

## COMPARISON OF TWO CHEMOTHERAPY REGIMEN: DOXYCYCLINE-RIFAMPICIN AND DOXYCYCLINE COTRIMOXAZOL IN THE BRUCELLOSIS PATIENTS AHVAZ, IRAN, 2004-2006

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### ABSTRACT

**Objective:** To compare two drugs regimen, doxycycline-rifampicin and doxycycline-cotrimoxazol in the treatment of brucellosis patients

**Methodology:** It is a comparative clinical study conducted in Ahwaz a city southwest Iran, from April 2004 to January 2006. This study was conducted on 102 nomads' patients with brucellosis. The diagnostic criteria were the finding of  $\geq 1/80$  (Wright) with a 2 mercaptoethanol (2 ME)  $\geq 1/40$ , in association with compatible clinical findings (back pain, sweating and fever). Patients were enrolled into the two antimicrobial therapy groups, doxycycline plus rifampicin (DR group) and doxycycline plus co-trimoxazole (DC group). The data in the two groups were statistically compared with SPSS by chi square test.

**Results:** Failure of treatment was seen in one (1.94%) and 5 (9.81%) cases treated in the DC group and DR group, respectively. Relapse was seen in three cases (5.88%) treated in the DC group and in six cases (11.76%) treated in the DR group. Failure of treatment plus relapse was seen in four (7.84%) and 11 (21.56%) cases treated in the DC group and DR group, respectively ( $p < 0.05$ ). Risk for relapse and failure of treatment in DR group was 2.75 times higher than DC group.

**Conclusion:** This study showed that co-trimoxazole plus doxycycline regimen has a better therapeutic effect than doxycycline plus rifampicin regimen.

**KEYWORDS:** Chemotherapy, Co-trimoxazole, Doxycycline, Brucellosis.

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### INTRODUCTION

The global burden of human brucellosis remains enormous, yet its optimal treatment remains based on traditional combinations of doxycycline with either rifampicin or streptomycin.<sup>1</sup> Human brucellosis is a multisystem disease that may present with a broad spectrum of clinical manifestations. The primary goals of therapy for brucellosis are to improve the symptoms, reduce complications and prevent relapses. The choice of a regimen and duration of antimicrobial therapy should be based on the location of the disease and the underlying conditions.<sup>2</sup> The combination therapies recommended by the World Health Organization (WHO) for treatment of brucellosis are doxy-

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cycline plus rifampicin or doxycycline plus streptomycin. Although highly successful results have been obtained with these two regimens, but relapse rates are as high as 14.4%. The most effective and the least toxic chemotherapy for human brucellosis is still undetermined.<sup>3</sup> In countries with high prevalence of tuberculosis and brucellosis like Iran, frequently usage of rifampicin (not combined with other anti TB drugs) in treatment for brucellosis can result in resistant *Mycobacterium tuberculosis*. We have some limitation on treatment of brucellosis in area, where Iranian nomads are living, such as: the risk of emergence of drug resistant *Mycobacterium tuberculosis* and lack of health service facilities (injection equipment and expert personnel. For these health problems we conducted this study to compare an oral anti brucellosis regimen with a traditional regimen.

## METHODOLOGY

This randomized clinical trial was conducted on patients with uncomplicated brucellosis in the private clinic and infectious disease ward of Razi hospital affiliated to Joundishapour University, Ahwaz, Iran, from April 2004 to January 2006.

The patients were nomads who were living in the mountain in the north of Khuzestan a province located in the southern west of Iran. The diagnostic criteria were the finding of  $\geq 1/80$  standard tube agglutination titer (STAT) of antibodies to brucella (Wright) with a 2 mercaptoethanol (2 ME)  $\geq 1/40$ , in association with compatible clinical findings such as: back pain, sweating and fever according to National Program against Brucellosis (NPB) in Iran.<sup>4,5</sup> Exclusion criteria were: age less than 15 years, pregnancy, spondylitis, endocarditis, meningoencephalitis, previous history of brucellosis, and antimicrobial therapy for more than seven days before enrollment. One hundred five patients with brucellosis were enrolled into the two antimicrobial therapy groups. Fifty two patients were included in doxycycline plus rifampicin group (DR group) and 53 patients were included in doxycycline plus

co-trimoxazole group (DC group). The dosage of drugs was: doxycycline (100mg twice a day), co-trimoxazole (2 adult tablets, 960mg twice a day) and rifampicin (300mg every 8 hour).<sup>5</sup> Although rifampicin is administrated as a single dose of 600-900 mg per day but, for epidemiological and cultural reasons (especially patients tolerance) NPB recommends it in divided dose. Course of treatment in both groups was 8 weeks.<sup>5</sup> Clinical and laboratory responses were evaluated for a six months period of follow up. The patients were tested by Wright and 2 ME tests at the end of treatment, three months and six month after completion of treatment. Appropriate clinical response was defined by subsiding fever, back pain and sweating. Relapse was said to have occurred when the indicative clinical picture reappeared and reduced titers of Wright and 2 ME after completion of therapy, increased again. Therapeutic failure was defined by persisted fever, sweating or back pain at the end of treatment. The data in the two groups were statistically compared with SPSS version 11.5. The chi square test was used to compare the therapeutic effect of two regimens. Ninety-five percent confidence intervals were calculated when appropriate. Differences with a P value of  $<0.05$  were considered significant.

