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Clinical Evaluation of Rosoxacin for the Treatment of Chancroid

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One hundred seven men with *Haemophilus ducreyi*-positive chancroid were assigned to receive 300 mg of rosoxacin as a single dose or 150 mg twice daily for 3 days. Ulcers and buboes were followed clinically and bacteriologically for 1 month. Of 40 evaluable males on the 3-day regimen, 38 (95%) were cured, while only 14 of 23 (61%) males on the single-dose regimen were cured; this regimen was discontinued. There was one ulcer relapse at day 21 in both groups; the one relapse in the single-dose group had a persistent culture-positive bubo. Eight of nine (89%) buboes followed to the endpoint on the 3-day rosoxacin regimen were cured, versus three of six (50%) on the single-dose regimen. Adverse effects were mainly related to the central nervous system but were minor and did not require intervention. None of the treatment failures was due to organisms resistant to rosoxacin, and failure of the single-dose regimen presumably was related to duration of tissue levels rather than to drug resistance. Administration of 150 mg of rosoxacin twice daily for 3 days is an effective regimen for the therapy of chancroid and is a reasonable alternative to other short-course regimens.

Chancroid caused by *Haemophilus ducreyi* is the most common cause of genital ulcer diseases in Kenya (7). Several single-dose or short-course drug regimens have proven to be effective for the therapy of chancroid, but at present the combination of trimethoprim-sulfametrole is the first line of therapy in Kenya (6, 11–13). With the increasing resistance of *H. ducreyi* to sulfonamides and trimethoprim, however, alternative and effective drug regimens must be identified (1, 4). Rosoxacin, a new oral quinolone antimicrobial agent, has proven its efficacy as a single 300-mg oral dose for uncomplicated gonococcal infection (2, 3, 5, 14). It also exhibits excellent in vitro activity against *H. ducreyi* with a MIC for 90% of strains tested of ≤0.004 μg/ml. Rosoxacin has a half-life of 4 to 6 h and has been shown to achieve peak serum levels that are several hundred times the MIC for *H. ducreyi* with a single dose of 150 mg (9). In this study, we compared the safety and efficacy of two regimens of rosoxacin for the treatment of men with *H. ducreyi*-positive chancroid.

MATERIALS AND METHODS

One hundred seven men at the Nairobi Special Treatment Clinic were enrolled in the study between January and March 1984. Inclusion criteria included genital ulcers with clinical characteristics of chancroid, negative dark-field examination for *Treponema pallidum*, and positive cultures for *H. ducreyi*. Prior to enrollment in the study, informed verbal consent was obtained from all patients who expressed a willingness to comply with procedures and return for follow-up. Criteria for exclusion from the study and final evaluation included prior history of allergy to related drugs (nalidixic acid), antimicrobial therapy during the previous 14 days, or subsequent evidence of either syphilis (serological) or herpes genitalis (culture).

Therapeutic regimens. Patients were treated alternately in a randomized manner to receive either (i) 300 mg of rosoxacin in a single oral dose, or (ii) 150 mg of rosoxacin orally twice daily for 3 days.

After 74 patients were entered into the study, the single-dose regimen was discontinued because of the high failure rate in this treatment group. An additional 33 patients were then treated in a nonrandomized manner with the six-dose regimen.

Evaluation and follow-up. Initial evaluation included demographic and historical data, along with examination of the external genitalia. Ulcers were characterized by number, site, size, and clinical features. Buboes defined as tender inguinal adenopathy >1 cm in diameter, were examined for fluctuance, consistency, and size. Dark-field examination was performed on all ulcers, along with cultures for *H. ducreyi* and herpes simplex virus. Urethral discharge, if present, was examined by Gram stain and cultured for *H. ducreyi* and *Neisseria gonorrhoeae*. Fluctuant buboes were aspirated and cultured for *H. ducreyi*. Syphilis serology by the rapid plasma reagin and *Treponema pallidum* hemagglutination assay was also performed at the initial visit. Patients were requested to return for follow-up on days 3, 7, 10, 14, and 21. Follow-up evaluation included review of compliance and adverse effects of therapy, along with clinical response of ulcers and buboes. Cultures for *H. ducreyi* were repeated, and syphilis serology was repeated at day 10. Definition of healing for ulcers was full re-epithelialization; and for buboes healing was loss of tenderness, fluctuance, and reduction in size. Failure was nonhealing with or without a positive culture on day 7 of therapy.

