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Oral Ciprofloxacin versus Ceftriaxone for the Treatment of Urethritis from Resistant *Neisseria gonorrhoeae* in Zambia

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***Neisseria gonorrhoeae* strains resistant to treatment with penicillin, tetracycline, and/or spectinomycin are increasing in prevalence in many parts of the world. In Zambia, 52% of *N. gonorrhoeae* isolates produced β-lactamase in 1986. Few oral regimens have proven effective for treatment of resistant *N. gonorrhoeae*. We conducted a prospective, double-blind, randomized clinical trial of 250 mg of ciprofloxacin given orally versus 250 mg of ceftriaxone given intramuscularly for treatment of uncomplicated gonococcal urethritis in adult males. Two hundred men were enrolled and treated. The two groups were comparable in age (27.5 years), prevalence of latent syphilis (14 and 10%), and human immunodeficiency virus infection (32 and 38%). Of 165 patients with cultures positive for *N. gonorrhoeae* who returned for follow-up, ciprofloxacin cured 83 of 83 (100%), including 26 with penicillinase-producing *N. gonorrhoeae* (PPNG) and 21 with *N. gonorrhoeae* with chromosomally mediated resistance to multiple antibiotics (CMRNG), and ceftriaxone cured 81 of 82 (98.7%), including 30 with PPNG and 19 with CMRNG. Both treatment regimens were well tolerated. *Chlamydia trachomatis* in urethral exudate was found by direct fluorescent-antibody microscopic examination or by culture in 10 (5%) participants. All *N. gonorrhoeae* isolates were inhibited by ceftriaxone at 0.06 μg/ml, except one which was inhibited at 0.125 μg/ml, while ciprofloxacin inhibited all isolates at 0.03 μg/ml. Ciprofloxacin is a safe and effective therapy for uncomplicated gonococcal urethritis, including that caused by PPNG and CMRNG in human immunodeficiency virus-infected men.**

Although the incidence of gonorrhea in the United States has been decreasing over the past 10 years, this trend may be reversing among some groups (7). During this time, the treatment of gonorrhea has been complicated by the emergence of strains resistant to penicillin, tetracycline, and spectinomycin (10, 17, 18, 29; J. S. Moran and J. M. Zenilman, Rev. Infect. Dis., in press). The number of reported cases of penicillinase-producing *N. gonorrhoeae* (PPNG) in the United States increased almost eightfold between 1984 and 1988 to 33,491 cases annually (24; Statistics Branch, Division of Sexually Transmitted Diseases, Centers for Disease Control, Atlanta, Ga.). In Zambia, gonorrhea was the most commonly diagnosed sexually transmitted disease in 1986 with 26,744 cases reported annually, compared with 13,772 cases of chancroid (Health Statistics, Government of Zambia). The percentage of isolates producing β-lactamase at the Dermato-Venereology Clinic at the University Teaching Hospital in Lusaka increased from 3.2% in 1980 to 52% in 1986 (11; our unpublished data), necessitating the use of kanamycin, gentamicin, or spectinomycin as the parenteral therapy of choice for gonococcal urethritis.

Ciprofloxacin, a new fluorinated carboxyquinolone, achieves high concentrations in urethral and prostatic secretions and is very active in vitro against *N. gonorrhoeae* (23, 28). It is effective as single-dose oral therapy for gonococcal urethritis (1, 2, 23), but only limited experience has been acquired with penicillinase-producing strains (PPNG) or *N. gonorrhoeae* strains resistant to penicillin and tetracycline by a chromosomally mediated mechanism (CMRNG). We conducted a study in an area with a high prevalence of gonococci having both types of resistance to determine the efficacy of a single dose of orally administered ciprofloxacin compared with single-dose parenteral ceftriaxone for the therapy of uncomplicated gonococcal urethritis.

