ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1996, p. 1720–1721 Vol. 40, No. 7
0066-4804/96/$04.00+0

Dose-Ranging Study of CP-99,219 (Trovafloxacin) for Treatment of Uncomplicated Gonorrhea

EDWARD W. HOOK III,[1,2]* GLORIA B. PINSON,[1] CAROL J. BLALOCK,[1] AND RAYMOND B. JOHNSON[3]

Department of Medicine, Division of Infectious Diseases, The University of Alabama at Birmingham,[1] and Sexually Transmitted Disease Control Program, Jefferson County Department of Health,[2] Birmingham, Alabama, and Pfizer Central Research, Groton, Connecticut

Received 22 January 1996/Returned for modification 12 March 1996/Accepted 13 April 1996

Thirty-nine patients with uncomplicated gonorrhea were randomized to receive single, oral 50-, 100-, or 200-mg doses of trovafloxacin (CP-99,219), a new quinolone antibiotic. All 31 evaluable patients were cured of infection. Trovafloxacin was well tolerated. The trovafloxacin MICs at which 50 and 90% of 36 *Neisseria gonorrhoeae* isolates are inhibited were 0.002 and 0.004 mg/liter, respectively (MIC range, <0.0005 to 0.008 mg/liter). These preliminary studies suggest that trovafloxacin is effective for the treatment of uncomplicated gonorrhea at single oral doses as low as 50 mg.

Despite recent declines in *Neisseria gonorrhoeae* infections, the disease remains common (2). For more than two decades gonorrhea therapy has been complicated by increasing levels of antimicrobial resistance because of both plasmid-mediated and chromosomally mediated mechanisms (2, 9, 10, 12). Currently, broad-spectrum cephalosporin and quinolone antibiotics are recommended for the treatment of uncomplicated gonorrhea (1). In many settings the reliability, oral administration, favorable safety profile, and lower cost of quinolone antibiotics have made them the preferred agents for the treatment of gonorrhea. The use of quinolone antibiotics for the treatment of gonorrhea has been tempered by questions regarding their safety in children, as well as by reports of treatment failures and laboratory evidence of decreasing levels of susceptibility of the organism to antimicrobial agents (1, 3, 4, 8). Trovafloxacin (CP-99,219) is a new quinolone antibiotic which is highly active against *N. gonorrhoeae* and *Chlamydia trachomatis* (6, 7, 11). In addition, preliminary data suggest that this drug will be acceptable for therapy in children. As a prelude to further studies, we performed a dose-ranging study to evaluate three doses of trovafloxacin as therapy for uncomplicated urogenital gonorrhea.

The study described here was an open, randomized, noncomparative, dose-ranging study. Participants were randomly assigned to receive single, oral doses of trovafloxacin of 50, 100, or 200 mg. The study was continued until 30 evaluable patients (at least half of whom were female) had been enrolled.

Participants were recruited from the Jefferson County Department of Health Sexually Transmitted Diseases Clinic in Birmingham, Ala. Eligibility criteria included age of 18 years or older and receipt of written informed consent. Women were considered to have probable gonorrhea if they reported recent sexual exposure to a male partner with urethral gonorrhea, if they had a positive culture for *N. gonorrhoeae* without treatment in the interval since the culture was obtained, or if Gram staining of a cervical discharge showed gram-negative diplococci within polymorphonuclear leukocytes. Males were eligible if they had a urethral discharge which showed gram-negative intracellular diplococci within polymorphonuclear leukocytes. *N. gonorrhoeae* isolation at the time of enrollment in the study was required for evaluability. Patients were excluded from participation if they were pregnant or nursing; gave a history of hypersensitivity or intolerance to quinolone antibiotics; had taken systemic antibiotics within 72 h of enrollment; had clinical evidence of complicated gonococcal infection, pelvic inflammatory disease, or any other infection which might require antibiotic treatment; had conditions which might affect drug absorption; had previously been enrolled in the protocol; or if, in the investigator's opinion, were not anticipated to comply with protocol requirements.

At enrollment patients underwent a screening physical and a genitourinary examination. Urogenital (cervical specimens for women and urethral specimens for men) and pharyngeal specimens for *N. gonorrhoeae* culture were obtained from all patients. Rectal swabs for culture were also obtained from all women. Cultures of genital specimens for *C. trachomatis* were also performed for all patients.

Treatment efficacy was evaluated 5 to 9 days following enrollment with repeat cultures. Efficacy was assessed by using posttreatment culture results without regard to persistent signs, symptoms, or history of sexual reexposure. Patients infected with *C. trachomatis* at the time of enrollment were treated at the follow-up visit.

Specimens for *N. gonorrhoeae* isolation were inoculated onto modified Thayer-Martin medium and were cultured as described previously (5, 10). β-Lactamase production was assessed by the chromogenic cephalosporin method. Antibiotic MICs were determined by agar dilution in GCA agar base (Becton-Dickinson, Baltimore, Md.) containing 1% IsoVitaleX and doubling dilutions of antibiotics (5, 10). High-level (TetM) plasmid-mediated tetracycline resistance was presumptively defined on the basis of tetracycline MICs of ≥16 mg/liter. Isolates were considered to have chromosomally mediated resistance to tetracycline on the basis of MICs of 2.0 to 8.0 mg/liter or to penicillin if the isolate did not produce β-lactamase and MICs of penicillin were ≥2 mg/liter. *C. trachomatis* cell cultures were performed in microtiter plates as described previously (5).

