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Efficacy of Ciprofloxacin for Treatment of *Brucella melitensis* Infections

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The effectiveness of treatment of human brucellosis caused by *Brucella melitensis* with ciprofloxacin alone was investigated in a prospective nonrandomized study. Subjects with central nervous system involvement, endocarditis, or severe renal dysfunction; children under 16 years of age; and pregnant women were excluded from the study. Of 19 patients, 16 completed the study; 7 were diagnosed as having acute systemic brucellosis, and 9 had acute brucella arthritis-diskitis. A rapid response to ciprofloxacin was seen in all 16 patients, but the blood cultures of 1 patient remained positive and the treatment was changed. During a 104-week follow-up period, 4 of the 15 responding patients relapsed or were reinfected within 8 to 32 weeks after completion of therapy. We conclude that treatment with ciprofloxacin alone, although effective for the acute symptoms, is associated with an appreciable rate of relapse; therefore, it should be given with other agents for treatment of brucellosis.

Brucellosis is a common illness in developing countries. The disease remains hyperendemic in Kuwait, Saudi Arabia, and the Mediterranean region. This is due to the prevalence of infected domestic animals in these regions: camels, goats, and sheep. The most effective, least toxic chemotherapy for human brucellosis is still undecided. *Brucella melitensis* is susceptible to a wide variety of antibiotics. In Saudi Arabia, the MICs and MBCs of streptomycin, gentamicin, and netilmicin are similar but there is an appreciable gap between the MICs and the MBCs of rifampin, tetracycline, and trimethoprim-sulfamethoxazole.

Brucella species are facultative intracellular parasites; therefore, it is important to treat patients with antimicrobial agents which penetrate macrophages and are bactericidal. Ciprofloxacin is a broad-spectrum synthetic fluoroquinolone which inhibits the growth of gram-positive and gram-negative bacteria. High oral bioavailability, high concentration in tissue, and rapid bacterial killing make it attractive for the treatment of intracellular infections (4, 10, 13). In vitro studies have shown that all clinical isolates of *B. melitensis* tested prior to therapy were susceptible to ciprofloxacin (3, 6, 14).

This prospective nonrandomized study was designed to evaluate the efficacy of orally administered ciprofloxacin alone in the treatment of brucellar infections.

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MATERIALS AND METHODS

From 1988 to 1989, a prospective nonrandomized study of patients diagnosed as having brucellosis at the ambulatory care service facility of King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia, was done. The Pharmacy and Therapeutics Committee and the Research Committee approved the study prior to its inception.

Patients with central nervous system involvement or endocarditis were excluded from the study. Individuals who had received antimicrobial therapy after recognition of the initial symptoms, pregnant women, those under 16 years of age, those allergic to nalidixic acid or its derivatives, and those with severe renal dysfunction were also excluded.

The diagnostic criteria used were isolation of *Brucella* species from blood or other tissues or fluids or positive serology, i.e., total agglutinating antibodies (agglutination titer, 1:640) in the presence of compatible clinical findings. Patients initially seen with acute onset of fever, chills, sweating, and malaise with positive brucella serology or positive brucella culture were defined as having acute systemic brucellosis. Patients with positive synovial fluid cultures for *Brucella* species were defined as having acute brucella arthritis, and patients initially seen with pain over the involved vertebral bodies and positive bone scans were defined as having acute brucellosis with diskitis-spondylitis.

Reappearance of symptoms after the end of therapy was considered a relapse or reinfection, because as it is difficult to differentiate between these two in endemic areas.

Upon admission to the study, patients underwent clinical examinations and laboratory tests for complete blood count, erythrocyte sedimentation rate, hepatic and renal profiles, brucella titer, and blood culture. Radiological studies were performed in accordance with the symptoms of the patients.

B. melitensis was isolated from blood and synovial fluid by using BACTEC NR 6A bottles in conjunction with BACTEC 660 (Becton-Dickinson, Towson, Md.). All of the isolates were identified as recommended by Hausler et al. (9). MICs were determined by broth dilution (8) using Mueller-Hinton broth and an inoculum of 10^5 to 10^6 CFU/ml.

