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# Dose-Ranging Study of Fleroxacin for Treatment of Uncomplicated *Chlamydia trachomatis* Genital Infections

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**Men and women with suspected or proven genital infections caused by *Chlamydia trachomatis* were enrolled in a double-blind study to evaluate the efficacy and tolerability of fleroxacin. Patients received either 400, 600, or 800 mg once daily for 7 days and were monitored approximately 2, 4, and 7 weeks after initiation of therapy. In men monitored for at least 6 weeks or until failure of the therapy, fleroxacin failed to eradicate *C. trachomatis* in three of eight on the 400-mg regimen, in one of four on the 600-mg regimen, and in four of seven on the 800-mg regimen. All five women monitored for at least 6 weeks became culture negative. There was no association between in vitro susceptibility of *C. trachomatis* to fleroxacin and outcome, with MICs being 4 to 8 μg/ml for almost all isolates tested. Among those with positive cultures for *Ureaplasma urealyticum* initially, the first follow-up cultures remained positive in 8 (29%) of 28 men and 8 (50%) of 16 women. Independent of culture results, men with nongonococcal urethritis receiving 800 mg of fleroxacin were significantly more likely to show a clinical response than men receiving 400 or 600 mg (93 versus 54%). Adverse events were frequent, often severe, and dose related. Insomnia and photosensitivity reactions were the most important. The adverse reactions and unacceptably high rates of microbiologic failure resulted in premature termination of the study.**

Infections due to *Chlamydia trachomatis* are frequent and are associated with significant sequelae (12). Tetracyclines are the recommended treatment of choice for the eradication of *C. trachomatis* (7), with erythromycins, sulfonamides, and rifampin being alternative choices (2). None of these antimicrobial agents is reliably effective against *Neisseria gonorrhoeae*. In contrast, many of the new fluoroquinolones are exceedingly active against *N. gonorrhoeae*, and several also demonstrate promising activity against *C. trachomatis* (15). New fluoroquinolones are also typically well tolerated (8).

Fleroxacin (Ro 23-6240; AM-833) is a new trifluorinated quinolone which has very high bioavailability, a relatively long serum half-life (8 to 12 h), and good to high tissue penetration (14). The objective of this double-blind study was to evaluate the in vivo efficacy and tolerability of three dosage regimens of fleroxacin in the treatment of uncomplicated genital infections with *C. trachomatis* and genital mycoplasmas in men and women.

## MATERIALS AND METHODS

**Study population.** Men and women 18 years of age and older who presented to the Vancouver and Calgary Sexually Transmitted Disease Clinics were eligible for the study if they or their partners had a syndrome associated with increased likelihood of the presence of *C. trachomatis*. For men this included nongonococcal urethritis, a recent prior test for *C. trachomatis* that was reported to be positive, or sexual contact with a partner with mucopurulent cervicitis or a positive test for *C. trachomatis*. For women this included mucopurulent cervicitis, a recent prior test for *C. trachomatis* that was reported to be positive, or sexual contact with a male with nongonococcal urethritis or a positive test for *C. trachomatis*. Nongonococcal urethritis was defined as the presence of urethral discharge of less than 1 month duration in association with a urethral smear demonstrating a mean of 5 or more polymorphonuclear leukocytes per oil immersion microscopic field (magnification, ×1,000) in at least five fields, a Gram stain that did not reveal gram-negative diplococci suggestive of *N. gonorrhoeae*, and a subsequent negative urethral culture for *N. gonorrhoeae* (1). Mucopurulent cervicitis was diagnosed only in nonmenstruating women and was defined as the presence of cervical mucus that appeared yellow or green when viewed on a white-tipped swab plus 10 or more polymorphonuclear leukocytes per ×1,000 oil immersion microscopic field of a Gram stain of endocervical mucus in areas with few or no epithelial cells (1).

Exclusion criteria included use of antimicrobial agents in the preceding month, history of hypersensitivity to quinolones, a positive culture for *N. gonorrhoeae*, clinical evidence of a complicated infection (epididymitis in men and endometritis or salpingitis in women), voiding within the previous 4 h for men, and pregnancy, a missed period, breast feeding, or failure to use an effective method of contraception for women.