Microbiology. *H. ducreyi* was cultured on two media that have been described previously: (i) gonococcal agar base (GIBCO Laboratories, Calgary, Alberta, Canada) with bovine hemoglobin and fetal calf serum; (ii) Mueller-Hinton agar base with lysed horse blood and fetal calf serum (4, 8).

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TABLE 1. Characteristics of men with chancroid treated with a 300-mg, single-dose regimen or a 150-mg, six-dose, 3-day regimen

Characteristic	Therapy	
	Single dose (n = 37)	Six doses (n = 70)
Mean age (yr ± SD)	26.1 ± 5.5	25.5 ± 4.8
Mean incubation period (days ± SD)	7.0 ± 7.0	5.9 ± 4.7
Mean ulcer duration (days ± SD)	11.7 ± 5.9	11.3 ± 6.9
Mean size of largest ulcer (mm ± SD)	11.3 ± 10.3	8.4 ± 8.3
No. with buboes	12 (32%)	18 (26%)
No. seen to endpoint	23 (62%)	40 (57%)

Both media also contained vancomycin and CVA enrichment (GIBCO). *N. gonorrhoeae* was cultured on modified Thayer-Martin medium. Herpes simplex virus was detected by its cytopathic effect on tissue culture with human amnion cells. Susceptibility testing (MICs) of the *H. ducreyi* isolates was performed by the agar dilution method as described previously (4).

Statistical analysis. Statistical analysis of proportions was performed by the chi-square test or the Fisher exact test and Student's t test. Healing of ulcers and buboes was analyzed separately.

RESULTS

One hundred seven men with *H. ducreyi*-positive ulcers were treated: 37 with the single-dose regimen and 70 with the 3-day regimen. No significant difference between groups was observed when patient characteristics were compared (Table 1). A total of 4 of 28 (14%) patients on single-dose rosoxacin and 1 of 60 (2%) on the 3-day regimen were culture positive for *H. ducreyi* on day 3 of therapy. Six patients receiving single-dose rosoxacin were culture positive on day 7 and all six were treatment failures. By day 3, four patients were cured with the 3-day regimen, whereas no cures had occurred at this visit with single-dose rosoxacin therapy (Table 2). Significantly more patients were cured with the 3-day rosoxacin therapy regimen compared with the single-dose therapy regimen ($P < 0.01$). Because of the unacceptably high failure rate with the single-dose therapy, this regimen was discontinued. In patients who were ultimately cured, there was no significant difference in the mean time to healing between groups ($P > 0.05$). One patient in each group had recurrent ulcers on day 21 without a history of further sexual contact. One of these had a bubo which failed to heal following single-dose rosoxacin therapy.

Thirty patients had buboes on entry. Of these, 15 were adequately followed to the endpoint (Table 2). Of the six buboes cultured on entry (aspiration or drainage), five were culture positive for *H. ducreyi* (two in the single-dose rosoxacin group and four in the 3-day rosoxacin group). All three bubo failures following single-dose rosoxacin therapy were culture positive at the endpoint. The one bubo failure following 3 days of rosoxacin therapy was classified as a clinical failure on day 21, but had almost resolved by day 32 without further therapy. In patients who were cured, there was no significant difference between groups in the length of time to bubo healing ($P > 0.5$) and no consistent temporal relationship between ulcer healing and bubo healing; i.e., some buboes healed before ulcers and vice versa. Generally, clinical failure correlated with bacteriologic failure for both buboes and ulcers.

Susceptibility testing of 59 *H. ducreyi* isolates from ulcers and buboes (including failures) to rosoxacin showed MICs from 0.001 to 0.004 μg/ml, with an MIC for 90% of strains tested of ≤0.004 μg/ml. The MIC of isolates was similar between groups, and there was no significant difference in the MICs of pretreatment and failure isolates.

More patients on the six-dose rosoxacin regimen reported adverse effects on day 3 of therapy (Table 3). Symptoms included dizziness (six patients), headache (one patient), generalized pruritis (three patients), nausea (one patient), diarrhea (one patient), and dysuria (one patient). There was no significant difference in the total number of adverse effects between both groups ($P > 0.1$). These adverse effects were mild, did not require medical intervention, and subsided rapidly after completion of therapy.

TABLE 2. Cumulative percent cure rates in response to therapy with a 300-mg, single-dose regimen or a 150-mg, six-dose, 3-day regimen of rosoxacin

Days of follow-up after treatment	% Cure rate for [a]:			
	Ulcer		Bubo	
	One dose (n = 23)	Six doses (n = 40)	One dose (n = 6)	Six doses (n = 9)
3	0	10	17%	11%
7	39	28	17	33
10	52	65	17	67
14	61	85	50	67
21	61	95[b]	50	89[c]

[a] The mean times to cure (in days ± standard deviation) were as follows for ulcers: one dose, 8.6 ± 2.6; six doses, 10.7 ± 4.8 ($P > 0.05$). For buboes the values were as follows: one dose, 10.3 ± 6.4; six doses, 11.1 ± 6.5 ($P > 0.5$).
[b] $P < 0.001$.
[c] $P > 0.1$.