Brucella serology was performed by a microtiter agglutination test with Wellcome reagents (Darford, England). Total titers and titers following treatment with 2-mercaptoethanol were determined on a routine basis. Although titers of 1:160 to 1:320, in the absence of a fourfold rise, are considered diagnostic in the United States and Europe, we

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TABLE 1. Patient characteristics of clinical features

Patient no. (age [yr] sex)[a]	Before therapy					Duration of:		Relapse
	Fever	Arthralgia-arthritis	Blood culture	Synovial fluid culture	Brucella agglutination titer	Treatment (wk)	Follow-up	
1 (54/M)	+	+	−	N/A[b]	2,560	6	8 mo	+
2 (60/M)	+	+	−	+	1,280	6	24 mo	−
3 (60/M)	+	+	−	N/A	2,560	6	24 mo	−
4 (55/M)	+	−	+	N/A	2,560	6	24 mo	−
5 (35/F)	+	−	+	N/A	1,280	6	24 mo	−
6 (65/M)	+	+	−	N/A	5,120	6	24 mo	−
7 (44/F)	+	−	−	N/A	1,280	6	24 mo	−
8 (48/F)	+	+	−	N/A	1,280	6	24 mo	−
9 (70/M)	+	+	+	+	20,480	6	2 mo	+
10 (30/F)	+	−	−	N/A	1,280	6	24 mo	−
11 (63/M)	+	+	+	N/A	640	6	3 wk	Resistance
12 (55/M)	+	+	+	+	640	6	3 mo	+
13 (55/M)	+	+	−	+	5,120	8	24 mo	−
14 (19/M)	+	+	−	N/A	10,240	6	24 mo	−
15 (50/M)	+	+	−	N/A	5,120	12	24 mo	−
16 (69/M)	+	+	+	N/A	1,280	8	3 mo	+

[a] M, male; F, female.
[b] N/A, not applicable.

used ≥1:640 as the cutoff, as recommended by Kiel and Khan (11) and Smith and Qadri (15) for serodiagnosis of brucellosis in endemic areas.

The patients were then administered a course of ciprofloxacin orally. Twelve patients were given 750 mg three times daily for 6 weeks, two were given 750 mg three times daily for 8 weeks, one received 500 mg three times daily for 6 weeks, and one was given 500 mg twice daily for 12 weeks. The dosages and durations were adjusted on the basis of body weight, liver enzymes, and articular involvement, mainly arthritis and diskitis. When liver enzyme levels were elevated, the dose of ciprofloxacin was reduced; in cases of articular involvement, the duration of treatment was prolonged. Patient compliance during therapy was determined by counting the tablets at each visit and measuring the drug level by high-pressure liquid chromatography (5). During the course of therapy, patients were evaluated at weeks 1, 3, and 6 and at the end of the course. After completion of therapy, patients were reassessed at months 1, 3, and 6 and every third month thereafter, as well as whenever clinical symptoms reappeared. During each visit, the same clinical, analytical, and serological assessments performed upon admission to the study were done.

A STAT GRAPHICS V 3.0 statistics package was used for statistical analysis.

RESULTS

Nineteen patients met the eligibility requirements for this study. Three patients were excluded during the treatment period because of noncompliance. Of the remaining 16, 12 were men and 4 were women and they ranged in age from 19 to 70 years (mean ± standard deviation, 52 ± 14.1). Eight patients (50%) had at least one culture positive for *B. melitensis*; four had positive blood cultures, two had positive synovial fluid cultures, and two had positive cultures from both blood and synovial fluid. All 16 patients had significant serologic results for *B. melitensis* (Table 1).

A clinical response was seen in all patients within 5 days of treatment. Temperature was normal by day 7 in all 16 patients, and back pain and knee effusion disappeared in 1 to 3 weeks. Despite clinical improvement, blood cultures of 1 patient remained positive after 3 weeks of treatment, which was changed to tetracycline plus rifampin. At the end of treatment, all 15 remaining patients were free of symptoms (Table 2), as was the patient later given conventional therapy, whose symptoms cleared up within 6 weeks of the change in treatment.

During therapy, ciprofloxacin was well tolerated and all 16 patients complied with the course of therapy. Two patients complained of mild gastrointestinal disturbance, one developed a maculopapular rash, and a fourth had transient elevation of transaminases. However, all of these adverse reactions were self-limiting and did not necessitate interruption or cessation of therapy.

