Comparison of the efficacy of two months of treatment with co-trimoxazole plus doxycycline vs co-trimoxazole plus rifampin in brucellosis

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Summary

Background: To compare the efficacy of two different regimens in treatment of brucellosis.

Methods: This randomised clinical trial study was conducted on 280 patients with brucellosis in Babol, Iran, from April 1999 to January 2002. One of the following two regimens was randomly prescribed for two months: co-trimoxazole plus doxycycline (CD group) and co-trimoxazole plus rifampin (CR group).

Results: 140 patients with the mean age of 35.56 (16.2) years, and 140 patients with the mean age of 31.39 (18) years, were treated with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin, respectively. Clinical manifestations and laboratory test results were similar in both groups (p >0.05), except in sex and clinical types (p <0.05).

Failure of treatment was seen in 10 (7.1%) and 23 (16.4%) cases treated in the CD group and CR group, respectively (95% CI, 0.174 to 0.862; OR = 0.387; p = 0.020). Relapse was seen in 12 cases (8.6%) treated in the CD group and in 14 cases (10%) treated in the CR group (95% CI, 0.365 to 1.87; OR = 0.826; p = 0.646). Failure of treatment plus relapse was seen in 22 (15.7%) and 37 (26.4%) cases treated in the CD group and CR group, respectively (95% CI, 0.278 to 0.929, OR = 0.508; p = 0.028). Risk for developing of failure of treatment and relapse in patients treated with co-trimoxazole plus rifampin was 1.96 times higher than those treated with co-trimoxazole plus doxycycline. Among the relapsed patients, 18 (69.2%) cases occurred within 6 months after completion of therapy, and most of them in uncomplicated patients.

Conclusion: using two months of treatment, the efficacy of co-trimoxazole plus doxycycline is better than co-trimoxazole plus rifampin.

Key words: Brucellosis; treatment; regimens of therapy; Co-trimoxazole; Rifampin; Doxycycline

Introduction

Brucellosis is an important public health problem throughout the world, especially in the Mediterranean region, the Indian subcontinent, Mexico, and parts of Central and South America [1, 2].

Human brucellosis is a systemic infection that can involve many organs and tissues [1, 3]. The best regimen for the treatment of brucellosis has not been clearly determined [4]. For many years, the standard treatment for brucellosis has been combination therapy with streptomycin plus tetracycline or doxycycline [1]. The reported relapse rates with this regimen were between 5.3–8% [5–7]. Streptomycin must be administered by the parenteral route for 14–21 days. Ototoxicity, nephrotoxicity, and hypersensitivity reactions can follow the administration of streptomycin [8]. In 1986 the World Health Organisation recommended the use of a 6-week course of doxycycline plus rifampin in the treatment of human brucellosis [9]. Several researchers reported a relapse rate between 14–17% for this regimen [6, 7, 10]. Single-agent therapy with drugs such as co-trimoxazole, doxycyclin, rifampin and ciprofloxacin has been abandoned owing to the high relapse rates, and a combination of two drug regimens is now preferred [5, 11–12]. Administration of doxycycline and rifampin for shorter periods of time has been associated with a relapse rate of 30 to 40% [4, 6]. Aglar et al. treated 20 patients with brucellosis

by ciprofloxacin plus rifampin for 30 days, and the relapse rate was 15% [13]. Experience with other oral regimens of treatment like co-trimoxazole plus rifampin or co-trimoxazole plus doxycycline in the treatment of brucellosis is very limited. We conducted a randomised clinical trial to compare the efficacy of co-trimoxazole plus rifampin versus co-trimoxazole plus doxycycline with a two month duration of therapy for human brucellosis.

Patients and methods

From April 1999 to January 2002, consecutive patients with brucellosis who attended the Department of Infectious Diseases, Yahyanejad Teaching Hospital, Babol Medical University, were enrolled into the study. The Department of Infectious Diseases, serves more than 1.5 million people living in two cities, Babol and Amol, and the surrounding villages in the north of Iran.