MATERIALS AND METHODS

Patient population. The study was conducted at the Dermato-Venereology Clinic at the University Teaching Hospital in Lusaka, Zambia. Adult males between 18 and 50 years of age who presented with urethral discharge containing intracellular gram-negative diplococci (as determined by microscopic exam) were invited to participate in the study. Subjects were excluded for the following reasons: a history of antimicrobial treatment within 14 days, a history of allergy to beta-lactam antibiotics or quinolones, evidence of extraurethral gonococcal disease or genital ulcer disease, or clinical evidence of immunodeficiency.

Study design and treatment. The study was a prospective, double-blind, randomized, placebo-controlled comparative trial. After voluntary informed consent was given, blood was obtained for a complete blood count and for serologic tests for syphilis and human immunodeficiency virus (HIV) (Recombigen; Cambridge Bioscience, Worcester, Mass.). A confirmatory test for HIV antibody was done by an indirect fluorescent-antibody technique (Virgo; Electro-Nucleonics Inc., Columbia, Md.). Patients were placed in treatment groups by random table to receive either ciprofloxacin (250 mg orally) plus sterile saline (1 ml) for intramuscular injection or ceftriaxone (250 mg) in 1 ml of 1% xylocaine

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TABLE 1. Characteristics of patients evaluable on days 3 to 5 and 7 to 10 after therapy

Drug	No. treated	Age (yr) (mean ± SD)	Patient characteristic: No. (%) with: Syphilis-positive serology[a]	PPNG	CMRNG[b]	HIV antibody[a]	*C. trachomatis*	No. cured/no. evaluable on days: 3–5	7–10
Ciprofloxacin	83	27 ± 5.6	14 (17)	26 (31)	21 (25)	27 (33)	4 (5)	83/83	58/58
Ceftriaxone	82	28 ± 5.6	8 (10)	30 (37)	19 (23)	32 (39)	4 (5)	81/82	54/54

[a] Differences between values in column are not statistically significant ($P \leq 0.05$).
[b] Penicillin and tetracycline MIC, ≥2.0 μg/ml.

intramuscularly plus a placebo capsule by mouth, identical in appearance to ciprofloxacin capsules. Because ceftriaxone is yellow in solution, unlike saline, the double-blind nature of the trial was maintained by sheathing the syringe. Patients were observed for 30 min in the clinic. They were requested to abstain from sexual contact until after the second follow-up visit at 10 days. At the follow-up visits, 3 to 5 and 7 to 10 days after therapy, urethral cultures for *N. gonorrhoeae* were taken and patients were questioned about side effects of the medication. Repeat specimens for chlamydiae were not taken. At the second follow-up, those with serology reactive for syphilis were treated with benzathine penicillin in appropriate doses and follow-up visits for repeat serology tests were scheduled. Patients with *Chlamydia* infection, as determined by direct fluorescent-antibody examination, were treated with tetracycline (500 mg) four times daily for 7 days. Follow-up for all sexual partners was recommended. Those with antibody to HIV were referred to trained counselors within the dermato-venereology clinic for management.

Isolation of *N. gonorrhoeae* and *Chlamydia trachomatis*. Urethral, rectal, and pharyngeal specimens for *N. gonorrhoeae* as well as urethral swabs for *Chlamydia* culture and direct fluorescent-antibody examination of urethral smears (MicroTrak, Syva Corp., Palo Alto, Calif.) were obtained from all patients. *N. gonorrhoeae* strains were isolated and identified by standard techniques. Production of β-lactamase was determined by a ceph-lactam disk (Remel, Lenexa, Kans.). A heavy inoculum of an 18-h subculture of each isolate was placed in a mixture of glycerol and Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) in a ratio of 1:1 and placed at −70°C or in liquid nitrogen. Urethral swabs for *C. trachomatis* were placed into 0.2 M sucrose-phosphate-buffered solution and stored at −70°C for culture in the United States. Gonococci and chlamydiae were transported under dry ice. *Chlamydia* cultures were done under contract with the University of Washington.