**Study protocol.** At the initial visit, individuals were questioned as to symptoms, prior use of antimicrobial agents, sexual history, and possible exclusion criteria. A standard genital examination was then performed, during which specimens were collected by using standard techniques. Specimens were collected for detection of *C. trachomatis* and *N. gonorrhoeae* from the urethras of men and women; the endocervix; the rectums of women and homosexual or bisexual men; and the pharynges of men and women who admitted to orogenital sexual contact. Specimens for the detection of genital mycoplasmas were obtained from the urethras of men and the vaginas of women. The first 10 ml of voided urine was obtained from men for the detection of pyuria and trichomonads and for culture for genital myco-

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plasmas. Serum was obtained for a serologic test for syphilis and for safety profiles. An attempt was made to evaluate and to either enroll or treat all sexual partners.

Patients were then given fleroxacin to take as four tablets once daily for 7 days. The tablets contained placebo or active medication so that the patients received either 400, 600, or 800 mg of fleroxacin daily. Tablets were taken with or immediately after meals at approximately the same time each day. Both individuals and investigators were blind to the actual regimen received. Individuals were given a diary to record time of taking medications, time of meals, symptoms (new or old), and intercourse, if any. Patients were requested not to have sexual intercourse during the whole study, but particularly before the first follow-up visit. If they did have sexual intercourse they were requested to use a condom. They were advised not to use antacids.

All individuals were requested to return for follow-up 14 ± 3, 28 ± 5, and 49 ± 7 days after initiation of treatment. Men were requested to arrive without having voided for 4 or more hours. All were asked to return their medication bottle and diary at the first follow-up visit. They were questioned about symptoms, possible adverse reactions, compliance with medication, and resumption of sexual intercourse. If they had resumed sexual intercourse they were also asked if it was with a new or old partner, whether the partner had been treated, and whether or not a condom was used. With the exception of syphilis serology, the safety profile, and repeat cultures for *N. gonorrhoeae*, all studies initially performed were repeated at all follow-up visits. The safety profile was repeated at the first follow-up visit only.

**Laboratory methods.** All diagnostic tests were performed in a standard manner (6). Cultures for *C. trachomatis* were performed in vials, using cycloheximide-treated McCoy cells stained with iodine in Vancouver or with fluorescein-conjugated monoclonal antibody in Calgary. All negative specimens were passed to new monolayers at least once, and specimens showing inclusions were passed to demonstrate persistence of inclusions.

**Evaluation of response.** Microbiologic response and clinical response were based upon the status at the initiation of treatment. For those with a positive clinical or laboratory result initially, cure was defined as lack of the positive finding at the initial follow-up visit and at all follow-up visits through at least 5 weeks after the end of treatment. A repeat positive result at follow-up was defined as persistence if it was positive at the first follow-up visit or recurrence if it was negative posttreatment but subsequently became positive again. Persistence or recurrence was considered to indicate a failure of the regimen if the individual was compliant with taking medications and did not resume sexual intercourse before the positive posttreatment result, had sexual intercourse but always used a condom, or had sexual intercourse without using a condom but with treated partners only. All other positive results posttreatment were not considered to be regimen failures.

Retreatment was initiated during the study period only if (i) (in men) symptoms of urethritis plus urethral discharge plus increased numbers of polymorphonuclear leukocytes were demonstrated in urethral secretions or in the first voided urine sediment, (ii) one or more follow-up cultures for *C. trachomatis* were positive, or (iii) the initial course could not be completed because of adverse reactions.

**Assessment of in vitro activity against *C. trachomatis*.** Isolates which were saved and could be propagated in vitro were subsequently tested for susceptibility to fleroxacin and doxycycline by using our usual methods (4).

TABLE 1. Microbiologic response to treatment of *C. trachomatis* infection with fleroxacin

| Sex and follow-up time (days) | No. culture negative at follow-up/no. initially positive with daily fleroxacin dose (mg) of: | | | Total culture negative/total initially positive (%) |
|---|---|---|---|---|
| | 400 | 600 | 800 | |
| Male | | | | |
| >27 | 6/9 | 4/5 | 3/7 | 13/21 (62) |
| >45 | 5/8 | 3/4 | 3/7 | 11/19 (58) |
| Female | | | | |
| >31 | 3/3 | 1/1 | 2/2 | 6/6 (100) |
| >45 | 2/2 | 1/1 | 2/2 | 5/5 (100) |

