were questioned about side effects, symptoms, and sexual activity. Physical examination was repeated, as were swabs for endourethral Gram stain and N. gonorrhoeae, C. trachomatis, and U. urealyticum cultures. Men with postgonococcal urethritis (defined below) at follow-up and men with C. trachomatis at follow-up were treated with tetracycline (500 mg) orally four times daily for 7 days.

Microbiologic cure of gonorrhea was defined as a negative culture for N. gonorrhoeae 6 or more days posttreatment. Postgonococcal urethritis was considered present when N. gonorrhoeae-negative urethritis appeared or persisted beyond 14 days posttreatment. In this context, urethritis was defined as symptoms plus a urethral discharge plus objective evidence of urethral inflammation (a mean of five or more polymorphonuclear leukocytes per oil immersion field in a Gram-stained smear of an endourethral swab).

Cultures for N. gonorrhoeae were performed by using standard media and techniques. Identification of oxidase-positive, gram-negative diplococci as N. gonorrhoeae was confirmed by a fluorescens-antibody test. Penicillinase production was detected by a rapid chromogenic cephalosporin method. Cultures for C. trachomatis were performed by using cycloheximide-treated McCoy cells in vials (3), and all initially negative specimens were passed at least once onto new monolayers. In Vancouver, swabs for U. urealyticum were streaked onto A7 agar and placed into U9 broth (3), while in Calgary, GM medium and bromothymol broth were employed (7).

A total of 170 men were enrolled in the study. Three were excluded because their initial cultures for N. gonorrhoeae were subsequently found to be negative (despite positive Gram stains). Another 21 men (13 treated with cefixime and 8 treated with amoxicillin) were excluded from further analysis since they failed to return for at least one follow-up visit. Thus, there were 146 evaluable cases: 99 received cefixime, and 47 were treated with amoxicillin and probenecid. A total of 31 (21%) of the cases occurred in homosexual
or bisexual men, and there was no significant difference between the two treatment groups with regard to sexual preference. Of the 146 evaluable men, 60 (41%) returned for only one follow-up visit, 48 (33%) returned for two follow-up assessments, and 38 (26%) were seen on three or more occasions posttherapy.

The majority of evaluable cases in both treatment groups had gonococcal urethritis without involvement of other sites (91 or 99 cefixime-treated and 43 of 47 amoxicillin-treated patients). In the cefixime group, six men had concomitant infection of the urethra and pharynx, one had both pharyngeal and anorectal infection, and one had a positive culture only from the pharynx. Two men who received amoxicillin had both pharyngeal and urethral gonorrhea, one had anorectal and urethral infection, and another had a positive anorectal culture alone.

Table 1 demonstrates the rate of eradication of N. gonorrhoeae from the various sites for both cefixime and amoxicillin. There were no significant differences between either regimen, and both cefixime and amoxicillin were highly effective in eradicating urethral N. gonorrhoeae. The one patient with apparent cefixime failure was probably reexposed to an untreated sexual partner, while both patients with amoxicillin failure were definitely reexposed. Cefixime was successful in curing six of eight pharyngeal infections, versus two of two treated with amoxicillin. One of the patients who were not cured may have been reexposed, but the other was not. The sole patient with anorectal gonorrhea treated with cefixime was cured, while amoxicillin failed to eradicate one of two anorectal infections (the patient was not reexposed). There were three penicillinase-producing isolates of N. gonorrhoeae: all were urethral in origin, all were from cefixime-treated patients, and all were eradicated.

In men with nongonococcal urethritis, C. trachomatis was recovered at the initial visit or the first follow-up visit in 23 (24%) of 97 males given cefixime and 14 (30%) of 46 amoxicillin-treated patients (no significant difference). Both regimes were ineffective in eradicating or preventing concomitant chlamydial infection: of men with C. trachomatis isolated before therapy, 11 of 13 cefixime-treated and 8 of 9 amoxicillin-treated patients remained culture-positive at the first follow-up visit. Another 10 men who received cefixime and 5 given amoxicillin were initially found to be chlamydia-positive at the first follow-up visit.

Similarly, U. urealyticum usually was not eradicated by either regimen. A total of 17 cefixime-treated men and 18 who received amoxicillin were U. urealyticum positive before therapy. Of these, 11 and 12, respectively, were found at the first follow-up to have persistent colonization of the urethra. There were also five patients in the cefixime group in whom U. urealyticum was first detected at the initial follow-up visit. There was no apparent relationship between the disappearance or persistence of U. urealyticum at follow-up and the absence or presence of chlamydia-negative postgonococcal urethritis (which occurred in seven cefixime-treated and five amoxicillin-treated men).

Side effects were common with both treatment regimens and occurred in 31 and 30% of cefixime- and amoxicillin-treated men, respectively (Table 2). All adverse effects were mild and resolved spontaneously. The most common complaints were lower gastrointestinal in nature and included diarrhea, loose stools, and cramping abdominal pain.

Thus, in this study, a single 800-mg oral dose of cefixime was shown to be highly effective (99% cure rate) in eradicating N. gonorrhoeae from the male urethra. However, the number of cases of pharyngeal and anorectal infection was too small to draw any firm conclusions as to the efficacy of cefixime at these sites. Likewise, only three isolates of penicillinase-producing N. gonorrhoeae were encountered in this study (although all were cured by cefixime).

Previous studies of the therapy of gonorrhea have demonstrated that penicillins and other β-lactam antibiotics are not effective in eradicating or preventing concomitant chlamydial infection (1, 8), and the same was true of cefixime in this study. This was not unexpected, since cefixime has little in vitro activity against C. trachomatis (2). Thus, if used in the treatment of urethral gonorrhea in men, cefixime should be administered in conjunction with tetracycline or another agent active against C. trachomatis.

In addition to its apparent efficacy (at least in uncomplicated urethritis in men), cefixime may also prove useful in the treatment of gonorrhea because it is a well-tolerated and easy-to-administer (single oral dose of four capsules) regimen. If, as in vitro susceptibility data suggest, it is effective in vivo against penicillin-resistant N. gonorrhoeae, then cefixime will offer clear advantages over standard regimens in much the same fashion as quinolones do. Clearly, further studies are warranted to determine the efficacy of cefixime in females, at nongenital sites, and in infections due to resistant N. gonorrhoeae.

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### LITERATURE CITED