Exclusion criteria were: age less than 10 years, pregnancy, spondylitis, endocarditis, meningoencephalitis, previous history of brucellosis, and antimicrobial therapy for more than 7 days before enrollment. The diagnostic criteria were the finding of ≥1/320 standard tube agglutination titer (STAT) of antibodies to brucella with a 2 mercaptoethanol (2 ME) ≥1/160, in association with compatible clinical findings. For all of these cases, confirmatory tests were also performed using Elisa with significant titers of IgM and IgG specific brucella antibodies.

We also assayed the full blood count (FBC), platelets, haemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) in all cases, and findings were compared with the normal ranges in references [14]. Diagnoses of sacroiliitis or peripheral arthritis were made by appropriate findings on physical examination and with use of coventional radiological imaging and bone scan. Clinical type (the onset of clinical symptoms and signs to diagnosis) was classified as acute (less than two months) and sub-acute and chronic (more than two months). Complications were considered to have arisen in all cases who had arthritis, sacroiliitis and epidydimo-orchitis. All the patients were aware of the disease,

its complications, duration of treatment, the side effects of drugs, and all of them gave written informed consent. About two years before beginning of this research, we performed a pilot study on 120 cases of brucellosis with both of these regimens for eight weeks and relapse with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin was seen in 10% and 25% of cases, respectively. All of these cases were available with no adverse of medication and all cases were followed for one year. The estimated sample size 280 (140 allocated per treatment arm) would have a power of 0.9, at a 95% confidence level, to detect a statistically significant difference between response rate with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin for two months.

Co-trimoxazole (trimethoprim-sulfamethoxasol) plus doxycycline (CD group) and co-trimoxazole plus rifampin (CR group) were randomly prescribed to patients. The dosage of doxycycline was 100 mg twice daily, and dosage of co-trimoxazole was 8 mg/kg/day of the trimethoprim component divided into 3 doses and the dosage of rifampin was 15 mg/kg once a day.

Before administration of these regimens, we prepared 280 cards and wrote regimen co-trimoxazole plus doxycycline or co-trimoxazole plus rifampin on each, separately. Every card was inserted in an envelope. All envelopes were mixed and put in a box. For every patient, an envelope was drawn and the regimen of therapy which was noted on the card was administered. During treatment, all patients were assessed every 20 days. After completion of therapy all cases were reassessed at three month intervals or whenever clinical symptoms reappeared. The follow up assay checked clinical symptoms and signs as well as evaluation of STAT, 2ME and brucella IgG and IgM antibodies titer with Elisa. Duration of follow-up for all cases was one year.

Relapse was said to have occurred when the indicative clinical picture reappeared and reduced titers of STAT, and 2 ME and brucella specific IgG titers after completion of therapy, increased again. Therapeutic failure was defined by symptoms or signs of the disease that persisted at the end of treatment. Failure of treatment was defined when patients had therapeutic failure, adverse effects of medication or refused to have follow up.

Statistical analysis

Data were analysed by SPSS version 10. The Student's t-test was used to compare mean values. A multivariate logistic regression model was used to estimate the difference between failure of treatment, relapse and relapse plus failure of treatment within the two regimens after adjustment with each treatment regimen for: age, sex, complications and clinical types of disease before treatment. This model was also used for comparison of the clinical manifestations among the two groups of patients. Cox proportional hazards regression was used to estimate time to "free of relapse" with the two regimens of treatment with the same covariates. Ninety-five percent confidence intervals (CIs) were calculated when appropriate. Differences with a P value of <0.05 were considered significant.

Table 1

Clinical findings of patients treated with co-trimoxazole plus doxycycline or co-trimoxazole plus rifampin.

Clinical Findings	Cotri*+ doxy** No. (%)	Cotri + rifam*** No. (%)
Arthralgia	91 (65)	94 (67.1)
Myalgia	41 (29.3)	53 (37.9)
Splenomegaly	9 (6.4)	10 (7.1)
Clinical type:		
Acute	100 (71.4)	108 (77.1)
Subacute and chronic arthritis:	40 (28.6)	32 (22.9)
Hip	4 (2.9)	9 (6.4)
Knee	19 (13.6)	12 (8.6)
Ankle	3 (2.1)	5 (3.6)
Shoulder	3 (2.1)	1 (0.7)
Elbow	1 (0.7)	0 (0)
Wrist	1 (0.7)	4 (2.9)
Polyarthritis	5 (3.6)	3 (2.1)
Arthritis + arthralgia	15 (10.7)	12 (8.6)
Sacroiliitis	5 (3.6)	15 (10.7)
Epididymo-orchitis	7 (5)	8 (5.7)