## RESULTS

A total of 62 men and 23 women were initially enrolled. Of the men, 45 were enrolled because of nongonococcal urethritis, 14 were enrolled as contacts of women with a report of a positive test for *C. trachomatis*, and 3 were enrolled with a report of a recent prior positive test for *C. trachomatis*. Cultures for *C. trachomatis* at the time of enrollment were positive in 19, 6, and 2 of the men in these three groups, respectively. Overall, including all three categories at enrollment, 55 of the men had nongonococcal urethritis. Among women, 12 were enrolled because of a report of a recent prior positive diagnostic test for *C. trachomatis*, 9 were enrolled as contacts of men with nongonococcal urethritis, and 2 were enrolled as contacts of men with a report of a positive test for *C. trachomatis*. Cultures for *C. trachomatis* at the time of enrollment were positive in 9, 2, and 0 of the women in these three groups, respectively. Overall, six women had mucopurulent cervicitis, of whom five had positive cultures for *C. trachomatis*.

In total, *C. trachomatis* was initially isolated from 27 (44%) men and 11 (48%) women, *Ureaplasma urealyticum* was isolated from 30 (48%) men and 20 (87%) women, and large-colony mycoplasmas that were most likely *Mycoplasma hominis* were isolated from 4 (7%) men and 9 (39%) women.

Six individuals did not return for any follow-up, and three received incomplete courses of medication because adverse reactions resulted in premature cessation of treatment.

Table 1 shows the microbiologic outcome for those who initially had a positive culture for *C. trachomatis* at enrollment and were monitored either to the time of clinical or microbiologic failure necessitating retreatment or for different durations of follow-up. All microbiologic failures were detected at the first follow-up culture. Fleroxacin did not reliably eradicate *C. trachomatis* from men at any dose, and there was no apparent dose response. All women had repeatedly negative posttreatment cultures.

Table 2 shows the microbiologic status at the first follow-up visit for those who initially had a positive culture for a genital mycoplasma at enrollment. Treatment was associated with negative cultures in most, but many remained culture positive. There were no clear trends towards increasing efficacy with increasing dose.

Men who initially had nongonococcal urethritis appeared to show greater improvement on higher doses. Irrespective of culture status for *C. trachomatis* at follow-up, in those men monitored either to diagnosis of nongonococcal urethritis at follow-up or to at least 46 days after initiation of

TABLE 2. Microbiologic response to treatment of genital mycoplasmas at the first follow-up visit according to the daily dose of fleroxacin

| Infecting organism(s) and sex | No. culture negative at first follow-up visit/no. initially positive with daily fleroxacin dose (mg) of: | | | Total culture negative at first follow-up/total initially positive (%) |
|---|---|---|---|---|
| | 400 | 600 | 800 | |
| *U. urealyticum* | | | | |
| Male | 5/7 | 9/13 | 6/8 | 20/28 (71) |
| Female | 3/4 | 0/7 | 5/5 | 8/16 (50) |
| Large-colony mycoplasmas | | | | |
| Male | 1/1 | 3/3 | 0/0 | 4/4 (100) |
| Female | 0/1 | 3/3 | 3/3 | 6/7 (83) |

treatment if nongonococcal urethritis was not diagnosed at follow-up, persistence of nongonococcal urethritis was decreased on the 800-mg regimen (Table 3; two-tailed Fisher's exact test, $P < 0.02$).

Table 4 shows the MICs of fleroxacin and doxycycline for isolates of *C. trachomatis* from this study according to whether the isolate came from a man who was culture positive posttreatment and was considered to be a treatment failure or from a man or a woman who became culture negative and was considered to be a treatment success. Also shown are the results for three isolates that we have used as controls for many years (3). There was no apparent difference between groups. MICs of fleroxacin were 2.0 to 8.0 μg/ml, independent of the source of the isolate. In four pairs of pretreatment and posttreatment isolates, results were identical or were at most one dilution different. MBC results were similar to MIC results for all strains.

Adverse reactions were frequent, particularly at higher doses. Adverse reactions that the individuals considered severe arose in 4 of 26 (15%) on the 400-mg regimen, in 13 of 27 (48%) on the 600-mg regimen, and in 21 of 26 (81%) on the 800-mg regimen. The dose relationship was statistically significant ($P < 0.001$ [chi-square test]). Especially frequent or troublesome were sleep disturbances and photosensitivity reactions. Adverse reactions are described in more detail in a companion report (5).