Antimicrobial susceptibility testing. Isolates were tested in the sexually transmitted disease research lab at Johns Hopkins University, Baltimore, Md. The MICs of ceftriaxone, ciprofloxacin, penicillin, tetracycline, spectinomycin, and kanamycin were determined by the agar dilution method by using standard techniques (16). Isolates without plasmid-mediated resistance were defined as resistant by chromosomal mediation (CMRNG) if the MIC of penicillin and tetracycline was ≥2.0 (10). Isolates were determined to be resistant to spectinomycin if the MIC was ≥128 μg/ml and resistant to kanamycin if the MIC was ≥32 μg/ml (16).

Statistical methods. Discrete variables were analyzed by chi-square analysis with the Yates continuity correction or by the two-tailed Fisher exact test. Continuous variables were analyzed by Student's *t* test.

RESULTS

Study population. Two hundred men were enrolled and treated. The ciprofloxacin and ceftriaxone groups were comparable in age (27.5 years), prevalence of latent syphilis (14% and 10%), HIV infection (32 and 38%), number with chlamydiae (determined by smear or culture) (5%), number returning for follow-up (85 in each group), number with cultures negative for *N. gonorrhoeae* (2 and 3), and number infected with PPNG or CMRNG. Approximately one-third of the subjects were infected with HIV. No patient had neutropenia or lymphopenia, and none had clinical evidence of immunosuppression. Characteristics of patients who were evaluable on days 3 to 5 are given in Table 1.

Clinical and microbiologic results. No patient had a culture positive for *N. gonorrhoeae* from the rectum or pharynx. Of the 165 patients who returned for follow-up evaluation and who had a positive pretreatment culture for *N. gonorrhoeae*, only one patient (in the ceftriaxone group) had a positive posttreatment urethral culture (Table 1). The patient admitted sexual reexposure to an untreated partner. All 112 patients who returned for follow-up at 7 to 10 days remained free of infection. Only one patient reported post-gonococcal urethritis symptoms, i.e., slight dysuria. Pretreatment urethral specimens showed *C. trachomatis*. The other seven patients infected with *C. trachomatis* did not complain of urethritis symptoms on follow-up.

Toxicity and tolerance. Both ciprofloxacin and ceftriaxone were well tolerated by all patients. None complained of gastrointestinal or central nervous system symptoms, and no allergic reactions were observed or reported. Mild discomfort at the site of injection was noted in those receiving either intramuscular ceftriaxone or placebo.

Antimicrobial susceptibility of *N. gonorrhoeae*. Susceptibility data for ciprofloxacin and ceftriaxone were as follows. The MICs for 50 and 90% of isolates tested were 0.004 and 0.008 μg/ml, respectively, for both drugs. MIC ranges were ≤0.001 to 0.03 μg/ml for ciprofloxacin and ≤0.001 to 0.125 μg/ml for ceftriaxone. Of 195 pretreatment isolates tested, 65 produced β-lactamase. Additional testing on 180 isolates revealed that a high proportion of the non-PPNG strains were resistant to penicillin and tetracycline (82 of 117 [70%] at ≥1.0 μg/ml and 38 of 117 [32%] at ≥2.0 μg/ml), indicating chromosomally mediated resistance (CMRNG). No high-level tetracycline resistance (MIC, ≥16 μg/ml) was detected. Overall, only 5% of isolates were susceptible to tetracycline at ≤0.25 μg/ml. No resistance to spectinomycin or kanamycin was detected.

DISCUSSION

Ciprofloxacin (250 mg administered orally) and ceftriaxone (250 mg administered intramuscularly) were equally

effective in eradicating *N. gonorrhoeae*, including PPNG and CMRNG strains, from males with uncomplicated urethritis. This was true irrespective of concomitant HIV infection. Both agents were well tolerated and had minimal side effects. However, ciprofloxacin had the distinct advantage of oral administration, which obviated the need for use of sterile needles and syringes in a health care environment where these were limited. Pharyngeal and rectal infection did not occur. Preliminary studies suggest that ciprofloxacin may be effective in treating pharyngeal and rectal gonococcal infection (23; Moran and Zenilman, in press).

