ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1987, p. 67–69
0066-4804/87/010067-03$02.00/0

Vol. 31, No. 1

Single-Dose Ceftriaxone for Chancroid

M. I. BOWMER,[1] H. NSANZE,[2] L. J. D'COSTA,[3] J. DYLEWSKI,[4] L. FRANSEN,[5] P. PIOT,[5] AND A. R. RONALD[4]*

Department of Medicine, Memorial University, St. John's, Newfoundland A1B 3B6,[1] and Department of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba R3E OW3,[4] Canada; Department of Medical Microbiology, University of Nairobi,[2] and City Council Special Treatment Clinic,[3] Nairobi, Kenya; and Department of Microbiology, National Institute, Antwerp, Belgium[5]

Received 18 December 1985/Accepted 2 October 1986

Men with genital ulcers that were culture positive for *Haemophilus ducreyi* were treated with intramuscular ceftriaxone and randomized to three different dose regimens. All but 1 of 50 men treated with 1 g of intramuscular ceftriaxone were cured. Similarly, 0.5 and 0.25 g cured 43 of 44 men and 37 of 38 men, respectively. A single dose of 250 mg of intramuscular ceftriaxone is an effective treatment for chancroid.

Increasing awareness of antimicrobial agent-resistant *Haemophilus ducreyi* strains has led us to search for alternate treatment regimens for chancroid (7). A 10-day course of erythromycin and a 1-week course of amoxicillin in combination with clavulanic acid are each satisfactory treatments, with cure rates of over 95% (2, 10). More recently, we have shown that a single dose of trimethoprim-sulfametrole (11) or of rifampin in combination with trimethoprim (12) can cure most patients with chancroid in Kenya. However, additional effective single-dose treatment regimens are necessary due to the recent emergence of trimethoprim-resistant *H. ducreyi* strains in Thailand (13).

Ceftriaxone is remarkably effective against *H. ducreyi* in vitro, with MICs of 0.015 mg/liter or less for all isolates tested. In the present study, we compared three different single-dose intramuscular ceftriaxone regimens for the treatment of men with genital ulcer disease due to *H. ducreyi*.

MATERIALS AND METHODS

Between April and December 1982, male patients presenting at the Nairobi Special Treatment Clinic with a clinical syndrome compatible with chancroid were enrolled in the study. Men were eligible if they were older than 18 years, had had no antimicrobial therapy in the preceding week, were willing to return for follow-up, and were negative for *Treponema pallidum* on dark-field examination. The external genitalia were examined, and the number, size, and clinical characteristics of the ulcers were noted. Buboes, defined as tender inguinal or femoral lymph nodes enlarged to more than 1 cm, were examined for fluctuance, consistency, and size. Ulcers were cultured for *H. ducreyi* and herpes simplex virus by techniques described in an earlier publication (11). All ulcers were cultured on two different media, which in combination have been shown to support the growth of *H. ducreyi* from samples of ulcers from over 80% of patients with clinical chancroid (8). Agar dilution ceftriaxone and other cephalosporin MICs for *H. ducreyi* were determined as described previously (4). One or more dark-field examinations were performed on samples of all ulcers. Serum was obtained for serologic tests for syphilis initially and at 10 and 28 days.

Patients who had positive cultures for *H. ducreyi* and no evidence of *T. pallidum* infection were assigned by a preconstructed random sequence to treatment with ceftriaxone in a dose of 1.0, 0.5, or 0.25 g. The ceftriaxone was administered intramuscularly after dilution in 1% xylocaine. The evaluator was unaware of the treatment regimen selected.

The men were requested to return for follow-up visits after 3, 7, 10, 14, and 28 days. At follow-up visits, they were asked about sexual contacts, symptoms, and adverse effects of therapy. Ulcers and buboes, if present, were reevaluated and cultured.

Clinical cure was defined as the point at which complete epithelialization of the ulcer occurred. Bacteriological cure was defined as eradication of *H. ducreyi* in all cultures obtained after treatment. Clinical failure was said to have occurred when the ulcer failed to improve by day 7 or progressed on any visit after day 7.

RESULTS

After giving verbal informed consent, 182 patients with clinical chancroid and ulcer cultures positive for *H. ducreyi* were entered into the study. Sixty-eight were treated with 1.0 g, 60 with 0.5 g, and 54 with 0.25 g of ceftriaxone. There were no significant differences in age, duration of disease, ulcer size, or ulcer number between groups.

The results of therapy are shown in Table 1. Fifty patients, or 28% of the men entered into the study, failed to return for adequate follow-up to ensure complete resolution. One patient treated with 1 g, two treated with 0.5 g, and three treated with 0.25 g of ceftriaxone were culture positive at the day 3 visit. However, only three of these six patients went on to become clinical failures, one in each group. The ulcers in the other three patients healed, and the ulcer cultures were negative when repeated at 1 week.

