Comparative Study of Ceftriaxone and Aqueous Procaine Penicillin G in the Treatment of Uncomplicated Gonorrhea in Women

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Uncomplicated gonorrhea of 122 mucosal sites in 51 women was successfully treated with either a single intramuscular dose of 250 mg of ceftriaxone (23 patients) or two intramuscular doses of 4.8 × 106 U of aqueous procaine penicillin G (28 patients). Women treated with ceftriaxone had 22 cervical, 12 urethral, 10 anal canal, and 5 pharyngeal infections. All 122 pretreatment isolates were inhibited by 0.0125 μg or less of ceftriaxone per ml. The minimal concentration needed to inhibit 90% of isolates was 0.006 μg/ml for ceftriaxone and 0.2 μg/ml for penicillin G. Ceftriaxone was very well tolerated and caused no toxicity.

Ceftriaxone (Ro 13-9904) is a new third-generation cephalosporin with enhanced in vitro activity against most gram-negative aerobic bacteria (2–4, 12, 14), including Neisseria gonorrhoeae (2, 5, 8, 9, 12, 14). All gonococcal strains tested, whether β-lactamase positive (9, 12) or negative (2, 5, 8, 9, 12, 14), were sensitive to 0.03 μg/ml or less. The pharmacokinetics of ceftriaxone make it favorable for treating gonorrhea (10, 11); a single intramuscular 0.5-g dose in 1% lidocaine (10) produces peak serum levels of 42 μg/ml, with an elimination half-life of 7.0 h, uniquely long among β-lactam antibiotics. The lidocaine diluent apparently does not alter either elimination parameters or bioavailability of ceftriaxone, whereas it considerably reduces intensity and frequency of pain at the injection site (10).

In a dose-ranging study of single intramuscular injections of 125, 250, and 500 mg, 46 men with uncomplicated gonorrhea were successfully treated (5), providing good evidence of clinical efficacy. Comparison trials with Centers for Disease Control recommended treatment regimens (1) seemed justified, and we report herein the results of a comparative study of 250 mg of ceftriaxone and 4.8 × 106 U of aqueous procaine penicillin G (APPG) in the treatment of uncomplicated gonorrhea in women.

MATERIALS AND METHODS

After giving informed written consent, 64 women 18 years of age or older with proven (culture-positive) or suspected (history of exposure to a man with documented gonococcal urethritis) uncomplicated gonorrhea were enrolled in the study. Women with histories of allergy to β-lactam antibiotics, antimicrobial therapy within the preceding 2 weeks, complications of gonorrhea, or any recent serious illness were excluded.

Patients were selected by a computer-generated randomization schedule (Hoffmann-La Roche Inc., Nutley, N.J.) to receive either 250 mg of ceftriaxone (dissolved in 1.0 ml of 1% lidocaine) as a single intramuscular dose or 4.8 × 106 U of APPG as two intramuscular doses with 1 g of probenecid by mouth. All injections were given into gluteal muscles. To be evaluable, women must have had positive cultures for N. gonorrhoeae on the day of treatment and must have returned for a test-of-cure within 4 to 7 days. Treatment success was defined by negative cultures for N. gonorrhoeae at the test-of-cure visit. Adverse reactions to treatment were monitored by a questionnaire about symptoms and by pre- and posttreatment complete blood counts, quantitative platelet counts, hemoglobin, hematocrit, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, and urinalyses.

Two cotton-tipped swab specimens each were obtained from the endocervix, urethra, anal canal, and posterior pharynx of all women at pretreatment and test-of-cure visits, directly inoculated onto modified Thayer-Martin medium, and placed in a 36°C incubator containing 3 to 7% CO2 for 36 to 48 h. Isolates presumptively identified as N. gonorrhoeae by routine methods were confirmed by a rapid carbohydrate degradation microtube method (Carr Microbiologicals, Wichita, Kans.) and tested for β-lactamase production by a chromogenic cephalosporin (Glaxo Group Research Ltd., Greenford, Middlesex, England) filter paper method. Isolates were placed in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) with 10% glycerol and frozen at −70°C.

Susceptibility to ceftriaxone (Hoffmann-La Roche) and penicillin G (Eli Lilly & Co., Indianapolis, Ind.) was determined by the Steers replicator agar dilution method (13). Isolates were grown for 24 h on gonococcal agar base (Difco Laboratories, Detroit, Mich.)
containing 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.) and hemoglobin. A suspension was made in Mueller-Hinton broth, adjusted to a 0.5 McFarland standard, and diluted 10⁻¹ to give an inoculum size of approximately 10⁷ CFU/ml. Samples of 0.003 ml were inoculated into the medium containing twofold dilutions of antibiotic. Plates were incubated for 24 h and read, using no growth as the endpoint.