Thirty-nine participants (16 men and 23 women) were enrolled in the study. The median age for the men and women was 23 years (ranges, 19 to 30 and 18 to 47 years, respectively); 37 participants were African American and 2 were white. One

* Corresponding author. Mailing address: Department of Medicine, Division of Infectious Diseases, 229 Tinsley Harrison Tower, 1900 University Blvd., Birmingham, AL 35294-0006. Phone: (205) 934-5191. Fax: (205) 934-5155. Electronic mail address: ehook@uabid.dom.uab.edu.

TABLE 1. Eradication of *N. gonorrhoeae* by trovafloxacin at various sites of infection

Site of infection	No. of patients cured/no. of patients evaluable after the following treatment:		
	50 mg (n = 9)	100 mg (n = 12)[a]	200 mg (n = 10)
Urethra or cervix	9/9	11/11	10/10
Rectum	1/1	1/1	3/3
Throat	2/2	4/4	2/2
Total sites cured	12/12	17/17	14/14
Total patients cured	9/9	12/12	10/10

[a] In one female participant, the only anatomic site from which enrollment specimens for culture were positive was the rectum.

man did not return for follow-up, and seven women were nonevaluable as a result of negative cultures of specimens from all sites obtained at the time of enrollment.

N. gonorrhoeae was isolated from genital sites of 30 of 31 evaluable patients. One woman had negative cervical specimen cultures and a positive rectal swab culture for *N. gonorrhoeae*. Infections at all sites in 31 patients were cured, including 30 genital infections, 5 rectal infections, and 8 pharyngeal infections (Table 1). There were no treatment failures at any dose, and no new sites of infection were detected at follow-up. *Chlamydia* infections were detected in five participants (three women and two men) and were present in three participants at follow-up. No clinically significant laboratory abnormalities or adverse events were detected at the time of follow-up.

In vitro susceptibility testing of 36 pretreatment *N. gonorrhoeae* isolates showed antimicrobial resistance to be relatively common (Table 2). Five isolates produced β-lactamase, 12 had plasmid-mediated tetracycline resistance, and 12 had chromosomally mediated resistance to penicillin G or tetracycline. Nonetheless, all isolates were susceptible to trovafloxacin; the MICs at which 50 and 90% of isolates are inhibited were 0.002 and 0.004 mg/liter, respectively (range, <0.0005 to 0.008 mg/liter).

Our data suggest that trovafloxacin is a promising drug for the treatment of sexually transmitted diseases (STDs). Single oral doses as low as 50 mg cured all urogenital gonococcal infections as well as infections at traditionally more difficult to cure sites such as the rectum and pharynx. These data, coupled with reports of the substantial in vitro and in vivo activities of trovafloxacin against *C. trachomatis* (7, 11), suggest that trovafloxacin may be useful for the treatment of both uncomplicated STDs and complications such as pelvic inflammatory disease.

TABLE 2. Susceptibilities of 36 pretreatment *N. gonorrhoeae* isolates to antimicrobial agents[a]

Antimicrobial agent	MIC (mg/liter)[b]			
	Geometric mean	50%	90%	Range
Trovafloxacin	0.002	0.002	0.004	<0.0005–0.008
Ciprofloxacin	0.003	0.002	0.008	0.001–0.03
Ceftriaxone	0.006	0.004	0.015	0.002–0.06
Cefixime	0.016	0.015	0.03	0.008–0.125
Penicillin G[c]	0.3	0.250	2.0	0.03–2.0
Tetracycline[d]	0.7	1.00	2.0	0.06–2.0

[a] Four of 40 isolates did not survive freezing for MIC testing.
[b] 50% and 90%, MICs at which 50 and 90% of isolates are inhibited, respectively.
[c] Excluding data for five isolates which produced β-lactamase.
[d] Excluding data for 12 isolates with high-level, plasmid-mediated resistance to tetracycline.

The role of quinolone antibiotics for STD management continues to evolve (1, 3). Recent reports suggest that gonococci with high-level fluoroquinolone resistance, as previously reported for isolates from Southeast Asia, are now being seen sporadically in North America (3). In addition, prospective monitoring of gonococcal antimicrobial susceptibilities suggest that while resistance is not currently a threat to their utility, the susceptibilities of *N. gonorrhoeae* isolates to quinolone antibiotics (1, 3, 9) are gradually declining in several regions. Despite these trends, the excellent safety profile, lower costs, continued high therapeutic efficacy, and ease of administration will no doubt continue to make quinolone antibiotics the preferred agents for gonorrhea therapy in many areas. Finally, reappraisal of the potential for quinolones to cause arthropathy in children (4, 8) has led to suggestions that they may be appropriate for use in younger patients as well as in adults. This may be particularly true for trovafloxacin which, unlike other quinolones, has had no deleterious effects on cartilage formation in beagle puppies, even after prolonged administration of relatively high doses of medication (8a).

In summary, trovafloxacin is a new quinolone antibiotic which is highly active against *N. gonorrhoeae* and which appears to be highly effective for the treatment of uncomplicated gonorrhea at single oral doses as low as 50 mg. Further evaluation of trovafloxacin for the treatment of gonorrhea is warranted.

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