Azithromycin and Gentamicin Therapy for the Treatment of Humans with Brucellosis

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Ten patients with brucellosis were treated with azithromycin and gentamicin to assess the treatment’s safety and efficacy. Seven patients had an excellent therapeutic response at the end of therapy; however, relapse was noted in 3. When relapse was considered in combination with an initial lack of efficacy, 5 patients (50%; 95% confidence interval, 18.7%–81.3%) did not respond to therapy; these results do not favor the use of azithromycin to treat brucellosis in humans.

The combination of tetracyclines and either an aminoglycoside or rifampin is effective in the treatment of brucellosis in humans; however, relapse remains a significant problem [1]. Moreover, for patients for whom tetracycline is contraindicated (i.e., pregnant women and children <8 years old), no other antibiotic offers a consistent treatment option that is as effective as doxycycline in the treatment of acute brucellosis [2]. Therefore, better treatments for humans with brucellosis are needed.

In one early study [3], combination therapy with erythromycin and streptomycin was as effective as therapy with tetracycline and streptomycin. Farid et al. [3] treated 94 patients who had brucellosis. Relapse was seen in 7 (13.2%) of 53 patients who received combinations of erythromycin and streptomycin for 21 days. The relapse rate was similar in 21 patients (14.3%) treated with tetracycline and streptomycin and in 20 patients (10%) treated with tetracycline as monotherapy. However, 16 patients (30%) treated with erythromycin and streptomycin had moderate to severe adverse gastrointestinal effects, compared with 10% of patients who received tetracyclines ($P = .03$). In this study, a high dosage of oral erythromycin (1 g q6h) was given for 21 days. Other studies that used lower dosages (2 g/day) for 1–2 weeks showed worse results (13 relapses among 21 patients) [4]. Therefore, this combination therapy was promptly abandoned because of severe and frequent side effects.

Azithromycin is an azalide with in vitro activity against *Brucella melitensis* (MIC$_{90}$ range, 0.5–2 µg/mL) [5–7]. Azithromycin is significantly more active than erythromycin (and other macrolides) against *Brucella* species, showing an MIC$_{90}$ that is 8-fold lower than that of erythromycin [6]. Furthermore, azithromycin is concentrated and persists in phagocytic cells (neutrophils and macrophages), and it does not interfere with their bactericidal activity [8, 9]. Such properties suggest that azithromycin might be useful in the treatment of *Brucella* species, which are known to survive and multiply within host cells. In a murine model of brucellosis, azithromycin that was administered orally for 10 days reduced the infection significantly, but it was not able to cure the animals as effectively as doxycycline that was administered for a longer period [10]. In a more recent study, azithromycin that was administered for 7 or 14 days achieved an effective primary cure and prevented relapse in a murine model of brucellosis [11].

Azithromycin may be an effective therapy for treatment of brucellosis, but, to our knowledge, its use has not been assessed in humans. We report the findings of a pilot investigation that studied treatment with azithromycin for 21 days plus gentamicin for the first 7 days of therapy among 10 patients with acute brucellosis.

**Materials and methods.** The study was done from December 1997 through September 1999 in 2 general hospitals in Spain. Eligible patients were at ≥8 years of age and had brucellosis diagnosed, as defined below. The diagnostic criteria included either (1) isolation of a *Brucella* species from samples of blood or other fluids or tissues, or (2) the finding of antibodies to *Brucella* species at a titer of >1:160, by use of a standard tube agglutination method, in association with at least 2 of the following compatible clinical findings: fever, arthralgias, weight loss, hepatosplenomegaly, or signs of focal disease. Patient exclusion criteria included a known or suspected hypersensitivity (or other contraindication) to azithromycin or aminoglycosides, severe concomitant disease, and effective antimicrobial therapy within 7 days before the patient entered.
the study. We also excluded patients with CNS involvement, spondylitis, or endocarditis. Eligible patients received azithromycin in a single daily dose of 500 mg (or 10 mg/kg/day if the body weight was <50 kg) for 21 days, and they received gentamicin in a dose of 240 mg (or 5 mg/kg/day if the body weight was <50 kg) given im once daily for the first 7 days of treatment. Azithromycin was taken orally at least 1 h before or 2 h after a meal.