RESULTS

Of 64 women treated (32 with ceftriaxone and 32 with APPG), 13 (20.3%) were not evaluable, 8 (12.5%) had negative pretreatment cultures, and 5 (7.8%) failed to return for a test-of-cure culture within 4 to 7 days. Of the 51 evaluable women, 23 received ceftriaxone and 28 received APPG. All infected sites were cured (Table 1). Aside from minor pain on injection, no patient experienced adverse reactions to either treatment, and no important posttreatment laboratory abnormalities were observed.

Pretreatment isolates were obtained from 122 sites in 56 women. All were β-lactamase negative. Ceftriaxone was very active against these isolates, as only 42 (34%) required 0.0015 μg/ml or more for inhibition and the most resistant one required only 0.0125 μg/ml. The minimal concentrations of ceftriaxone needed to inhibit 50 and 90% of isolates were 0.0015 and 0.006 μg/ml, respectively. When compared with the minimal concentration of 0.2 μg of penicillin per ml needed to inhibit 90% of isolates, ceftriaxone was more than 30 times as active.

A comparison of the geometric mean minimal inhibitory concentration of ceftriaxone for isolates from the cervix, urethra, and anal canal was not meaningful because so many isolates required less than 0.0015/μg/ml (Table 2). This also prevented a valid statistical comparison with the geometric mean minimal inhibitory concentration for the small number of pharyngeal isolates, which appear to be more resistant.

DISCUSSION

Since 1974, 4.8 × 10⁶ U of APPG as two intramuscular doses, together with 1 g of probenicid by mouth, has served as the standard for therapeutic efficacy in uncomplicated gonorrhea at all sites in both men and women. The APPG regimen does, however, have important shortcomings, including inconsistent manufacturer supplies, low patient acceptability (owing to discomfort from the two large 5-ml injections, frightening toxic procaine reactions, which in our clinic occur with rates of 1 to 3% and allergic reactions), vulnerability to N. gonorrhoeae-produced β-lactamase, and rising cost.

In vitro, ceftriaxone is many times more active than penicillin G (5, 8, 9, 12). Because of this high activity, together with its high serum levels and very long half-life, it is not surprising that, in a dose-ranging study in men (5) and in our study in women, 250 mg was completely effective at all sites. Importantly, pharyngeal gonorrhea, which is particularly difficult to cure, was successfully treated in three men by Handsfield et al. (5) with only 125 mg and in five women by us with 250 mg.

Ceftriaxone was very acceptable to our patients because the drug is highly soluble in 1% lidocaine diluent, permitting the use of a small needle; the 1-ml volume is small, and injection can be accomplished in a deltoid muscle with little discomfort. No clinically important hemato logical (including depressed quantitative platelet counts), urinary, or biochemical abnormalities occurred.

Neither we nor Handsfield et al. (5) treated infections caused by β-lactamase-producing N. gonorrhoeae, but in vitro studies indicate that these strains are as susceptible to ceftriaxone as are β-lactamase-negative strains (9, 12). Although the third-generation cephalosporins marketed to date are very expensive by gram weight, on a cost-per-treatment basis ceftriaxone has the potential to compete with the recommended spectinomycin regimen and perhaps with the APPG regimen as well.

Except in homosexual men, simultaneous exposure to syphilis and gonorrhea is extremely rare (7). Nonetheless, it is encouraging to note that ceftriaxone was very effective in the treat-
ment of syphilis in the rabbit model. The 50% curative dose was 1.45 μmol/kg (0.96 mg/kg) (6). Therefore, ceftriaxone may be shown to abort incubating (early, seronegative) syphilis while treating gonorrhea in humans.

No β-lactam antibiotic in a single dose has been proven effective in the treatment of genital Chlamydia trachomatis infections. In that chlamydia infections are extremely common and often coexist with gonococcal infections in heterosexual men and women (7), it may sometimes be desirable to follow ceftriaxone treatment of gonorrhea with a 7-day course of a tetracycline (e.g., 0.5 g of tetracycline hydrochloride four times a day). A combined regimen utilizing the anti-chlamydial action of tetracycline and the convenience and compliance advantages of single-dose amoxicillin or ampicillin treatment of gonorrhea has already been suggested by the Centers for Disease Control (1).

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LITERATURE CITED