Few oral regimens have shown efficacy in treating gonococcal urethritis caused by organisms resistant to penicillin, spectinomycin, or tetracycline (18; Moran and Zenilman, in press). The quinolone class of antimicrobial agents offers new alternatives for oral therapy of resistant gonorrhea. While the nonfluorinated quinolone rosoxacin and fluorinated quinolones such as norfloxacin, ciprofloxacin, ofloxacin, and enoxacin have also been effective in treating gonorrhea, only a limited number of patients with PPNG or CMRNG have been reported (1, 2, 4, 6, 9, 21, 23; Moran and Zenilman, in press). The present study clearly demonstrates the utility of oral ciprofloxacin for the therapy of PPNG and CMRNG infections.

The prevalence of *C. trachomatis* (5%) in this study was similar to that in other central African countries (20) and much lower than the 14 to 36% seen in contemporary heterosexual men with gonorrhea in the United States (3). While ciprofloxacin has in vitro activity against *C. trachomatis*, a single dose has not been effective in eradicating *C. trachomatis* from either the urethra or the rectum (1, 2, 23). In addition, the quinolones ofloxacin and ciprofloxacin have not been effective in treating syphilitic orchitis in the rabbit model (22, 27; R. J. Rice, Y. A. Jeanlouis, J. Crawford, B. Craig, and S. A. Larsen, Abstr. Annu. Meet. Am. Soc. Microbiol. 1986, A-36, p. 7). Ceftriaxone is effective against incubating and early syphilis (12). Even though the prevalence of genital chlamydial infections in Africa is low, in view of the high prevalence of syphilis in our study population, it may be prudent to follow therapy of gonorrhea treated with a quinolone or aminocyclitol with tetracycline to treat incubating or early latent syphilis as well as the relatively few but important *C. trachomatis* infections. Ciprofloxacin, along with ceftriaxone, has been shown to be effective in treating chancroid (5).

Patterns of resistance to quinolones must be carefully monitored. Rosoxacin, a nonfluorinated quinolone, was commonly used for therapy of gonorrhea in the Philippines until 1986, when its use was discontinued because of treatment failures. Decreased susceptibility of *N. gonorrhoeae* strains to fluorinated quinolones such as ciprofloxacin has been reported from the Philippines (M. P. Joyce, R. H. Doe, D. S. Herip, G. H. Vaughan, B. B. Aying, T. Ponio, J. Lu, and J. C. Coolbaugh, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1061, 1989). Spread of these strains to other areas appears to be occurring (14).

Oral therapy for gonorrhea offers several advantages. These include ease of administration, patient acceptance, decreased cost, and fewer side effects compared with injections. Newer oral quinolones differ in pharmacokinetics and in vitro activity (6, 18, 21, 28). However, in view of the proven efficacy of single-dose therapy with newer quinolones for urethral gonorrhea (9, 22) and lack of single-dose efficacy against chlamydiae without significant adverse effects (13, 25), the main factors in choosing which quinolone to use are cost and adverse effects (13).

The cost of treating urethral gonorrhea with 250 mg of ciprofloxacin is $1.90 or $2.03 for 500 mg as recommended by the Centers for Disease Control (8), compared with $3.65 for 800 mg of norfloxacin. Parenteral therapy with ceftriaxone at the recommended dose of 250 mg (8) costs $7.25 or $3.62 for 125 mg as recommended by some (15). The cost for 2 g of kanamycin is $10.15, and 2 g of spectinomycin costs $12.11 (based on average wholesale price listings in Drug Topics Red Book, 1989). Nursing time and the cost of a needle and syringe must be added to the cost of parenteral medications.

The quinolones show promise in the therapy of gonococcal urethritis, including infections caused by resistant organisms, in men and in patients infected with HIV. Bacterial sexually transmitted diseases such as syphilis (26) and chancroid have not always responded well to usual antimicrobial therapy in HIV-infected individuals (19; D. Cameron, L. D'costa, G. Irungu, J. Ndinya-Achola, A. Ronald, and F. Plummer, 28th ICAAC, abstr. no. 1167, 1988). More experience is needed in the therapy of anal and pharyngeal gonorrhea before ciprofloxacin can be recommended. The quinolones would be contraindicated in pregnant women or patients under 16 years of age. Additional therapy will still be required in patients coinfected with *C. trachomatis*. Follow-up and treatment for syphilis will still be necessary.

