

Efficacy of rifampicin plus doxycycline versus rifampicin plus quinolone in the treatment of brucellosis

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ABSTRACT

Objective: The aim of this study was to compare the efficacy, tolerability and side effects of 2 treatment regimens for brucellosis.

Methods: Fifty-seven patients with brucellosis were followed up in our clinic. The patients were given rifampicin plus doxycycline or rifampicin plus quinolone. Thirty patients (group one) received rifampicin 600mg/daily plus doxycycline 100mg twice daily and 27 patients (group 2) received quinolones (ofloxacin 200mg twice daily peroral) plus rifampicin 600mg/daily. Both regimens were administered for 45-days. During the course of treatment, patients were followed for the disappearance of physical signs and symptoms. All patients were followed up at least 6-months after cessation of therapy. Diagnosis of brucellosis was established by utilizing the following criteria; Isolation of brucella species in blood, body fluids (Sceptor, Becton-Dickinson, United States of America), compatible clinical picture supported by the detection of specific antibodies at significant titers or demonstration, or both, of an at least 4 fold rise in antibody titer in serum specimens taken after 2-weeks. Significant titer was

determined to be $>1/160$ in the standart tube agglutination test (Brucella abortus Cromatest, Linear Chemicals, Spain).

Results: Of patients 14 (24.5%) were male and 43 (75.5%) were female. Mean age was 36.8 ± 11.3 years (range 15-65). Sacroiliitis was the most common involvement in both groups 9 (30%) versus 6 (22%), followed by peripheral arthritis 6 (20%) versus 6 (22%). In this study, relapse rate was found 7.2% and 6.7% for ofloxacin plus rifampicin and doxycycline plus rifampicin for a 6-week therapy ($p>0.05$). No significant adverse effects were associated with either combination

Conclusion: These results indicated that a 45-day course of doxycycline plus ofloxacin combination was as effective as the doxycycline plus rifampicin combination in patients with brucellosis.

Keywords: Brucellosis, rifampicin, doxycycline, quinolone, therapy, efficacy.

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Brucellosis is an important public health problem worldwide, mainly in the Mediterranean countries, including Turkey.¹ Fever, generalized malaise, arthralgia, chills and anorexia characterize the disease. The therapy of brucellosis is an important issue. The primary goals of therapy for brucellosis are to improve the symptoms, reduce complications and prevent relapses.² Due to the fact that brucellae

are intracellular pathogens and complete eradication of the microorganism with antibiotic therapy is difficult to achieve, relapse occurs.³ It was found that the relapse rate is 5-14% after treatment. Therefore, combine therapy is recommended in brucellosis management. The most commonly used antimicrobials are rifampicin, tetracycline/doxycycline, aminoglycosides, trimethoprim-

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sulfamethoxazole, quinolones.²⁻⁵ The World Health Organization (WHO) recommended the use of a 6 week course of doxycycline-rifampicin combination therapy as the treatment of choice in human brucellosis.⁶ Many studies showed 5%-16% relapse rate with rifampicin+doxycycline combination therapy for 45 days.^{3,7-9} Fluoroquinolones are successful drugs in the treatment of brucellosis due to the good penetration at intracellular areas.^{10,11} However, application of this drug alone in the clinical studies, has a high relapse ratio (21%-66%).¹²⁻¹⁴ Because of this it should not be used alone in the treatment of brucellosis.¹⁴

In this study, we compared the efficacy of treatment, patients' tolerability and side effects of the rifampicin-doxycycline therapy and the combination of rifampicin-quinolone for 45 days in patients with brucellosis.

Methods. Between January 1997 and February 2001, 57 patients with brucellosis had been followed at the Clinical Microbiology and Infectious Diseases Department, Çukurova University, Balcalı Hospital, Adana, Turkey. Diagnosis of brucellosis had been established by utilizing the following criteria; 1. Isolation of brucella species in blood, body fluids (Sceptor, Becton-Dickinson, United States of America), 2. Compatible clinical picture supported by the detection of specific antibodies at significant titers and demonstration of an at least 4 fold rise, or both in antibody titer in serum specimens had been taken after 2 weeks. Significant titer had been determined to be >1/160 in the standard tube agglutination test (STA) (Brucella abortus Cromatest, Linear Chemicals, Spain.) In addition to STA, the anti-Brucella Coombs test and the rose bengal test had also been used.

Complete blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and blood chemistry profile had been analyzed for all patients before therapy. The laboratory tests were also performed during the therapy period in the 2nd, 4th and 6th week. A radiographic study of lumbar spine; and of both sacroiliac joints in prone position, and another osteoarthricular location having suspicious sign were processed in each patient. Thirty patients (group one) had received rifampicin 600mg/daily plus doxycycline 100mg bid. Twenty-seven patients (group 2) had received quinolone (ofloxacin 200mg bid) plus rifampicin 600mg/daily. Both regimens had been continued for 45 days. During the course of treatment patients had been followed for the disappearance of physical signs and symptoms. All patients had been followed up at least for 6 months after cessation of therapy. Relapse was defined as the reappearance of signs or symptoms of the disease throughout the follow-up or by increasing values of STA test result, or both.

