Comparative Trial of Rifampin-Doxycline versus Tetracycline-Streptomycin in the Therapy of Human Brucellosis

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In an attempt to compare the efficacy of rifampin-doxycline with tetracycline-streptomycin for the treatment of human brucellosis, we administered both combinations for a 30-day period, similar to the period recommended by the World Health Organization in a prospective, randomized trial. Forty-six patients were included in the final study (36 men and 10 women); 41 had blood cultures positive for Brucella melitensis. The 28 patients in group A received tetracycline hydrochloride at doses of 0.5 g every 6 h or doxycycline at 100 mg every 12 h for 30 days plus 1 g of streptomycin a day for 21 days. The 18 patients in group B received rifampin at 15 mg/kg per day in a single morning dose plus 100 mg of doxycycline every 12 h for 30 days. For patients with focal disease from both groups, therapy was prolonged to 45 days. All patients underwent rigorous clinical and bacteriological long-term follow-up. There were no therapeutic failures in either group, and the defervescence period was similar for both groups (3.1 days for group A, 2.6 days for group B). Two patients (7.1%) from group A had relapses, as did seven (38.8%) from group B ($P = 0.024$), and blood cultures again became positive for $B$. melitensis in all of them. In both groups treatment was generally well tolerated. The results strongly suggest that the rifampin-doxycline combination is a less efficacious mode of therapy for brucellosis to prevent relapses than is the classical tetracycline-streptomycin combination when both are administered for 30 days. A more prolonged period of administration of the rifampin-doxycline combination may be required to obtain the same low relapse rate as that achieved with the classical tetracycline-streptomycin treatment.

The combination tetracycline-streptomycin has been proposed by the World Health Organization (WHO) as the treatment of choice for human brucellosis (11). However, this mode of antibiotic therapy, giving tetracycline chloride for 3 weeks and streptomycin for 2 weeks, has not achieved the complete eradication of the disease in some patients, who presented with a relapse in the months immediately after treatment, in particular those in whom the disease was caused by $B$. melitensis (25).

During the last decade, there have been several trials with other antibiotics for the treatment of brucellosis in an attempt to avoid the relapses and the inconvenience of intramuscular streptomycin administration and the toxicity of the classical treatment. Recently, the oral administration of rifampin-doxycline has been suggested as a promising alternative therapy for human brucellosis (6), but there is as yet little clinical experience with this combination, and the optimal duration of treatment remains still undetermined.

In an attempt to compare the efficacy of rifampin-doxycline versus tetracycline-streptomycin, we have undertaken a prospective, randomized trial in which both combinations were administered during a 30-day period, similar to the duration of therapy advised by the WHO.

MATERIALS AND METHODS

Patients. Between October 1981 and December 1982, 56 consecutive patients with brucellosis were admitted to our hospital and included in a prospective, randomized, comparative therapeutic protocol. Another patient with brucellar endocarditis was excluded. There were 45 men and 11 women with ages ranging from 12 to 61 years (mean ± standard deviation [SD], 33 ± 14 years). Eleven of the patients were goat or sheep herders; 39 acquired the disease through accidental contact with animals or by ingestion of milk products without proper sanitary control; one microbiological laboratory worker was infected at his place of work; and in the other five, no epidemiological contact could be traced.

Diagnosis. In 48 cases, the brucellosis was diagnosed through recovery of $B$. melitensis from the blood; in the other 8 patients, clinical findings were characteristic of the disease and Wrights agglutination titers were $>1:160$. Besides Wrights agglutination, Rose Bengal and Coombs antiglobulin tests were also done. Blood cultures were performed with the standard method of adding 5 ml of blood to a Castañeda medium and incubating for at least 6 weeks (24). $B$. melitensis were identified by the prevailing taxonomic criteria (12). Serological tests were done with a commercial antigen (Kniekerbockers) and antigen supplied by the Ministry of Agriculture, Fisheries and Food Central Veterinary Laboratory, Weybridge, Surrey, United Kingdom. Standard methods were used for all tests (2, 9, 18).

Definitions. Focal disease was defined as the presence of signs and symptoms, other than endocarditis or neurobrucellosis, of localization of the infection which persisted for more than 7 days. The defervescence period was defined as the number of days elapsed from the start of therapy until the patient became afebrile (temperature, $<37^\circ C$).