In the study, 4 (25%) of the 16 patients had recurrence of symptoms consistent with relapse or reinfection within 8 to 32 weeks and 1 failed to respond to initial therapy. Of the 4

TABLE 2. Summary of results

Parameter	Result
No. of patients in study	16
Male-female ratio	12:4
Mean age (yr)	52
No. with acute brucellosis	7
No. with acute arthritis	4
No. with acute diskitis	5
No. with positive blood cultures	4
No. with positive synovial fluid cultures	2
No. with positive blood and synovial fluid cultures	2
At end of therapy:	
No. of patients	16
No. cured (%)	15 (94)
No. with no response (%)	1 (6)
At follow-up (mean, 104 wk):	
No. of patients	15
No. free of disease (%)	11 (73)
No. with relapse or reinfection (%)	4 (27)

patients who relapsed, 2 had systemic brucellosis with positive blood cultures and 2 manifested arthritis-diskitis. Of the 15 patients who responded to therapy, 11 (73%) completed 104 weeks (2 years) of follow-up with no evidence of relapse or reinfection. The ages of the 5 patients who relapsed ranged between 54 and 70 years (mean ± standard deviation, 63 ± 7.5), which is not significantly different from those of the 11 relapse-free patients. Moreover, it was noted that three who relapsed and one who failed to respond were initially bacteremic. There was a significantly higher relapse and no-response rate in the bacteremic group (4 of 6 patients) than in the nonbacteremic group, in which only 1 of 10 relapsed (Fisher's exact test, $P = 0.035$). Further analysis showed that in the relapse and no-response group, 4 of 5 patients had arthritis and positive blood cultures compared with none of the 11 in the no-relapse group (Fisher's exact test, $P = 0.0027$).

DISCUSSION

The standard therapy for brucellosis is a combination of tetracycline and streptomycin, which is almost universally effective but fails to prevent relapse in 10 to 41% of cases (1, 7). The 41% relapse rate occurred in a study of only 27 patients and may not be representative of failure. Our study had a similarly small number of patients, with a relapse rate of 27%. A number of trials of therapies have failed to show a lower relapse rate. The relapse rates with different regimens have been reported as between 5 and 39% (7). Standard regimens of tetracycline or doxycycline plus streptomycin usually yield relapse rates of 10% or less; moreover, such relapse rates are usually seen with treatment regimens less than 6 weeks long. Relapse is not due to emergence of resistance but to intracellular persistence of *Brucella* species. Our patients had brucellosis with or without arthritis-diskitis infections and were treated with ciprofloxacin for 6 to 12 weeks. The relapse rate was 0% in our patients without arthritis-diskitis (Table 1), and these seven cases (no. 3, 6, 7, 8, 10, 14, and 15) were distinguished from the others by not having joint swelling or positive bone scans.

All patients became afebrile and asymptomatic during week 1 of treatment, including the patient whose therapy was considered a failure because of persistence of positive blood cultures for 3 weeks, accompanied by a rising MIC of ciprofloxacin (2). Ciprofloxacin was safe and well tolerated by most patients, and therapy was not discontinued because of any undesirable side effects. Four (27%) of our patients relapsed or failed to respond within 32 weeks of completion of therapy. None of the other patients showed any evidence of relapse or reinfection for 104 weeks (24 months after conclusion of treatment). Three of the patients who relapsed had positive blood cultures, and two of these also had positive synovial fluid cultures. The two patients who had positive cultures from synovial fluid only were cured with no recurrence of symptoms. This may indicate that the presence of a positive blood culture is an indication of severe infection and a higher incidence of relapse. The incidence of relapse in nonbacteremic patients was different from that of those studied by Lang et al. (12), and there was no significant difference between the relapse rates of the bacteremic patients in their study and those in ours.

On the basis of these results, we conclude that ciprofloxacin is well tolerated and easy to comply with. Our data have shown that ciprofloxacin gives a rapid response in human brucellosis when used alone. Because of high relapse rates in cases with arthritis-diskitis, therapy using a single drug does not seem feasible, and this appears to be true for ciprofloxacin as well. However, ciprofloxacin is a promising alternative to established drugs for inclusion in different combinations. In our study, which was small, ciprofloxacin was effectively used alone in systemic brucellosis without arthritis-diskitis. However, we acknowledge that further clinical studies of ciprofloxacin are needed to establish its efficacy in combination with other agents.

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