## RESULTS

One patient in the DR group due to spinal cord involvement and two patients in the DC group because of severe side effects were excluded from the study. Fifty one patients with the mean age of  $31.26 \pm 11.23$  years, and 51 patients with the mean age of  $29.89 \pm 9.81$  years, was treated with co-trimoxazole plus doxycycline and doxycycline plus rifampicin respectively. Failure of treatment was seen in one (1.94%) and 5 (9.81%) cases treated in the DC group and DR group, respectively. Relapse was seen in three cases (5.88%) treated in the DC group and in 6 cases (11.76%) treated in the DR group. Failure of treatment plus relapse was seen in four (7.84%) and 11 (21.56%) cases treated in the DC group and DR group, respectively ( $p < 0.05$ ). Risk for relapse and

Table-I: Clinical and laboratory findings among nomads with uncomplicated brucellosis

<i>Clinical findings</i>	<i>DR Group</i>	<i>DC Group</i>
Fever	29(56.86)	28(54.90)
Sweating	40(78.43)	41(80.39)
Arteralgia	40(78.43)	41(80.39)
Low back pain	48(94.11)	49(96.07)
Myalgia	40(78.43)	42(82.35)
Splenomegaly	10(19.60)	12(23.52)
Arthritis	8(15.68)	10(19.60)
Weight loss	7(13.72)	9(17.64)
Laboratory findings		
Wright test:		
1/80 and more	51(100)	51(100)
1/160-1/320	20(39.21)	22(43.13)
More than 1/320	11(21.56)	10(19.60)
2ME:		
1/40 and more	51(100)	51(100)
1/80-1/160	15(29.41)	14(27.45)
More than 1/160	6(11.76)	5(9.80)

failure of treatment in DR group was 2.75 times higher than DC group. All of relapses occurred within 6 months after completion of therapy. The results of this study are shown in (Tables-I, II, III).

## DISCUSSION

Although, standard treatment with doxycycline (200mg/day) given for 6-8 weeks plus streptomycin(1g/day intramuscular) for 2-3 weeks is the most effective therapy with at least relapse and complication. WHO recommend regimen of doxycycline plus rifampicin given for 6 weeks which has the advantage of oral administration.

This study showed a significant difference in therapeutic response between (co-trimoxazole plus doxycycline) and (doxycycline plus rifampicin) in the treatment of brucellosis

Table-II: Appropriate clinical and laboratory responses to antibacterial therapy in brucellosis

	<i>DR</i>	<i>DC</i>	<i>P value</i>
Clinical improvement			
EOT	49	50	1.0
3MT	43	49	0.045
6MT	40	49	0.007
Laboratory improvement			
EOT	46	50	0.20
3MAT	41	47	0.08
6MAT	40	47	0.05

Appropriate clinical response: Subsiding; fever, low back pain, arteralgia and sweating Laboratory improvement: decreasing of serological titer below 1/80 for Wright and 1/40 for 2ME EOT=End of treatment, 3MAT= 3 months after treatment, 6MAT= 6 months after treatment.

among Iranian nomads (92.15% vs., 78.43). This study also showed a significant difference in the failure of treatment and relapse rates between (co-trimoxazole and doxycycline) and (doxycycline plus rifampicin) regimens (7.84% vs., 21.56%). Present study showed that co-trimoxazole plus doxycycline is superior to doxycycline plus rifampicin. Due to lack of medical facilities such as safe injection and expert health care workers in remote area in which nomads are living, this regimen compared with standard treatment has the advantage of oral administration.

In our study the failure of treatment and relapse rates was 21.56% with rifampicin plus doxycycline that are similar to those reported by Ariza et al and Soltuglu et al in Spain and Saudi Arabia.<sup>6-9</sup> Solera et al<sup>10</sup> have reported relapse rates of 24% which is higher than

Table-III: Results of treatment with co-trimoxazole plus doxycycline and doxycycline plus rifampicin.

<i>Outcome of treatment</i>	<i>Regimen DC No and %</i>	<i>Regimen DR No and %</i>	<i>P-value</i>
Successful treatment	47 (92.15)	40 (78.43)	0.05
Failure of treatment	1 (1.94)	5 (9.81)	0.20
Relapse	3 (5.88)	6 (11.76)	0.48
Failure plus relapse	4 (7.84)	11 (21.56)	0.05
Total	51(100)	51(100)	

Regimen DC; Co-trimoxazole plus Doxycycline, Regimen DR; Doxycycline plus Rifampicin.

as shown in our study (7.84%) with co-trimoxazole plus doxycycline. There is very limited experience with the regimen of co-trimoxazole plus rifampicin in treatment of adult cases of brucellosis. Rushan et al<sup>11</sup> in a study from Iran reported failure of treatment and relapse rates with this regimen as 26.4%, other reports are related to children brucellosis with lower relapses and failure rates than adults. These differences may be due to less serious disease in children than in adults.<sup>12-15</sup> Experience with the regimen of co-trimoxazole plus doxycycline in treatment of adult cases of brucellosis is very limited. Our study reports 7.84% failure of treatment and relapse rates with co-trimoxazole plus doxycycline that is significantly lower than reported by Rushan (15.7%).<sup>11</sup>

As such in order to prevent emergence of resistance to rifampicin, a good anti tuberculosis drug, changing of this agent with doxycycline is preferred whenever possible. In view of the good results shown in our study and comparison with other studies we feel that co-trimoxazole plus doxycycline may be a good selection for treatment of human brucellosis in Iranian nomads.

### CONCLUSIONS

This study shows that co-trimoxazole plus doxycycline regimen has a better therapeutic effect and lower treatment failure & relapse rate than doxycycline plus rifampicin regimen

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