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K S MacDonald, D W Cameron, L D'Costa, J O Ndinya-Achola, F  
A Plummer and A R Ronald  
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## Evaluation of Fleroxacin (RO 23-6240) as Single-Oral-Dose Therapy of Culture-Proven Chancroid in Nairobi, Kenya

KELLY S. MACDONALD,<sup>1</sup> D. WILLIAM CAMERON,<sup>1,2</sup> LOURDES J. D'COSTA,<sup>3</sup>  
JACKONIAH O. NDINYA-ACHOLA,<sup>2</sup> FRANCIS A. PLUMMER,<sup>1,2</sup> AND ALLAN R. RONALD<sup>1\*</sup>

Departments of Internal Medicine and Medical Microbiology, University of Manitoba, Winnipeg, Manitoba R3E 0Z3, Canada,<sup>1</sup> and Department of Medical Microbiology, University of Nairobi,<sup>2</sup> and Nairobi City Council Special Treatment Clinic,<sup>3</sup> Nairobi, Kenya

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Chancroid is gaining importance as a sexually transmitted disease because of its association with transmission of human immunodeficiency virus type 1 (HIV-1). Effective, simply administered therapy for chancroid is necessary. Fleroxacin is effective against *Haemophilus ducreyi* in vitro. We performed an initial randomized clinical trial to assess the efficacy of fleroxacin for treatment of chancroid in Nairobi, Kenya. Fifty-three men with culture-positive chancroid were randomly assigned to receive either 200 mg (group 1) or 400 mg (group 2) of fleroxacin as a single oral dose. Groups 1 and 2 were similar with regard to severity of disease, bubo formation, and HIV-1 status. A satisfactory clinical response to therapy was noted in 23 of 26 patients (88%) in group 1 and 18 of 23 patients (78%) in group 2. Bacteriological failure occurred in 1 of 26 evaluable patients (4%) in group 1 and 4 of 23 evaluable patients (17%) in group 2. Two of 37 HIV-1-seronegative men (5%) and 3 of 11 HIV-1-infected men (27%) were bacteriological failures. Fleroxacin, 200 or 400 mg as a single oral dose, is efficacious therapy for microbiologically proven chancroid in patients who do not have concurrent HIV-1 infection. Among HIV-1-infected men, a single dose of 200 or 400 mg of fleroxacin is inadequate therapy for chancroid.

Chancroid is a common and debilitating sexually transmitted disease in developing countries, and, while less common, it is being observed more frequently in North America (2, 11). This disease is assuming more global importance because of its highly significant statistical association with human immunodeficiency virus type 1 (HIV-1) transmission (4, 12; K. MacDonald, D. W. Cameron, L. J. D'Costa, J. O. Ndinya-Achola, F. A. Plummer, and A. R. Ronald, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 821, 1987; F. A. Plummer, J. N. Simonsen, D. W. Cameron, J. O. Ndinya-Achola, J. K. Kreiss, M. Gakinya, P. Waiyaki, P. Karasira, M. Cheang, P. Piot, A. R. Ronald, M. Bosire, J. Kimata, L. J. D'Costa, and E. N. Ngugi, submitted for publication). Seroepidemiologic studies of HIV-1 prevalence and incidence suggest that chancroid increases the risk of men being infected by HIV-1-seropositive female partners (4, 12; MacDonald et al., 27th ICAAC). Studies have also shown that chancroid is associated with greatly increased susceptibility of women to HIV-1 infection (Plummer et al., submitted). Control of chancroid by using effective, acceptable, and affordable therapy may be essential for the control of HIV-1 in Africa.

Plasmid- and chromosomally mediated antimicrobial resistance of *Haemophilus ducreyi* has complicated identification of optimal therapy for chancroid (1, 7). Almost all strains are resistant to ampicillin by plasmid-mediated  $\beta$ -lactamase production (7). Trimethoprim-sulfamethoxazole as a single oral dose has been the standard therapy for chancroid in Nairobi, Kenya, but this regimen is ineffective in Thailand because of trimethoprim resistance (10, 13).

In Kenya, we have evaluated therapy with the quinolone agents rosoxacin (5), enoxacin (8), and ciprofloxacin (9). In vitro, these agents are effective against *H. ducreyi*, with MICs for 90% of isolates tested of less than 0.25  $\mu$ g/ml for all

agents; *H. ducreyi* resistance to the quinolones has not been described. Inhibitory levels in serum for at least 48 h are necessary to eradicate *H. ducreyi* (3). Most quinolones have serum half-lives of under 6 h. Fleroxacin, with a longer serum half-life of 8 to 12 h, high oral bioavailability, excellent tissue penetration, and an MIC for 90% of isolates of 0.06  $\mu$ g/ml, is a promising single-dose therapy for chancroid (6, 14).