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LITERATURE CITED

1. **Avonts, D., L. Fransen, J. Vielfont, A. Stevens, and K. Hendricks.** 1988. Treating uncomplicated gonococcal infection with 250 mg or 100 mg ciprofloxacin in a single oral dose. Genitourin. Med. **64**:134.
2. **Aznar, J., R. Prados, A. Rodriguez-Pichardo, I. Hernandez, C. de Miguel, and E. J. Perea.** 1986. Comparative clinical efficacy of two different single-dose ciprofloxacin treatments for uncomplicated gonorrhea. Sex. Transm. Dis. **13**:169–171.
3. **Bell, T. A., and J. T. Grayston.** 1986. Centers for Disease Control guidelines for prevention and control of *Chlamydia trachomatis* infections. Ann. Intern. Med. **104**:524–526.
4. **Black, J. R., J. M. Long, B. E. Zwicl, B. S. Ray, M. S. Verdon, S. Wetherby, E. W. Hook III, and H. H. Handsfield.** 1989. Multicenter randomized study of single-dose ofloxacin versus amoxicillin-probenecid for treatment of uncomplicated gonococcal infection. Antimicrob. Agents Chemother. **33**:167–170.
5. **Bodhidatta, L., D. N. Taylor, A. Chitwarakorn, K. Kuvanont, and P. Echeverria.** 1988. Evaluation of 500- and 1,000-mg doses of ciprofloxacin for the treatment of chancroid. Antimicrob. Agents Chemother. **32**:723–725.
6. **Boslego, J. W., C. B. Hicks, R. Greenup, R. J. Thomas, H. A. Weiner, J. Ciak, and E. C. Tramont.** 1988. A prospective randomized trial of ofloxacin vs. doxycycline in the treatment of uncomplicated male urethritis. Sex. Transm. Dis. **15**:186–191.
7. **Centers for Disease Control.** 1989. Trends in gonorrhea in homosexually active men–King County, Washington, 1989. Morbid. Mortal. Weekly Rep. **38**:762–764.
8. **Centers for Disease Control.** 1989. 1989 sexually transmitted diseases treatment guidelines. Morbid. Mortal. Weekly Rep. **38**(S-8):21–24.
9. **Covino, J. M., M. Cumming, B. Smith, S. Benes, K. Draft, and W. M. McCormack.** 1990. Comparison of ofloxacin and ceftriaxone in the treatment of uncomplicated gonorrhea caused by penicillinase-producing and non-penicillinase-producing strains.

Antimicrob. Agents Chemother. **34**:148–149.