Two patients, each treated with the 1-g dose, had recurrence of the ulcer. One relapsed 2 weeks following complete healing. Another had recurrence following sexual reexposure, and the ulcer was presumably a reinfection. Overall, the initial cure rates in these three groups of men with chancroid were 98, 98, and 97% for the 1.0-, 0.5-, and 0.25-g ceftriaxone groups, respectively. The response of the ulcers to the three treatment regimens was identical. In each group, over 90% of the ulcers had resolved completely by day 14. The median duration to complete healing varied from 8 to 10 days, and the rate of healing was primarily dependent on the original ulcer size.

One-third of the patients in each group had buboes. These responded equally well to each of the treatment regimens

* Corresponding author.

TABLE 1. Ulcer response to three ceftriaxone regimens

Parameter	No. (%) of patients at intramuscular ceftriaxone dose (g):		
	1.0	0.5	0.25
No. entering study (positive *H. ducreyi* culture)	68	60	54
Positive culture at first follow-up visit (72 h)	1	2	3
Clinical failure (7 days)	1	1	1
No. cured/no. seen (% cured) at:			
3 days	13/61 (21)	5/58 (9)	5/51 (10)
7 days	34/55 (62)	21/53 (40)	23/41 (56)
10–14 days	49/50 (98)	39/44 (89)	34/38 (89)
15–21 days	48/50 (96)	42/44 (95)	36/38 (95)
Recurrence of ulcers during follow-up	2	0	0
Delayed healing (28 days)	0	2	2

without requiring surgical drainage or further antimicrobial agent treatment.

The intramuscular injections were well tolerated. No allergic reactions and no sterile abscesses were identified during follow-up.

The susceptibility of *H. ducreyi* to ceftriaxone and five other cephalosporins is shown in Table 2. All isolates produced β-lactamase, and all were susceptible to 0.003 mg or less of ceftriaxone per liter. Ceftriaxone is the most active of all the cephalosporins investigated to date against *H. ducreyi*.

DISCUSSION

The pharmacokinetics of ceftriaxone, combined with its remarkable in vitro efficacy, have made it an excellent drug for the single-dose treatment of gonococcal urethritis and gonococcal ophthalmia neonatorum (3, 5). A dose of 125 mg intramuscularly has been effective in gonococcal infections, effectively eradicating infection from all sites (5). The present study shows that ceftriaxone in a dose as low as 250 mg cures over 97% of patients with genital ulcer disease caused by *H. ducreyi*. Due to the efficacy of each of the three regimens, we failed to demonstrate any relationship between dose and response. Taylor et al. have reported an equally high cure rate in patients with chancroid in Thailand treated with 250 mg of ceftriaxone (14). Earlier studies showed that the eradication of *H. ducreyi* and cure of chancroid required drug levels in blood above the MIC for *H. ducreyi* for between 36 and 48 h (1). An intramuscular dose of 250 mg of ceftriaxone provides antibacterial agent levels above the MIC for *H. ducreyi* for about 72 h (9).

TABLE 2. Susceptibility of *H. ducreyi* to six cephalosporins

Drug	MIC (μg/ml)[a]		
	50%	90%	Range
Ceftriaxone	0.002	0.002	0.001–0.004
Cefoperazone	0.063	0.25	0.016–0.5
Ceftazidime	0.063	0.125	0.016–0.125
Cefamandole	0.5	2.0	0.031–4.0
Cefoxitin	2.0	4.0	1.0–4.0
Cefaclor	16.0	32.0	4.0–32.0

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.

The persistence of *H. ducreyi* in ulcer cultures taken at 72 h for 3 of 145 patients who subsequently went on to resolution without additional treatment is unexplained. We have not observed this in earlier studies.

Will *H. ducreyi* acquire resistance to ceftriaxone? The use of subtherapeutic doses to treat sexually transmitted infections may permit the stepwise emergence of resistance or appearance of plasmids mediating a unique β-lactamase. Continuing surveillance is required.

T. pallidum infection frequently occurs concomitantly with *H. ducreyi*. Ceftriaxone has been shown to be bactericidal for *T. pallidum* (6), and the single-dose regimen prescribed for gonococcal infection may be effective for incubating syphilis infections. However, more prolonged treatment regimens are required to cure patients with *T. pallidum* infection (E. W. Hook III, R. E. Roddy, and H. H. Handsfield, Meet. 6th Int. Soc. Sex. Transm. Dis. Res., poster no. 172). All patients with genital ulcers should have one or preferably two dark-field examinations and serologic tests to exclude syphilis prior to the use of a therapeutic agent such as ceftriaxone, which may make the dark-field examination negative without eradicating *T. pallidum* from other sites.