The persistence of symptoms or signs of the disease or both by the end of therapy was considered therapeutic failure. Relapse was defined as the reappearance of signs or symptoms of the disease or new positive blood cultures after therapy.

Treatment groups. Group A. Group A included 32 patients with odd-numbered ages who were given either tetracycline hydrochloride at an oral dose of 0.5 g four times a day for 30
days (16 patients) or doxycycline at an oral dose of 100 mg twice a day for 30 days (16 patients) plus 1 g of intramuscular streptomycin for 21 days. Patients were given either tetracycline hydrochloride or doxycycline because they also were included in a long-term, large-number comparative study to test the assumption that both drugs are equally effective for the treatment of brucellosis.

Group B. The 24 patients with even-numbered ages in group B were treated with oral rifampin at 15 mg/kg per day taken in a single morning dose plus 100 mg of oral doxycycline twice a day for 30 days.

For patients with focal disease from either group, oral treatment with tetracycline hydrochloride or doxycycline and rifampin was prolonged for 45 days, and streptomycin was maintained for 21 days. The study was initially designed to include a large number of patients, but the high percentage of relapses in group B prompted us to abandon it for ethical reasons; thus, a matching number of patients in both groups was not achieved.

Follow-up. At least four blood samples for culture were taken from each patient before therapy was started, and all patients were carefully evaluated during treatment. Samples for blood culture were also taken on days 7 and 15 of treatment.

After being discharged from the hospital, patients were asked to return on an outpatient basis. Routine blood cultures and serological and clinical evaluations were done monthly during the first 3 months posttherapy and every 3 months thereafter over a 1- or 2-year period.

Statistical analysis. The chi-square test with Yates correction and the exact Fischer test were used for statistical analysis.

RESULTS

Patients. Four patients from group A and six from group B were excluded because they did not take the prescribed drugs correctly (five patients) or had a follow-up of less than 6 months (five patients). The final number of patients in group A was 28 (15 received tetracycline hydrochloride, and 13 received doxycycline), and the final number in group B was 18. There were 22 men and 6 women with ages ranging from 13 to 61 years (mean ± SD, 33 ± 14 years) in group A and 14 men and 4 women aged from 12 to 54 years (34 ± 14 years) in group B. Twenty-four patients from group A and 17 from group B had blood cultures positive for Brucella melitensis before therapy. Six patients from group A had focal disease, including sacroiliitis (three patients), spondylitis (one patient), liver abscess (one patient), and orchitis (one patient), as did four patients from group B who had sacroiliitis (one patient), spondylitis (one patient), prostatitis (one patient), and orchitis (one patient). The duration of symptoms before therapy ranged from 6 to 180 days (mean ± SD, 38 ± 47 days) in group A and from 7 to 60 days (26 ± 24 days) in group B. The follow-up period for group A was from 6 to 23 months (mean ± SD, 16 ± 5 months) and from 6 to 24 months for group B (16 ± 6 months).

Response to therapy. Both groups showed a favorable clinical response during therapy. The defervescence period was from 1 to 6 days for group A (mean ± SD, 3.1 ± 1.2 days) and from 1 to 4 days for group B (2.6 ± 1.1 days). There were no therapeutic failures. During treatment, positive blood cultures persisted in two patients from group A at days 7 and 15, respectively, although both had become asymptomatic. Nevertheless, both patients recovered without relapse, and blood cultures became negative shortly afterwards. All blood cultures for group B were negative during treatment.

Two patients from group A (7.1%) had relapses at 6 and 7 months posttherapy, respectively, whereas seven patients from group B (38.8%) (P = 0.024) had relapses at 1 month (1 patient), 2 months (5 patients), and 3 months (1 patient) posttherapy. None of the patients with focal disease who had been treated for 45 days (6 patients in group A; 4 patients in group B) relapsed. If these patients are excluded from the final analysis, the difference of relapse rate remains significant: 2 of 22 patients in group A (9%) and 7 of 14 in group B (50%) (P = 0.018). Blood cultures for all nine patients became positive again for B. melitensis. Patients who relapsed were treated with doxycycline for 30 days plus streptomycin for 15 days. Later course for these patients was satisfactory except for one cirrhotic patient, who died 7 months later with Escherichia coli septicaemia.