* Cotri; co-trimoxazole **doxy; doxycycline ***rifam; rifampin
A logistic regression model did not show any differences between clinical manifestations in these two groups of patients except in sex (95% CI, 0.310 to 0.912; OR = 0.532; p = 0.022) and clinical types (95% CI, 0.223 to 0.856; OR = 0.437; p = 0.016)

Results

140 patients (74 males, and 66 females) with a mean age (sd), 35.56 (16.2) years (range 12 to 81 years) and 140 cases (76 males and 64 females) with a mean age, 31.39 (17.88) years (range 10 to 79 years) were treated with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin, respectively. During the study 2 (1.4%) cases in the co-trimoxazole plus doxycycline group had adverse effects of medications (erythema multiform in one case, vomiting in one case), 3 (2.1%) cases refused follow up, and 5 (3.6%) cases had therapeutic failure. In patients treated with co-trimoxazole plus rifampin, adverse effects of medications were seen in 7 (5%) cases (three cases had skin rash and 4 cases had vomiting), 3 (2.1%) of cases refused follow up, and therapeutic failure was seen in 13 (9.3%) cases. Therefore, 130 patients (68 males, 62 females) with the mean age 35 (16.17) years and 117 patients (61 male, 56 female) with the mean age, 34.26 (17.1) years were treated and followed for one year for the regimen co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin, respectively. Characteristics of patients at baseline are shown in table1. There was no difference between mean age in these two groups of patients (p = 0.059). The clinical manifestations among patients treated by these regimens were similar (p >0.05) except in sex (OR = 0.532; 95% CI, 0.310 to 0.912; p = 0.022) and clinical types (OR = 0.437; 95% CI, 0.223 to 0.856; p = 0.016) (table 1). Titer of STAT ranged from 1/320 to 1/5120 and titer of 2–ME was between 1/160 and 1/1260. Complete blood count, haemoglobin level, platelet count and erythrocyte sedimentation rate were in the normal range for most of the 280 patients and the distribution of these findings are shown in table 2.

Failure of treatment was seen in 10 (7.1%) and 23 (16.4%) cases treated with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin, respectively (95% CI, 0.174 to 0.862; OR = 0.387; p = 0.020). There were no differences between patients who had failure of treatment and those who had not regarding sex (95% CI, 0.592 to 2.763; OR = 1.282; p = 0.526), age (95% CI, 0.454 to 2.122; OR = 0.982; p = 0.963), complications (95% CI, 1.287 to 6.394; OR = 2.869; p = 0.01), and clinical types (95% CI, 0.337 to 1.983; OR = 0.817; p = 0.656). Relapse was seen in 12 cases (8.6%) treated with co-trimoxazole plus doxycycline and in 14 cases (10%) treated with co-trimoxazole plus rifampin (95% CI, 0.365 to 1.87; OR = 0.826; p = 0.646). There were no differences between patients who had relapse and those who had not for sex, age, complications, and clinical types. Failure of treatment plus relapse was seen in 22 (15.7%) and 37 (26.4%) cases treated with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin, respectively (95% CI, 0.278 to 0.929; OR = 0.508; p = 0.028) (table3). The risk for developing of failure of treatment and relapse in patients

Table 2

Laboratory test results in patients treated with co-trimoxazole plus doxycycline or co-trimoxazole plus rifampin.

Laboratory tests		Co-trimoxazole + doxycycline No. (%)	Co-trimoxazole + rifampin No. (%)
CBC	normal	125 (89.3)	119 (85)
	leucopenia	3 (2.1)	6 (4.3)
	leucocytosis	12 (8.6)	15 (10.7)
Haemoglobin	normal	115 (82.1)	119 (85)
	anaemia	25 (17.9)	21 (15)
Platelets	normal	137 (97.9)	134 (95.7)
	thrombocytosis	3 (2.1)	6 (4.3)
Sedimentation rate	normal	121 (86.4)	118 (84.3)
	high	19 (13.6)	22 (15.7)
	CRP positivity	83 (59.3)	85 (60.7)
	RF positivity	11 (7.9)	7 (5)