Table 1 - Clinical characteristics and findings of 2 treatment groups.

Therapy	First group n=30 (%) (Rifampicin+doxycycline)	2nd group n=27 (%) (Rifampicin+ofloxacin)
Sex: Male-Female	8 (26.6) - 22 (73.3)	6 (22.2) - 21 (77.7)
Symptom >10 days	25 (83.3)	25 (92.6)
Fever (>38°C)	25 (83.3)	24 (88.9)
Arthralgia -myalgia	26 (86.6)	23 (85.2)
Hepatomegaly	7 (23.3)	11 (40.7)
Splenomegaly	28 (93.3)	10 (37)
Arthritis	6 (20)	6 (22.2)
Sacroiliitis	9 (30)	6 (22.2)
ESR (>5mm/h)	23 (76.7)	20 (74)
CRP positivity	18 (60)	16 (59.2)
Standard agglutination test >1/160	28 (93.3)	24 (88.9)
Blood culture positivity	2 (6.7)	1 (3.7)
Relapse rate	2 (6.7)	2 (7.4) p>0.05
n - number, ESR- erythrocyte sedimentation rate CRP - C reactive protein		

Clinical characteristics of both groups were compared using t test and significance of difference was tested through chi-square test.

Results. Of 57 patients, 14 (24.5%) were male, 43 (75.5%) were female and mean age was 36.8 ± 11.3 years (range 15-65). A temperature higher than 38°C was recorded in 25 (83.3%) patients at group one and 24 (88.9%) patients at group 2. The most common complaints in patients were arthralgia 26 (86.6%) at group one versus 23 (85.2%) at group 2, fever 25 (83.3 %) at group one versus 24 (88.9%) at group 2. Hepatomegaly and splenomegaly were detected in 7 (23.3%) and 28 (93.3%) patients at group one; and were detected in 6 (20%) and 10 (37%) patients at group 2. When we analyzed the results in both groups, we did not find any difference of clinical findings. Sacroiliitis was the most common involvement in both groups 9 (30%) compared with 6 (22%), followed by peripheral arthritis 6 (20%) in comparison to 6 (22%). There were no statistically significant hematological and biochemical differences between patients' group one and group 2. Only 3 (5.2%) patients had had positive

blood cultures for brucellosis. The baseline characteristics and findings of patients were determined at **Table 1**. The possible source of infection was identified in 37 (65%); 29 (78.3%) of whom had been consuming unsanitary dairy products, especially fresh cheese, 8 (21.6%) of whom had had direct animal contact; as a butcher or farm worker. No source had been identified in 20 (35%) patients. Treatment was usually well tolerated, in both groups, although some patients had mild and reversible adverse effect as gastric discomfort; no case had severe adverse effects for discontinuation of therapy.

Discussion. Brucellosis is a common zoonosis in many parts of the world.¹⁵ Brucellosis with or without osteoarthricular involvement usually presents non-specific clinical manifestations such as fever, malaise, sweating, hepatomegaly, and splenomegaly 1. In this study, we had found no significant difference regarding any of these features between either groups and also we had found no significant differences in hematological and biochemical findings between both groups. In our study, the most frequent osteoarthricular involvement of brucellosis was sacroileitis (26%).

In brucellosis, the aim of a treatment regimen is to control the acute illness and to prevent both complications and relapses 2. The choice of regimen and duration of antimicrobial therapy should be based on the presence of focal disease and underlying conditions which contraindicate certain specific antibiotics.⁹ Treatment with single agent and shorter duration carries a high risk for relapses. It is recommended that combination therapy including rifampicin and doxycycline be used. The combination of ofloxacin plus rifampicin showed similar results to that of doxycycline plus rifampicin when they were both applied during 6 weeks. Most studies have shown that therapy of brucellosis is associated with a relapse rate of less than 5%.^{8,16, 17} In our study, relapse rate had been found 7.4% and 6.7% for ofloxacin plus rifampicin and doxycycline plus rifampicin for a 6 week therapy ($p>0.05$). Agalar et al¹⁸ reported relapse rates of 15% and 10% for ciprofloxacin plus rifampicin and rifampicin plus doxycycline for a 4 week therapy in brucellosis. In the study by Akova et al¹⁷ the efficacy of doxycycline plus rifampicin was compared with the efficacy of ofloxacin plus rifampicin. It was found that the combination of ofloxacin plus rifampicin is as effective as doxycycline plus rifampicin. They reported relapse rates of 3.2% and 3.3% for ofloxacin plus rifampicin and doxycycline plus rifampicin for 6 weeks therapy. Acocella et al¹⁶ reported relapse rate of 5%, and Solera et al⁸ reported date relapse rate of 16% for doxycycline plus rifampicin combination therapy in brucellosis.

It was concluded, that a 45-day course of rifampicin plus quinolone combination was as effective as the doxycycline plus rifampicin combination in patients with brucellosis. No serious adverse effects were associated with either combination. Mild gastric complaints were frequent and were attributed to the doxycycline. As a result, the 2 regimes were associated with good initial clinical response and good tolerance. Our patients had become asymptomatic within the 2nd week of therapy.

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