In both groups, the treatment was usually well tolerated. Two patients from group A treated with tetracycline hydrochloride complained of epigastric pain and vomiting and were switched to doxycycline. One patient receiving doxycycline had mild gastric complaints, another had candidal vaginitis, and a third had skin rash; however, in no case were the effects severe enough to warrant suspension of the therapy. Two patients taking streptomycin had mild and reversible eight cranial nerve impairment. In group B, therapy was well tolerated, and only one patient had mild gastric complaints.

Analysis of relapses. All patients who relapsed had symptoms or signs or both suggesting brucellosis during the relapse. It must, however, be emphasized that in three patients the clinical findings appeared 2 or 3 weeks after blood cultures became positive again. Two patients had only mild clinical symptoms during relapse despite new positive blood cultures. In only one patient were there severe clinical symptoms during relapse; arthritis and pericarditis, which had not been present on initial manifestation of the infection, became evident in this patient (Table 1). There were no differences between who relapsed and those who did not with respect to age, sex, or duration of the disease before therapy.

The study of the antibiotic susceptibility performed in six of the nine cases (one in group A and five in group B) showed the same susceptibility in initial isolates and strains isolated after relapse (data not shown).

DISCUSSION

In vitro studies have shown that the majority of Brucella spp. strains are very susceptible to rifampin (7, 10). In addition, the excellent penetration into the cells (16; F. Regnier, Thèse de Médecine, Université de Montpellier, Montpellier, France, 1978) and the satisfactory results obtained in trials with experimentally induced brucella in mice (21) suggest that rifampin might be useful in the therapy of brucella infections in humans. Based on preliminary study results, some authors claim that rifampin alone may be an effective mode of therapy for human brucellosis (1, 13–15, 19, 20, 26). However, in the majority of those studies, rifampin was administered over long periods, very heterogeneously, and with only short-term follow-up for relapses. In contrast, other authors (6, 23) state that brucellosis should not be treated with rifampin alone because of the high number of relapses. Because of this and because of the possibility that brucella strains may become resistant to rifampin during treatment as occurs in other infections, an association with other antibiotics has been suggested (6).
The combination of rifampin and trimethoprim tested in the therapy of brucellosis induced in mice (22) gave poor results, as it did in human brucellosis (J. Ariza, F. Gudiol, P. Fernandez Viladrich, J. Garau, G. Ruf, and J. Líñares, 3rd Mediterr. Congr. Chemother. abstract no. 54, 442, 1982).

Over recent years, the combination of rifampin-doxycycline has been suggested as an effective mode of therapy for brucellosis (5). Some in vitro studies have shown a synergistic activity of this antibiotic association against the majority of B. melitensis strains (6). However, reports regarding the treatment of brucellosis in humans with this combination have been limited to only a few studies (5, 6; F. Martínez-Luengas, M. Montejo, J. J. Alonso, G. M. Inclán, J. Barrón, I. Alberola, and C. Aguirre, Proc. 12th Int. Congr. Chemother., p. 935–936, 1982; L. Buzón, S. Martin, M. Marín, O. Soto, D. Reverte, and E. Bouza, 12th Int. Congr. Chemother. abstr. no. 126, p. 1237, 1981).

Two recent studies comparing rifampin-doxycycline and tetracycline-streptomycin combinations showed relapse rates of less than 6% for both associations (A. Bertrand, 4th Mediterr. Congr. Chemother., Rhodes, Greece, abstr. no. 274, 1984; J. Kosmidis, 4th Mediterr. Congr. Chemother., Rhodes, Greece, abstr. no. 275, 1984). However, the antibiotic combinations were administered for 45 days rather than the shorter periods classically recommended. The rate of relapse reported for B. melitensis brucellosis treated with the WHO-recommended schedule of tetracycline for 3 weeks and streptomycin for 2 weeks is approximately 15% (8, 17). Because of the possibility that tetracycline administered over longer periods might result in a lower relapse rate (3, 4), we decided on a 30-day antibiotic regime for patients without focal disease and a 45-day regime for patients with focal disease.