Normal ranges for full blood count (4300–10 800/mm³), for haemoglobin (male; 13–18 g/dl and in female; 12–16 g/dl). Normal platelet counts; 130 000–400 000/mm³
Normal ranges for erythrocyte sedimentation rate
Westergren, <50 years of age: for males 0–15 mm/h and for females 0–20 mm/h and for >50 years of age in males 0–20 mm/h and in females 0–30 mm/h
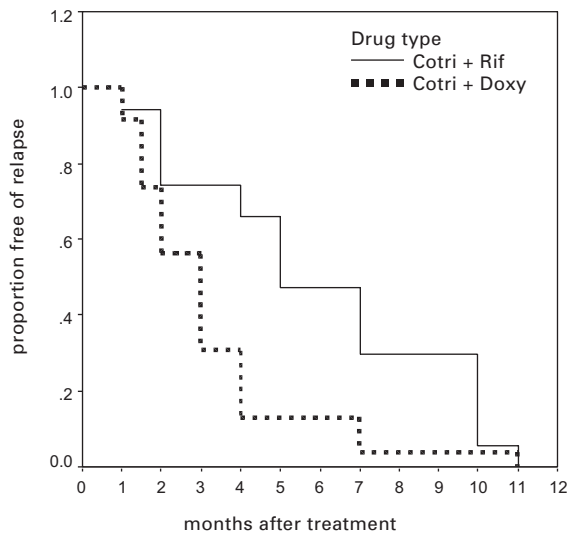
Table 3

Results of treatment with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin.

Outcome of treatment	regimen CD N = 140	regimen CR N = 140	CD/CR OR	95%	P-value
Failure of treatment	10 (7.1)	23 (16.4)	0.387	0.174 to 0.862	0.020
Relapse	12 (8.6)	14 (10)	0.826	0.365 to 1.87	0.646
Failure of treatment plus relapse	22 (15.7)	37 (26.4)	0.508	0.278 to 0.929	0.028
Successful treatment	118 (84.3)	103 (73.6%)	1.968	1.076 to 3.6	0.028

Regimen CD; Co-trimoxazole plus Doxycycline, Regimen CR; Co-trimoxazole plus Rifampin

Figure 1

Cumulative proportion of patients with no relapse in each study group. After adjustment for baseline characteristics in Cox model, the risk of relapse was 1.16 times higher in the co-trimoxazole plus rifampin group than in the co-trimoxazole plus doxycycline group (p = 0.646).

relapse and those who did not for sex, age, and clinical types but with regard to complications the difference was significant (95% CI, 1.301 to 4.916; OR = 2.529; p = 0.006). Successful treatment was seen in 118 (84.3%) cases treated with co-trimoxazole plus doxycycline and in 103 (73.6%) cases treated with co-trimoxazole plus rifampin (95% CI, 1.076 to 3.6; OR = 1.968; p = 0.028). Most cases of relapse occurred in uncomplicated cases (23 out of 26). Relapse occurred in 11 males and 15 females and in 18 cases (69.2%), relapse occurred less than 6 months after cessation of therapy (10 cases with co-trimoxazole plus doxycycline, 8 cases with co-trimoxazole plus rifampin). The cumulative proportions of patients with no relapse in each study group are shown in figure1. After adjustment for baseline characteristics, the risk of relapse was 1.16 times higher in the co-trimoxazole plus rifampin group than in the co-trimoxazole plus doxycycline group (95% CI, 0.365 to 1.87; OR = 0.826; p = 0.646).

treated with co-trimoxazole plus rifampin was 1.97 times that in patients treated with co-trimoxazole plus doxycycline. There were no differences between patients who had failure of treatment and

