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A randomized, comparative study of dual therapy (doxycycline–rifampin) versus triple therapy (doxycycline–rifampin–levofloxacin) for treating acute/subacute brucellosis

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ABSTRACT

Aim: The aim of this study was to compare both the efficacy and safety profile of the WHO-recommended, dual therapy (doxycycline–rifampin) to a quinolone-based, triple therapy (doxycycline–rifampin–levofloxacin) for treating acute/subacute brucellosis.

Patients and methods: We studied 107 consecutive, naïve patients with acute/subacute brucellosis admitted to Assiut University Hospital. Patients were randomly allocated to receive the dual therapy of doxycycline–rifampin (group-A) or to receive the triple therapy of doxycycline–rifampin–levofloxacin (group-B). Acute/subacute brucellosis was diagnosed based on the presence of: (1) contact with animals or fresh animal products, (2) suggestive clinical manifestations of less than one-year duration, and (3) positive antibody titer (1:160) by standard tube agglutination test.

Results: There was no significant difference between the two groups regarding their demographic data. Fever was the most frequent manifestation (96.3%). Epigastric pain was the most frequent adverse effect of treatment (12.1%). Group-A patients had a significantly higher relapse rate compared to group-B patients (22.6% versus 9.3%, p-value = 0.01). The rate of treatment adverse effects was higher among group-B patients, although not reaching statistical significance (20.4% versus 11.3%, p-value = 0.059).

Conclusions: Adding levofloxacin to the dual therapy for acute/subacute brucellosis (doxycycline–rifampin) may increase its efficacy in terms of lowering the relapse rate of the disease. Further, larger scale studies are needed before considering modifying the standard, dual therapy for brucellosis.

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Introduction

More than 500,000 cases of brucellosis are reported yearly to the World Health Organization (WHO) from 100 countries. Seroprevalence of brucellosis in Assiut Governorate (Egypt) was estimated to be 1.29% among the general population.[1] Bacteria of the genus *Brucella* cause disease with protean manifestations. Infection is transmitted to humans from animals as a consequence of occupational exposure or ingestion of contaminated milk products. *Brucella abortus* infection occurs worldwide with a reservoir in cattle. It is usually associated with mild to moderate sporadic disease; suppurative or disabling complications are rare. *Brucella melitensis*, with a reservoir in sheep, goats, and camels may cause severe, acute disease and disabling complications. It accounts for the majority of cases, distributed primarily in the Mediterranean region, Latin America, the Arabian Gulf, and the Indian subcontinent. Clinically, human brucellosis can be conveniently but arbitrarily divided into subclinical illness, acute or subacute disease, localized disease and complications, relapsing infection, and chronic disease. The WHO recommends doxycycline (200 mg/day) plus rifampin (600–900 mg/day) orally for six weeks for treating brucellosis. Up to 10% of patients with brucellosis experience relapses after antimicrobial therapy. Relapses usually occur three to six months after completion of therapy but may be seen up to two years after treatment.[2]

Combination drug therapy of brucellosis leads to shortening duration of symptoms, and decreases morbidity while, single drug therapy is associated with more relapse episodes and a higher rate of drug resistance.[3] Therapeutic failure and relapse develop in 8% and 16%, respectively, of patients with acute brucellosis receiving doxycycline plus rifampin for 45 days compared to 2% and 5.2% among patients receiving doxycycline plus streptomycin for the same duration.[4] Although regimens with aminoglycosides have higher therapeutic success rates, long-term use of such agents is associated with significant nephrotoxicity.

The use of quinolones for treating brucellosis is controversial. Reported by several studies, monotherapy with ciprofloxacin results in an unacceptably high probability of relapse.[5–7] In four out of six randomized, controlled trials, ofloxacin was the quinolone used in combination with rifampin. In three of these studies, the results were similar between the quinolone and the non-quinolone arms regarding initial treatment success and probability of relapse.[8–10] In one study of with spondylitis exclusively, the quinolone arm was found to be inferior to other treatment regimens in terms of initial treatment success and relapse rate.[11] In two randomized, controlled trials, ciprofloxacin was the quinolone used, combined with doxycycline[12] or rifampin[13]; the results were similar between the quinolone and the non-quinolone groups.

Theory

There are no studies in Egypt investigating the use of triple antimicrobial therapy for brucellosis. The aim of this study was to compare both the efficacy and safety profile of the WHO-recommended, dual antimicrobial therapy (doxycycline–rifampin) to a quinolone-based, triple therapy (doxycycline–rifampin–levofloxacin) for treating acute/subacute brucellosis among Egyptian patients.

Patients and methods

The study included 120 consecutive, naïve patients with acute/subacute brucellosis who had not received any antimicrobial therapy since the start of illness. The patients were admitted to the departments of Tropical Medicine (Fever Unit) and Internal Medicine during the period of May 2011 to November 2014. Acute/subacute brucellosis was diagnosed based on the presence of: (1) contact with animals or fresh animal products, (2) suggestive clinical manifestations of less than one-year duration (fever, chills, sweats, fatigue, arthralgia, myalgia, relative bradycardia, splenomegaly, lymphadenopathy, and hepatomegaly), and (3) positive antibody titer (1:160) by standard tube agglutination test (against *Brucella abortus*, *Brucella melitensis*, and *Brucella suis*). Pregnant and pediatric patients were excluded from the study. We defined therapeutic failure as persistence of the clinical manifestations of brucellosis at end of treatment (after six weeks of treatment). Relapse was defined as recurrence of the clinical manifestations with a single positive antibody titer within six months after ending therapy.[2]

The study patients were randomly allocated to two groups; 60 patients for each group. Group-A patients received the WHO-recommended, dual antimicrobial therapy for brucellosis (doxycycline 200 mg/day and rifampin 900 mg/day, for six weeks). Group-B patients received quinolone-based, triple therapy (doxycycline 200 mg/day, rifampin 900 mg/day, and levofloxacin 500 mg/day, for six weeks). Each drug used was produced by same pharmaceutical company and all drugs were administered orally, once daily. Doxycycline was given after breakfast; rifampin was given before breakfast; and levofloxacin was given 1 h before lunch. During inpatient attendance, the patients were assessed clinically on a daily basis; after discharge, they were assessed weekly on outpatient clinic visits. Complete blood count, liver chemistry panel, kidney chemistry panel, abdominal ultrasonography, and chest radiography were performed before the start of treatment. Laboratory investigations were repeated weekly to monitor for side effects. Directly observed therapy was applied during the period of inpatient attendance for all patients. The patients were discharged after normalization of body temperature for at least three days. After discharge, compliance with therapy was confirmed on weekly basis during outpatient clinic visits. After the end of therapy, the patients were assessed clinically on a monthly basis for six months to look for evidence of relapse.

Ethical considerations

The study was approved by the "Assiut Faculty of Medicine Clinical Research Ethical committee", and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Before enrollment in the study, all participants signed an informed consent. Before