DISCUSSION

The results of this study show that rosoxacin in a single, 300-mg oral dose is less effective than six doses of 150 mg over 3 days for the therapy of chancroid in males. The overall cure rate of 61% for the single-dose regimen, therefore, is unacceptably low, and this regimen cannot be recommended. However, the 3-day regimen, with a cure rate of 95%, was very effective and compares favorably with other successful short-course regimens used previously for treatment of chancroid (6, 11–13). There was more rapid eradication of *H. ducreyi* from ulcers with the 3-day regimen, with only one culture-positive patient on day 3. The persistence of *H. ducreyi* on days 3 and 7 in patients treated with the single-dose regimen correlated with treatment failure. Bubo healing was more rapid with the 3-day regimen of rosoxacin, and there was a higher cure rate than with the

TABLE 3. Adverse effects in response to therapy with one dose (300 mg) or six doses (150 mg) of rosoxacin

Symptoms	No. with reaction[a]	
	Single dose (n = 23)	Six doses (n = 40)
Central nervous system	2	5
Dermatologic		3
Gastrointestinal		2
Urinary	1	

[a] Of the patients in the single-dose-therapy regimen, 13% had reactions to the drug, and of the patients in the six-dose therapy regimen, 25% had reactions.

single-dose regimen. Bubo healing did not parallel ulcer healing in either group, and in fact the one bubo failure at day 21 on the 3-day regimen went on to healing without further therapy, making the actual cure rate 100% for buboes in this group. One patient in the 3-day rosoxacin group developed a bubo on day 3 of therapy but went on to heal completely. All bubo failures on single-dose rosoxacin therapy had persistence of *H. ducreyi*, and the one patient with ulcer relapse on single-dose rosoxacin therapy was in this group.

Rosoxacin has a half-life of 4 to 6 h and has been shown to achieve peak serum levels of 3.88 and 6.40 μg/ml after oral doses of 150 mg (1 h) and 250 mg (2 h), respectively (9). Rosoxacin is unusually effective in vitro against *H. ducreyi* and is currently the most active antibacterial agent investigated against *H. ducreyi*. Theoretically, levels in serum following an oral dose of 300 mg should remain above the MIC of *H. ducreyi* (≤0.004 μg/ml) for longer than 36 h. Is this sufficient to eradicate the organism? Why then should there be a distinct difference in the cure rate between the two treatment regimens? Treatment with 300 mg of rosoxacin as a single-dose regimen has proved to be effective for the therapy of uncomplicated gonococcal infection (2, 3, 5, 14). While trimethoprim-sulfametrole is highly effective as single-dose therapy for *H. ducreyi* infection (13), cefotaxime, which has a shorter half-life, has been less successful (11). Presumably, *H. ducreyi* infection requires more sustained inhibitory levels in tissue for eradication than are achieved by this single dose of rosoxacin, hence the better cure rate with the 3-day regimen. The occasional ulcer relapse in each group is predictable from past experience. In earlier studies, 2 to 6% of patients have had a recurrence after complete ulcer healing without history of re-exposure (10, 12). Reinfection cannot be totally excluded. *H. ducreyi* in buboes could be more difficult to eradicate, but this has not been proven. However, there were more bubo cures with the 3-day regimen (Table 2). None of the isolates from the treatment failures (ulcers and buboes) developed resistance to rosoxacin.

The most common adverse effects in both treatment groups were related to the central nervous system, but were less frequent than those reported previously (2, 3, 5, 14). Symptoms were mild and self-limiting and had no effect on normal activity. In one instance, the symptom recorded (dysuria) may not have been drug related.

Rosoxacin could be an alterate choice, for the therapy of chancroid, particularly in regions of the world in which trimethoprim-resistant *H. ducreyi* have emerged. It is prescribed orally, with few side effects. This trial demonstrates its effectiveness when prescribed as a 3-day, twice daily regimen. However, although not evident in this study, compliance is a potential problem, and other dosing schedules such as 600-mg single dose of rosoxacin should be evaluated. The drug is not yet marketed in most countries, but further clinical investigation is warranted in view of its efficacy against *N. gonorrhoeae* and *H. ducreyi*.

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