To test the efficacy of fleroxacin in clinical *H. ducreyi* infections, we performed a dose-finding study among men with culture-proven chancroid who were randomized to receive either 200 or 400 mg of fleroxacin as a single oral dose.

### MATERIALS AND METHODS

Men between the ages of 18 and 60 who presented to the Nairobi City Council Special Treatment Clinic, Nairobi, Kenya, with genital ulcer disease were entered into the study. Individuals whose cultures were positive by dark-field microscopy, who had positive cultures for *H. ducreyi*, and who had no treatment in the preceding week were randomized to receive either 200 mg (group 1) or 400 mg (group 2) of oral fleroxacin as a single dose. Verbal informed consent was obtained. Demographic and historical data were obtained in a standardized format interview. Patients were examined, and the number, size, tenderness, and other characteristics of ulcers and the presence and inflammation of inguinal lymph nodes were noted. Clinical evaluations were repeated at days 0, 3, 7, 14, and 28. Patients were cultured for *H. ducreyi* pre-enrollment and on each visit as long as the ulcer remained unhealed. Dark-field microscopy examinations were performed at the pre-enrollment visit, and serologic testing for syphilis was performed (rapid plasma reagin [RPR], Becton Dickinson, Mississauga, Ontario, Canada; microhemagglutination test for *Treponema pallidum*, Ames, Rexdale, Ontario, Canada) on days 0, 14, and 28. HIV-1

\* Corresponding author.

TABLE 1. Demographic, epidemiologic, and clinical characteristics of patients in group 1 treated with a single oral dose of 200 mg of fleroxacin and group 2 treated with a single oral dose of 400 mg of fleroxacin<sup>a</sup>

Characteristic	Group 1 (n = 30)	Group 2 (n = 23)
Age (yr ± SD)	24.3 ± 4.0	26.7 ± 6.5
Circumcision (no. of patients/total) (%)	12/25 (48)	7/17 (41)
No. of ulcers ± SD	2.4 ± 1.9	2.3 ± 1.8
Diam of largest ulcer (mm ± SD)	13.3 ± 8.3	12.6 ± 6.2
Estimated incubation period (days ± SD)	6.2 ± 3.8	4.9 ± 3.0
Duration of ulcer at presentation (days ± SD)	16.4 ± 11.9	13.4 ± 6.5
Buboes present (no. of patients) (%)	12 (40)	8 (35)
HIV-1 (no. of patients)		
Seropositive	3	5
Seroconversion	1	2

<sup>a</sup> *P* values, determined by *t* test and chi-square analysis, were not significant in all cases.

status was evaluated at enrollment and in follow-up by using a commercially available enzyme immunoassay (HTLV-III ELISA; Dupont DeNemours, Geneva, Switzerland) with confirmatory testing of reactive sera with immunoblotting (Western blot; Dupont DeNemours).

*H. ducreyi* cultures were performed as previously described (10). Ulcer swabs were directly inoculated on gonococcal agar base (GIBCO Laboratories, Madison, Wis.) with 1% bovine hemoglobin, 5% fetal calf serum, 1% coenzymes-vitamins-amino acids (CVA) (GIBCO), and vancomycin (3 µg/ml) and on Mueller-Hinton agar base with 5% chocolate-ized equine blood, 1% CVA, and 3 µg of vancomycin per ml.

Inoculated plates were transported to the laboratory within 4 h and incubated at 33°C in a humidified candle extinction jar. Plates were examined at 48 and 72 h. *H. ducreyi* was identified by colony morphology, Gram stain appearance, and oxidase reactivity.

The clinical healing rate of ulcers was analyzed by using survival analysis and compared by using the log rank test. Standard parametric and nonparametric two-tailed tests were used to compare sample proportions and means.

## RESULTS

Fifty-three *H. ducreyi* culture-positive men were enrolled. Thirty patients received 200 mg of fleroxacin as a single oral dose (group 1), and 23 patients received 400 mg as a single oral dose (group 2). The drug was well tolerated, and no adverse effects were reported or observed.

Table 1 compares the two treatment groups with respect to age, circumcision status, number and size of ulcers, presence of buboes, incubation period, duration of disease, and percent who were HIV seropositive. There were no significant differences in these characteristics.