Ceftriaxone has been demonstrated to be a remarkably effective agent for the single-dose treatment of sexually transmitted diseases due to *Neisseria gonorrhoeae* and *H. ducreyi*. Further studies are needed to determine its efficacy in patients with incubating or infectious syphilis.

ACKNOWLEDGMENTS

This study was supported by grants from Hoffmann-La Roche, Basel, Switzerland, and from the Medical Research Council of Canada (MA7495).

LITERATURE CITED

1. **Dylewski, J., H. Nsanze, L. D'Costa, L. Slaney, and A. R. Ronald.** 1985. Trimethoprim-sulfamethoxazole in the treatment of chancroid: comparison of two single-dose treatment regimens with a five-day regimen. J. Antimicrob. Chemother. **16**:103–110.
2. **Fast, M. V., H. Nsanze, L. J. D'Costa, F. A. Plummer, P. Karasira, I. W. Maclean, and A. R. Ronald.** 1982. Treatment of chancroid by clavulanic acid with amoxicillin in patients with beta-lactamase-positive *Haemophilus ducreyi* infection. Lancet **ii**:509–511.
3. **Haase, D. A., R. A. Nash, H. Nsanze, L. J. D'Costa, L. Fransen, P. Piot, and R. C. Brunham.** 1986. Single-dose ceftriaxone therapy of gonococcal ophthalmia neonatorum. Sex. Transm. Dis. **13**:53–55.
4. **Hammond, G. W., C. J. Lian, J. C. Wilt, and A. R. Ronald.** 1978. Antimicrobial susceptibility of *Haemophilus ducreyi*. Antimicrob. Agents Chemother. **13**:608–612.
5. **Handsfield, H. H., V. L. Murphy, and K. K. Holmes.** 1981. Dose-ranging study of ceftriaxone for uncomplicated gonorrhea in humans. Antimicrob. Agents Chemother. **20**:839–840.
6. **Johnson, R. C., R. F. Bay, and S. J. Wolgamot.** 1982. Comparison of the activities of ceftriaxone and penicillin G against experimentally induced syphilis in rabbits. Antimicrob. Agents Chemother. **21**:984–989.
7. **McNicol, P. J., and A. R. Ronald.** 1984. Plasmids of *Haemophilus ducreyi*. J. Antimicrob. Chemother. **14**:561–573.
8. **Nsanze, H., F. A. Plummer, A. B. N. Magwa, G. Maitha. J. Dylewski, and A. R. Ronald.** 1984. Comparison of media for the primary isolation of *Haemophilus ducreyi*. Sex. Transm. Dis. **11**:6–9.
9. **Patel, I. H., R. E. Weinfled, J. Konikoff, and M. Parsonnet.** 1982. Pharmacokinetics and tolerance of ceftriaxone in humans after single-dose intramuscular administration in water and procaine dilutions. Antimicrob. Agents Chemother. **21**:957–962.
10. **Plummer, F. A., L. J. D'Costa, H. Nsanze, P. Karasira, I. W.**

Maclean, P. Piot, and A. R. Ronald. 1983. Antimicrobial therapy of chancroid: effectiveness of erythromycin. J. Infect. Dis. **148**:726–731.

11. **Plummer, F. A., H. Nsanze, L. J. D'Costa, P. Karasira, I. W. Maclean, R. H. Ellison, and A. R. Ronald.** 1983. Single dose therapy of chancroid with trimethoprim-sulfametrole. N. Engl. J. Med. **309**:67–71.
12. **Plummer, F. A., H. Nsanze, L. J. D'Costa, A. B. N. Magwa, Y. Girouard, P. Karasira, W. Albritton, and A. R. Ronald.** 1983. Short course and single dose antimicrobial therapy of chancroid in Kenya: reports of studies with rifampin-trimethoprim and trimethoprim alone. Rev. Infect. Dis. **5**(Suppl. 3):565–572.
13. **Taylor, D. N., P. Echeverria, S. Hanchalay, C. Pitarangsi, L. Slootmans, and P. Piot.** 1985. Antimicrobial susceptibility and characterization of outer membrane proteins of *Haemophilus ducreyi* isolated in Thailand. J. Clin. Microbiol. **21**:442–444.
14. **Taylor, D. N., C. Pitarangsi, P. Echeverria, K. Panikabutra, and C. Suvongse.** 1985. Comparative study of ceftriaxone and trimethoprim-sulfamethoxazole for the treatment of chancroid in Thailand. J. Infect. Dis. **152**:1002–1006.