TABLE 3. Persistence of nongonococcal urethritis in men monitored until failure of treatment or for at least 6 weeks after initiation of treatment[a]

| Condition | No. with NGU/total no. in group with daily fleroxacin dose (mg) of: | | |
|---|---|---|---|
| | 400 | 600 | 800 |
| Initially culture positive for *C. trachomatis* | | | |
| *C. trachomatis* not eradicated at follow-up | 3/3 | 1/1 | 1/4 |
| *C. trachomatis* cultures negative at follow-up | 0/5 | 1/3 | 0/3 |
| NGU initially but culture negative for *C. trachomatis* | 3/8 | 5/8 | 0/8 |

[a] Persistence of nongonococcal urethritis (NGU) was defined as having occurred if symptoms plus urethral discharge plus increased numbers of polymorphonuclear leukocytes in urethral secretions were present.

TABLE 4. In vitro activity of fleroxacin and doxycycline against *C. trachomatis*

| Source of isolates | No. of strains with indicated MIC (μg/ml) of: | | | | | |
|---|---|---|---|---|---|---|
| | Fleroxacin | | | Doxycycline | | |
| | 2 | 4 | 8 | 0.016 | 0.032 | 0.064 |
| Controls | 0 | 2 | 1 | 0 | 3 | 0 |
| Treatment failures[a] | 1 | 3 | 2 | 0 | 4 | 2 |
| Treatment cures | 2 | 12 | 3 | 1 | 13 | 3 |

[a] In four cases, both pre- and posttreatment isolates were evaluated, but each pair was counted as a single isolate.

## DISCUSSION

In this study, fleroxacin was not reliable in eradicating *C. trachomatis* from the urethras of men. An early report (H. Meier-Ewert and O. Steele-Mortimer, Program Abstr. 15th Int. Congr. Chemother., abstr. no. 416, p. 176, 1987) of in vitro susceptibility of *C. trachomatis* to fleroxacin indicated lower MICs than we obtained, and results from different laboratories are still conflicting. However, our results as well as those of the ultimate publications by Steele-Mortimer and Meier-Ewert (11), Martin (D. H. Martin, Program Abstr. South. Soc. Clin. Invest., Clin. Res. **36**:21A, 1988), Endtz et al. (H. P. Endtz, J. M. Ossewaarde, and H. T. Weiland, Program Abstr. 2nd Int. Symp. N. Quinolones, p. 244, 1988), and Maeda et al. (9) indicated MICs in the range of 4 to 8 μg/ml. Clinical results published in abstract form have also been conflicting. Some have suggested good in vivo activity, whereas our results and those of Gundersen and Zalm (T. Gundersen and F. Zahm, Program Abstr. 2nd Int. Symp. N. Quinolones, p. 245, 1988) indicate unreliable activity. In the latter study, which used 400 mg once daily for 7 days, 2 of 11 remained culture positive at 5 to 9 days posttreatment and 4 of 10 were positive at 16 to 26 days posttreatment. In contrast, using a similar regimen, Söltz-Szöts and Sneider (H. Söltz-Szöts and S. Sneider, Program Abstr. 2nd Int. Symp. N. Quinolones, p. 249, 1988) reported that 16 of 19 patients were cured and questioned the possibility of reinfection in the three with positive posttreatment cultures. Pust et al. reported that with follow-up of 21 ± 5 days after treatment, 400 to 800 mg daily for 7 days eradicated *C. trachomatis* from all 19 assessable individuals (10).

It is our impression that fleroxacin will not be sufficiently active to be useful in treatment of chlamydial infections in men. It is possible that it will be active in women. Erythromycin and possibly clindamycin are more active in women than in men (2, 13), and we did not see any failures in the small number of women that we treated. Further studies of the treatment of women may clarify this issue.

There was some in vivo activity against genital mycoplasmas in both men and women. However, as with other quinolones, the activity was unreliable.

Despite the apparent discrepancy between our results in treatment of *C. trachomatis* and those of some other investigators, we believe that our results are valid for several reasons. Microbiologic failures were all documented by culture, and we were successful whenever we subsequently tried to increase the number of chlamydiae to do in vitro susceptibility studies. Microbiologic failures were always detected at the first follow-up visit, making reinfection very unlikely. In two of the men who were not retreated at the first follow-up visit, cultures were positive on two occasions before retreatment. In five of the eight men for whom

treatment failed, there was minimal or no clinical improvement with fleroxacin, and the three men who showed clinical improvement were on the 800-mg regimen. Although it is possible that men did not take their medication, all said that they took it, indicated on their diary cards that they took it, and returned their empty medication bottles, and six of eight noted adverse reactions. To exclude the possibility that the study medication was other than that intended, it was reassayed for activity by Hoffmann-La Roche Ltd., and the medication had the stated potency. Thus, we believe that our results are valid.