10. **Faruki, H., R. N. Kohmescher, W. P. McKinney, and P. F. Sparling.** 1985. A community-based outbreak of infection with penicillin-resistant *Neisseria gonorrhoeae* not producing penicillinase (chromosomally mediated resistance). N. Engl. J. Med. **313**:607–611.
11. **Hira, S. K., J. Kamanga, O. Mkandawire, J. S. Patel, and M. Balaji.** 1985. Cefotaxime and ampicillin in the treatment of uncomplicated gonococcal urethritis in Zambia. Eur. J. Sex. Transm. Dis. **3**:13–15.
12. **Hook, E. W., R. E. Roddy, and H. H. Handsfield.** 1988. Ceftriaxone therapy for incubating syphilis. J. Infect. Dis. **158**:881–884.
13. **Hooper, D. C., and J. S. Wolfson.** 1989. Treatment of genitourinary tract infections with fluoroquinolones: clinical efficacy in genital infections and adverse effects. Antimicrob. Agents Chemother. **33**:1662–1667.
14. **Jephcott, A. E., and A. Turner.** 1990. Ciprofloxacin resistance in gonococci. Lancet **335**:165.
15. **Judson, F. N.** 1989. Management of antibiotic-resistant *Neisseria gonorrhoeae*. Ann. Intern. Med. **110**:5–7.
16. **Knapp, J. S.** 1988. Laboratory methods for the detection and phenotypic characterization of *Neisseria gonorrhoeae* strains resistant to antimicrobial agents. Sex. Transm. Dis. **15**:225–233.
17. **Knapp, J. S., J. M. Zenilman, J. W. Biddle, G. H. Perkins, W. E. DeWitt, M. L. Thomas, S. R. Johnson, and S. A. Morse.** 1987. Frequency and distribution in the United States of strains of *Neisseria gonorrhoeae* with plasmid-mediated, high-level resistance to tetracycline. J. Infect. Dis. **155**:819–822.
18. **Kraus, S. J., G. H. Reynolds, and R. T. Rolfs.** 1988. Therapy of uncomplicated gonorrhea due to antibiotic-resistant *Neisseria gonorrhoeae*. Sex. Transm. Dis. **15**:234–243.
19. **MacDonald, K. S., D. W. Cameron, L. J. D'Costa, J. O. Ndinya-Achola, F. A. Plummer, and A. R. Ronald.** 1989. Evaluation of fleroxacin (RO 23-6240) as single-oral-dose therapy of culture-proven chancroid in Nairobi, Kenya. Antimicrob. Agents Chemother. **33**:612–614.
20. **Meheus, A., R. Widy-Wirski, J. D'Costa, E. Van Dyck, R. Delgadillo, and P. Piot.** 1984. Treatment of gonorrhoeae in males in the Central African Republic with spectinomycin and procaine penicillin. Bull. W.H.O. **62**:89–94.
21. **Pabst, K. M., N. A. Siegel, S. Smith, J. R. Black, H. H. Handsfield, and E. W. Hook III.** 1989. Multicenter, comparative study of enoxacin and ceftriaxone for the treatment of uncomplicated gonorrhea. Sex. Transm. Dis. **16**:148–151.
22. **Poitevin, M., M. Ly, M. Daubras, and F. Ichou.** 1988. In vivo evaluation of the susceptibility of *Treponema pallidum* to ofloxacin. Pathol. Biol. **36**:482–487. (In French.)
23. **Roddy, R. E., H. H. Handsfield, and E. W. Hook.** 1986. Comparative trial of single-dose ciprofloxacin and ampicillin plus probenecid for the treatment of gonococcal urethritis in men. Antimicrob. Agents Chemother. **30**:267–269.
24. **Rothenberg, R., and R. Voigt.** 1988. Epidemiologic aspects of control of penicillinase-producing *Neisseria gonorrhoeae*. Sex. Transm. Dis. **15**:211–216.
25. **Smith, B. L., M. Cummings, S. Benes, K. Draft, and W. M. McCormack.** 1989. Evaluation of difloxacin in the treatment of uncomplicated urethral gonorrhea in men. Antimicrob. Agents Chemother. **33**:1721–1723.
26. **Tramont, E. C.** 1990. Treponema pallidum (syphilis), p. 1794–1808. *In* G. L. Mandel, D. R. Gordon, and J. E. Bennett (ed.), Principles and practices of infectious diseases, 3rd ed. Churchill Livingstone Inc., New York.
27. **Veller-Fornasa, C., M. Tarantello, R. Cipriani, L. Guerra, and A. Peserico.** 1987. Effect of ofloxacin on *Treponema pallidum* in incubating experimental syphilis. Genitourin. Med. **63**:214.
28. **Wolfson, J. S., and D. C. Hooper.** 1989. Treatment of genitourinary tract infections with fluoroquinolones: activity in vitro, pharmacokinetics, and clinical efficacy in urinary tract infections and prostatitis. Antimicrob. Agents Chemother. **33**:1655–1661.
29. **Zenilman, J. M., C. J. Nims, M. A. Menegus, F. Nolte, and J. S. Knapp.** 1987. Spectinomycin-resistant gonococcal infections in the United States, 1985–1986. J. Infect. Dis. **156**:1002–1004.