Patients were monitored for therapeutic efficacy and signs of drug toxicity by analysis of clinical data; assessment of complete blood cell counts (with differential and platelet counts) and erythrocyte sedimentation rates; urinalysis; measurements of levels of creatinine, aspartate aminotransferase, alkaline phosphatase, albumin, total protein, bilirubin, and electrolytes; Brucella serological analysis; and culture of blood samples. The patients were evaluated at baseline, on days 8 and 15, and at the end of therapy. During these visits, the subjects were asked whether they had missed any dosing. After therapy ended, the patients were reassessed at months 1, 2, 3, 6, 9, and 12, as well as whenever clinical symptoms reappeared. The clinical response to treatment was classified in the following manner: no apparent response to the study drug or a worsening of the signs and symptoms after 7 days of therapy was considered “failure”; reappearance of symptoms or signs of the disease or a new positive result of blood culture during the 12 months after therapy was considered a “relapse”; and complete resolution of the signs and symptoms of infection and no relapse at follow-up was considered a “cure.” Safety was assessed on the basis of all reported adverse events and the results of laboratory tests and other investigations. Clinical adverse events were recorded and evaluated for severity, outcome, and relation to the study drugs.

The standard tube agglutination test, the rose bengal test, and the anti-Brucella Coombs’ test were done by use of standard methods [12] with commercial reagents (Knickerkoecker). Blood samples were cultured as reported elsewhere [12], and the cultures were incubated for 30 days by use of the BACTEC NR-900 system (Becton Dickinson—Spain). All isolates were identified as recommended by Hausler et al. [13]. Three of the isolated strains were sent to a reference center (Servicio de Microbiología, Universidad de Navarra, Pamplona, Spain) for confirmation and biotyping. All Brucella isolates were identified as B. melitensis: 2 were biovar 3 and 1 was biovar 1.

Results. Demographic variables and therapeutic responses are summarized in table 1. Of the 10 patients with acute brucellosis who were enrolled in this study, 7 completed the 21 days of azithromycin therapy and 3 discontinued treatment prematurely. One patient was unable to continue treatment after she broke out in a generalized rash, presumably in relation to azithromycin therapy on day 2 of therapy. Two other patients had objective evidence of treatment failure. A patient who presented with fever, sweats, weight loss, and lumbar pain continued to have fever and progressive lumbar pain and was withdrawn from therapy on day 8. In a second patient, symptoms improved during the first week, but fever and sternalclavicular arthritis developed during week 2 of treatment with azithromycin.

Seven of 10 patients achieved excellent therapeutic responses at the end of therapy; initially, 1 had shoulder arthritis and 6 had nonfocal brucellosis with fever, constitutional symptoms, and arthralgias. However, during the month after they finished therapy, 3 patients (30%; 95% CI, 6.7%–65.2%) had clinical relapse (table 1). Clinical suspicion of relapse was confirmed in 2 of them by means of isolation of Brucella from blood samples. The third patient who had relapse developed sacroilitis that was confirmed by means of MRI. Relapses were treated with doxycycline, 200 mg/day for 45 days, and streptomycin, 1.0 g/day for 15 days; clinical response was excellent for all patients. When relapse was considered together with initial lack of efficacy, 5 patients (50%; 95% CI, 18.7%–81.3%) failed to respond to therapy.

Side effects that were considered by the investigators to be related to treatment were reported in 4 (40%) of 10 patients (95% CI, 12.2%–73.7%). The most common treatment-related side effects involved the gastrointestinal tract (nausea in 1 patient, diarrhea in 1, and epigastric discomfort in 1). All side effects were judged to be mild, with the exception of 1 case of generalized skin rash. Abnormal laboratory test results that may have been related to azithromycin treatment were recorded for 3 patients (30%). Small increases in liver enzyme levels were observed in 3 patients, 1 of whom had a small transient decrease in WBC count (nadir, cells/L). In this study, im administration of gentamicin was well tolerated. Laboratory studies did not reveal any drug-related renal abnormalities. The mean (± SD) serum creatinine concentrations at baseline and after 7 days of gentamicin treatment were 0.90 ± 0.06 mg/dL and 0.88 ± 0.06 mg/dL, respectively.

Discussion. In patients who were treated with azithromycin for 21 days and with gentamicin for the first 7 days in this study, the failure rate of 50% was higher than that in our previous studies, in which doxycycline was given for 30–45 days and aminoglycosides were given for 1–2 weeks (with failure rates ranging from 5.9% to 22.9%) [14–16]. These findings are especially notable not only for the relapse of brucellosis within only a few weeks of stopping azithromycin therapy in 3 of 7 patients who completed 21 days of therapy but, also, for the apparent lack of a significant treatment effect in 2 patients, 1 of whom developed sternalclavicular arthritis during the second week while undergoing azithromycin therapy. This suggests that azithromycin could not prevent the development of osteoarticular complications.