Discussion

This comparative clinical trial demonstrated a significant difference in therapeutic response to co-trimoxazole plus doxycycline compared to co-trimoxazole plus rifampin in the treatment of human brucellosis. Although the relapse rate with co-trimoxazole plus doxycycline and co-trimoxazole plus rifampin in this study was 8.6% and 10% respectively, ie, similar, both failure of treatment and relapse should be considered in the selection of a regimen of treatment in brucellosis. The 15.7% failure of treatment and relapse rates with co-trimoxazole plus doxycycline are similar to those reported with the use of doxycycline plus rifampin for 45 days [6, 15–17]. Other investigators have reported relapse rates of 24% when they treated patients with doxycycline plus rifampin for 45 days [4] but Acocella et al. and Akova et al. reported therapeutic failure and relapse rates of 4.6 and 4.3% in their studies, respectively [18, 19]. Even with administration of netilmicin for 7 days plus doxycycline for 45 days, the rate of failure of treatment and relapse was reported at 20.3% which is higher that the result of our study with co-trimoxazole plus doxycycline [7].

Experience with the regimen of co-trimoxazole plus doxycycline in treatment of adult cases of brucellosis is very limited in the medical literature and to our knowledge this is the first report of the efficacy of co-trimoxazole plus doxycycline in treatment of human brucellosis with a large number of patients. Thus, the efficacy of this regimen of treatment is comparable with the regimen of doxycycline plus rifampin which was recommended by WHO [9].

The 26.4% failure of treatment and relapse with co-trimoxazole plus rifampin in the present

study is much higher than that reported with administration of doxycycline plus rifampin for 45 days [6, 15–17]. A few reports about the efficacy of co-trimoxazole plus rifampin in treatment of childhood brucellosis have been published. El-Eissa et al. and Shaalan et al. reported a 8% and 9% relapse rate respectively when they treated children with brucellosis by co-trimoxazole plus rifampin for 6 weeks [20, 21]. Lubani et al. and Tsolia et al. did not observe any relapse when they treated children with brucellosis with co-trimoxazole plus rifampin for more than 6 weeks of treatment [22, 23]. Therefore, the efficacy of this combination in children is better than adult cases of brucellosis. These differences may be due to less serious disease in children than in adults.

In brucellosis, the aim of a treatment regimen is to control illness and to prevent both complications and relapses. Treatment of patients should be prolonged, since the eradication of organisms from bone may be difficult [24]. Ariza et al. compared the efficacy of several regimens of therapy with different duration of treatment in Spain. They reported that the relapse rate with streptomycin plus tetracycline and doxycycline plus rifampin for 45 days was much lower than the relapse rate with doxycycline plus rifampin and trimethoprim plus rifampin for 30 days (10%, 7%, 47% and 42%, respectively) [25]. Several regimens of treatment have been suggested by researchers for treatment of brucellosis. With streptomycin 1 g/day for 2–3 weeks plus doxycycline for 6 weeks, the relapse rate was 5.3–8% [10, 16, 26]. In endemic areas of brucellosis, tuberculosis also may be common. Thus in order to prevent emergence of resistance to rifampin, a good anti tuberculous

drug, changing of this agent to doxycycline is preferred whenever possible and co-trimoxazole plus doxycycline may be a good selection. Antibiotic therapy has been considered the most important determinant of relapse rate in human brucellosis. With two months of treatment using these regimens, the relapse rate is relatively high and therefore studies with other oral regimens of therapy are recommended.

Many investigators have been seeking the best antibiotic regimens for lowering of the number of relapses. Akova et al. treated 31 patients with ofloxacin plus rifampin for 6 weeks and the relapse rate was 3.3% [19]. Other studies with larger number of cases with this regimen are needed. In the current study, 69.2% of the relapsed cases occurred within 6 months of cessation of therapy. Ariza and co-worker's reported that, more than 95% of relapse cases occurred during the first 6 months after therapy [25]. In that study, risk factors for developing of relapse from 86 relapsed cases of brucellosis were determined. They found that, less effective antibiotic therapy, positive blood cultures during initial disease, less than 10 days duration of the disease before treatment, male sex, and thrombocytopenia were the main risk factors for relapse

[25]. In our study, among 26 relapsed cases, 15 (57.7%) cases were female, which may be due to large number of female patients in our study in comparison with Ariza's study. In the present study, re-infection was not an important consideration for our patients who had neither occupational exposure to brucella species nor contaminated with dairy products after completion of treatment.

In conclusion, using two months of treatment, the efficacy of co-trimoxazole plus doxycycline is better than co-trimoxazole plus rifampin.

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