The initial response to therapy, the return to negative blood cultures, and the absence of therapeutic failures were similar in both groups.

Although we do not have a satisfactory explanation for the persistence of bacteremia at days 7 and 15 of therapy in two patients from group A, it did not appear to be of major importance with respect to final outcome, because neither patient relapsed, both became symptom free, and blood cultures became negative and have remained so until the present. These patients were therefore classified as cured.

Although the initial response to therapy was satisfactory, the high rate of relapse for group B (38.8%) after 30 days of rifampin-doxycycline therapy was in sharp contrast with that for group A (7.1%), which had been treated with the tetracycline-streptomycin combination for 30 days \((P = 0.024)\). This strongly suggests that a period of 30 days or less of treatment with rifampin-doxycycline is not adequate for the therapy of brucellosis in humans because of the unacceptably high percentage of relapses.

Nevertheless, the fact that none of the patients with focal disease from group B who received the rifampin-doxycycline combination over a 45-day period relapsed as well as the results reported for preliminary studies (A. Bertrand, 4th Mediterr. Congr. Chemother., Rhodes, Greece, abstr. no. 274, 1984; J. Kosmidis, 4th Mediterr. Congr. Chemother., Rhodes, abstr. no. 275, 1984) would suggest that the combination may be an effective mode of therapy when given over prolonged periods.

The evaluation of the efficacy of antibiotic modalities in the therapy of brucellosis is complicated by the characteristics of the disease which may at times make it difficult to correctly assess clinical findings and determine the true rate of relapses.

Our findings of few symptoms in patients who presented with relapse, relapse manifesting at 6 and 7 months posttherapy in two of our patients, and blood cultures becoming positive before the appearance of clinical symptoms of relapse in three cases all emphasize the need for rigorous and prolonged follow-up for relapses.

The difference between a true relapse and reinfection must also be taken into account. The majority of our patients who presented with relapse had symptoms within the first 2 months posttherapy; of the nine, only one worked under conditions favoring occupational disease, and it would therefore appear that the majority were true relapses rather than reinfections.

Both antibiotic regimes used in our study were usually well tolerated; only a few patients in group A had symptoms of mild intolerance or toxicity with tetracycline-streptomycin. Patients in group B showed good tolerance of the rifampin-doxycycline regime. However, the last is of little clinical importance and is not by itself a reason for recommending the combination over the classically recommended mode of therapy for brucellosis. From our results with this study, we concluded that oral rifampin-doxycycline taken for 1 month is a well-tolerated and comfortable mode of therapy for patients with brucellosis and can elicit an initial

### Table 1. Analysis of relapses

<table>
<thead>
<tr>
<th>Treatment, patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Defervesence period (days)</th>
<th>Relapse time (mo posttreatment)</th>
<th>Clinical features of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline-streptomycin</td>
<td>1</td>
<td>17</td>
<td>M</td>
<td>6</td>
<td>Fever, cough, headache (20 days after blood culture)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>43</td>
<td>M</td>
<td>3</td>
<td>Fever, arthritus, pericarditis, skin rash</td>
</tr>
<tr>
<td>Rifampin-doxycycline</td>
<td>3</td>
<td>30</td>
<td>M</td>
<td>1</td>
<td>Asthenia, sweating</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>36</td>
<td>M</td>
<td>3</td>
<td>Fever, arthralgia, asthenia</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>16</td>
<td>M</td>
<td>3</td>
<td>Fever, cough, odynophagia</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>16</td>
<td>M</td>
<td>3</td>
<td>Fever, cough, arthralgia</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>22</td>
<td>M</td>
<td>1</td>
<td>Fever, asthenia, myalgia</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>34</td>
<td>M</td>
<td>3</td>
<td>Fever, headache, malaise (15 days after blood culture)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>30</td>
<td>F</td>
<td>3</td>
<td>Fever, cough, odynophagia (15 days after blood culture)</td>
</tr>
</tbody>
</table>

* Durations of treatments are described in the text.
clinical improvement; however, the relapse rate is too high, and a more prolonged period of treatment appears to be necessary with this combination to obtain the low number of relapses achieved with the classically recommended treatment with tetracycline and streptomycin.

LITERATURE CITED