In conclusion, although fleroxacin eradicated genital pathogens from some individuals, all three regimens were associated with an unacceptably high rate of failure. The frequency of adverse reactions will limit the usefulness of fleroxacin at higher doses. However, the tolerability of the 400-mg regimen was acceptable in this study, and because of the considerable pharmacokinetic advantages of fleroxacin, it may prove to be useful for other conditions.

## ACKNOWLEDGMENT

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## LITERATURE CITED

1. **Bowie, W. R., and N. E. MacDonald (ed.).** 1989. 1989 Canadian guidelines for the diagnosis and management of sexually transmitted diseases, by syndrome, in children, adolescents and adults. Can. Dis. Weekly Rep. **15S1**:1–31.
2. **Bowie, W. R.** 1984. Epidemiology and therapy of *Chlamydia trachomatis* infections. Drugs **27**:459–468.
3. **Bowie, W. R., C. K. Lee, and E. R. Alexander.** 1978. Prediction of efficacy of antimicrobial agents in treatment of infections due to *Chlamydia trachomatis*. J. Infect. Dis. **138**:655–659.
4. **Bowie, W. R., C. E. Shaw, D. G. W. Chan, and W. A. Black.** 1987. In vitro activity of Ro 15-8074, Ro 19-5247, A-56268, and roxithromycin (RU 28965) against *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Antimicrob. Agents Chemother. **31**: 470–472.
5. **Bowie, W. R., V. Willetts, and P. J. Jewesson.** 1989. Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. Antimicrob. Agents Chemother. **33**: 1778–1782.
6. **Bowie, W. R., J. S. Yu, A. Fawcett, and H. D. Jones.** 1980. Tetracycline in nongonococcal urethritis: comparison of 2g and 1g daily for seven days. Br. J. Vener. Dis. **56**:332–336.
7. **Centers for Disease Control.** 1985. 1985 STD treatment guidelines. Morbid. Mortal. Weekly Rep. **34**(4S):75S-108S.
8. **Halkin, H.** 1988. Adverse effects of the fluoroquinolones. Rev. Infect. Dis. **10**(Suppl. 1):S258–S261.
9. **Maeda, H., A. Fujii, K. Nakata, S. Arakawa, and S. Kamidono.** 1988. In vitro activities of T-3262, NY-198, fleroxacin (AM-833; RO 23-6240), and other new quinolone agents against clinically isolated *Chlamydia trachomatis* strains. Antimicrob. Agents Chemother. **32**:1080–1081.
10. **Pust, R. A., H. R. Ackenheil-Köppe, W. Weidner, and H. Meier-Ewert.** 1988. Clinical efficacy and tolerance of fleroxacin in patients with urethritis caused by *Chlamydia trachomatis*. J. Antimicrob. Chemother. **22**(Suppl. D):227–230.
11. **Steele-Mortimer, O., and H. Meier-Ewert.** 1988. In vitro activity of fleroxacin against *Chlamydia trachomatis*. J. Antimicrob. Chemother. **22**(Suppl. D):65–70.
12. **Washington, A. E., R. E. Johnson, and L. L. Sanders, Jr.** 1987. *Chlamydia trachomatis* infections in the United States: what are they costing us? J. Am. Med. Assoc. **257**:2070–2072.
13. **Wasserheit, J. N., T. A. Bell, N. B. Kiviat, P. Wølner-Hanssen, V. Zabriskie, B. D. Kirby, E. C. Prince, K. K. Holmes, W. E. Stamm, and D. A. Eschenbach.** 1986. Microbial causes of proven pelvic inflammatory disease and efficacy of clindamycin and tobramycin. Ann. Intern. Med. **104**:187–193.
14. **Weidekamm, E., R. Portmann, C. Partos, and D. Dell.** 1988. Single and multiple dose pharmacokinetics of fleroxacin. J. Antimicrob. Chemother. **22**(Suppl. D):145–154.
15. **Wolfson, J. S., and D. C. Hooper.** 1985. The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob. Agents Chemother. **28**:581–586.