The maximum level of azithromycin in serum is only ~0.4 mg/L after an oral dose of 500-mg [17], and the MIC<sub>90</sub> for B.
Table 1. Characteristics of 10 patients with acute brucellosis treated with azithromycin and gentamicin.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Symptom duration, d</th>
<th>Focal disease</th>
<th>Blood culture result</th>
<th>STA titer&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td>45</td>
<td>None</td>
<td>–</td>
<td>160</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>M</td>
<td>15</td>
<td>None</td>
<td>+</td>
<td>80</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>45</td>
<td>Shoulder arthritis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
<td>640</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>M</td>
<td>15</td>
<td>None</td>
<td>+</td>
<td>1280</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>30</td>
<td>Sacroiliitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+</td>
<td>2560</td>
<td>Adverse effect</td>
<td>Withdrawn from study because of rash after 2 doses of azithromycin</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>20</td>
<td>None</td>
<td>–</td>
<td>320</td>
<td>Therapy failed</td>
<td>Persistent fever, arthralgias, and back pain 7 days after starting therapy; spondylitis was diagnosed 12 weeks later</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>M</td>
<td>18</td>
<td>None</td>
<td>–</td>
<td>2560</td>
<td>Therapy failed</td>
<td>Fever and sternoclavicular arthritis during week 2 after starting therapy; resolution after doxycycline-gentamicin therapy</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>M</td>
<td>6</td>
<td>None</td>
<td>+</td>
<td>1280</td>
<td>Relapse (C)</td>
<td>Clinical relapse with sacroilitis (MRI) 8 days after ending therapy; resolution after doxycycline-streptomycin therapy</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>M</td>
<td>9</td>
<td>None</td>
<td>+</td>
<td>640</td>
<td>Relapse (C/B)</td>
<td>Relapse with wrist bursitis 1 month after ending therapy. Resolution after doxycycline-streptomycin therapy</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>F</td>
<td>9</td>
<td>None</td>
<td>+</td>
<td>1280</td>
<td>Relapse (C/B)</td>
<td>Fever, malaise, and arthralgias 1 month after ending therapy; resolution after doxycycline-streptomycin therapy</td>
</tr>
</tbody>
</table>

NOTE. B, bacterial relapse; C, clinical relapse; STA, standard tube agglutination; +, positive; –, negative.

<sup>a</sup> Reciprocal titer.

<sup>b</sup> Diagnostic procedure, MRI.

<sup>c</sup> Brucella species were isolated from a synovial fluid samples from the shoulder.

*Brucella melitensis* had a range of 0.5–2 mg/L [5, 6]. On the other hand, although the pharmacokinetic profile of azithromycin is characterized by sustained high concentrations in cells and tissues [9, 10, 17], the activity of azithromycin against *Brucella* species is 6- to 8-fold lower at pH 5.0 than at pH 7.0 [18]. *Brucella* species grow and replicate in the phagolysosomes of macrophages, where the pH is 5.0 [19]. These data are supported by the results of animal studies. Domingo and colleagues [10, 20] reported that, for experimental brucellosis in mice, azithromycin was less effective than doxycycline used either alone or in combination with azithromycin and streptomycin. These authors think that *Brucella* species in intracellular conditions would be resistant to azithromycin (MIC, >8 μg/mL) [21].

Other drugs used in the treatment of brucellosis seem to be more effective. Rifampin (MIC range, 0.05–1 mg/L) also concentrates in neutrophils and reaches a higher serum concentration than does azithromycin [1]. Moreover, the activity of rifampin is increased 2- to 8-fold at pH 5.0, whereas the MIC of azithromycin increases to well above its breakpoint [18]. In our study, 6 patients who either failed to respond to therapy (5 patients) or withdrew because of side effects (1 patient) were eventually cured with combination regimens of rifampin plus gentamicin or doxycycline plus aminoglycosides (table 1).

We concluded that a regimen of azithromycin of 3 weeks’ duration plus gentamicin given during the first week results in a high rate of therapeutic failures and relapses. These results do not favor the use of azithromycin to treat brucellosis in humans.

References