Clinical follow-up revealed improvement or cure in 88% of group 1 patients and 78% of group 2 patients, with a total of seven treatment failures (Table 2). The difference in the rates of healing was not significant. The mean times to re-epithelization were 10.1 ± 4.6 (standard deviation) days in group 1 and 12.3 ± 6.4 days in group 2 (*P* = not significant). Delayed re-epithelization (beyond 15 days) occurred in three patients in group 1 and four patients in group 2. Two of 7 patients (29%) with delayed healing were HIV-1 seropositive, compared with 2 of 22 patients (9%) who healed promptly (*P* =

TABLE 2. Clinical and microbiological response of chancroid to two single-dose oral fleroxacin regimens

Characteristic	No. of patients	
	Group 1 (200 mg) (n = 30)	Group 2 (400 mg) (n = 23)
Evaluable	26	23
Clinical cure <sup>a</sup>	15	12
Microbiological cure	25	19
Clinical improvement <sup>b</sup>	8	6
Clinical failure	2	5
Microbiological failure	1	4
Reinfection	1	0

<sup>a</sup> Cure defined as complete re-epithelization.

<sup>b</sup> Refers to patients who were markedly improved on their last recorded visit but were not monitored to complete healing.

not significant). As has been demonstrated in previous studies, the most significant factor influencing time to re-epithelization was size of ulcer (8), with average widest ulcer diameter of 9.5 ± 4.9 mm in those who healed promptly and 18.5 ± 11.3 mm in those with delayed healing (*P* < 0.005). The presence of buboes did not delay re-epithelization, and, in this study, all ulcer cures were associated with resolution of buboes.

Microbiological cure was noted in 23 of 25 evaluable patients (92%) from group 1. Microbiological failure occurred in one patient with clinical failure, and another patient was reinfected after reexposure. Microbiological cure occurred in 19 of 23 patients (83%) in group 2. Microbiological failure occurred in four of the five patients who experienced clinical failure (Table 2).

There was no significant difference in microbiological cure rates between the two groups. Microbiological failure occurred in 3 of 11 patients (27%) who were HIV-1 seropositive or who seroconverted during follow-up and in 2 of 37 consistently seronegative patients (5%) (*P* = 0.07, Fisher's exact test).

## DISCUSSION

In this study, we demonstrated that fleroxacin is an effective therapy for chancroid, with cure rates similar to those of other regimens (3, 5, 8–10, 13). The microbiological cure rates (92 versus 83%) and clinical responses (88 versus 78%) with 200 or 400 mg of fleroxacin, respectively, are comparable. Doses higher than 200 mg do not appear to be necessary. The "acceptable response rate" following treatment for chancroid may need reevaluation. Formerly, a 90% cure rate for this "minor venereal disease" was adequate. With the probable epidemiologic association between HIV-1 transmission and genital ulcer disease, more dependable and predictably effective treatment is mandatory. In view of this, the cure rates demonstrated in this study of single-dose therapy are not acceptable per se.

What factors are associated with treatment failure? During this study, it became apparent that HIV-1 infection is associated with delayed healing and with treatment failure. If HIV-1-seronegative patients are evaluated, the microbiological cure rates were 100 and 91% in groups 1 and 2, respectively. Two of eight HIV-1-seropositive patients failed, as did one of three patients who seroconverted to HIV-1 during follow-up. Because of the small numbers examined, this difference in efficacy between HIV-seropositive and -seronegative individuals is not significant. However, evaluation of single-dose regimens in Nairobi by Cam-

eron et al. (D. W. Cameron, F. A. Plummer, L. J. D'Costa, J. O. Ndinya-Achola, and A. R. Ronald, 4th Int. Conf. AIDS, Stockholm, Sweden, 1988) showed a statistically significant difference in cure rates in HIV-seropositive and -seronegative patients.

The contribution of the immune system to recovery from chancroid is unknown. Presumably, an alteration in the host response from HIV infection accounts for the increased likelihood of relapse. Perhaps intracellular bacterial killing or the induction of serumcidal antibodies may be deficient. Of particular interest is the preliminary evidence that immune suppression occurring during acute HIV illness may also lead to increased risk of therapeutic failure of chancroid.

As the prevalence of HIV infection increases, optimal therapy for the treatment of chancroid in HIV-1-infected patients becomes an urgent priority. Single-dose therapy must be reevaluated, and a reliable treatment regimen must be determined.

The merits of quinolones for the therapy of chancroid in general and fleroxacin in particular, with its longer half-life, are considerable; further study is warranted.

Fleroxacin in single doses of 200 or 400 mg is efficacious therapy for microbiologically proven chancroid in the absence of HIV-1 infection. Fleroxacin may be superior to the standard single-dose therapy as resistance to other regimens becomes more widespread.

The treatment of chancroid in HIV-infected patients requires further study in view of the possible impact of chancroid on HIV-1 transmission. Evaluation of alternate treatment regimens is warranted.

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