

EARLY CLINICAL RESPONSE TO DIFFERENT THERAPEUTIC REGIMENS FOR HUMAN BRUCELLOSIS

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Abstract. Seventy-three cases of acute brucellosis were studied in relation to fever duration and hospital stay following different drug combinations, including gentamicin plus cotrimoxazole, rifampicin plus doxycycline, rifampicin plus cotrimoxazole, rifampicin plus tetracycline, streptomycin plus doxycycline, doxycycline plus cotrimoxazole, tetracycline plus cotrimoxazole, and tetracycline plus streptomycin. No statistical significant difference was found between these combinations regarding early clinical response in human brucellosis.

Several drugs have been shown to be effective against human brucellosis, including tetracycline,¹ streptomycin,² gentamicin,³ cotrimoxazole,⁴ rifampicin,⁵ and doxycycline.⁶ Combination chemotherapy with two drugs has been advocated to reduce the relapse rate of this disease.⁷ In this study, we compared the early clinical response of combinations of different therapeutic regimens in relation to defervescence and hospital stay.

PATIENTS AND METHODS

All patients with the diagnosis of acute brucellosis who were admitted to Abha General Hospital and Asir Central Hospital (Abha City, Saudi Arabia) during the period 1987–1994 inclusive were studied retrospectively. The study was approved by the Research and Ethics Committees of both hospitals. Cases with complications including endocarditis or neurobrucellosis were excluded. A total of 73 patients were included, 10 of whom had positive blood cultures for *Bruceella melitensis*, and 63 were diagnosed on clinical grounds by a positive standard tube agglutination test titer of 1:160 or higher. Forty patients had shown evidence of increasing agglutination titers taken one week or more after the initial test. The medical charts of these patients were reviewed with regard to age, sex, medication given, the time in days for their fevers to decrease to 37°C and remain normal after initiation of therapy, and the time to discharge in days after initiation of therapy.

The drug combinations used (Tables 1 and 2) were given at the usual recommended doses for children and adults. Gentamicin was given intravenously for 5–7 days. Streptomycin was given intramuscularly for 14 days. The other medications were given orally for 6–8 weeks.

The SPSS for Windows Statistical Package (SPSS, Inc., Chicago, IL) was used for statistical analysis. One-way analysis of variance was used to compare differences among all groups. The Duncan test was used to compare the difference between each two groups. Any *P* value less than or equal to 0.05 was considered statistically significant in both tests.

RESULTS

Seventy-three patients were studied. They had a mean \pm SD age of 23.68 ± 20.46 years (range = 8 months to 80 years); 57.5% were males. The mean \pm SD defervescence time for all groups was 4.32 ± 1.47 days (95% confidence interval [CI] = 3.97–4.66 days). The mean \pm SD time to

discharge for all groups was 7.75 ± 2.12 days (95% CI = 7.26–8.25 days).

Table 1 shows the fever response to the eight therapeutic regimens used. One-way analysis of the variance showed no statistical difference among all groups (*P* = 0.27); however, the Duncan test for comparing individual groups showed a significant difference between the group treated with rifampicin plus doxycycline (mean \pm SD = 3.33 ± 0.5 days) and the group treated with streptomycin plus doxycycline (mean \pm SD = 5.38 ± 1.41 days) (*P* < 0.05).

Table 2 compares the mean time to discharge between the eight therapeutic regimens. One-way analysis of the variance showed no statistical difference among all groups (*P* = 0.925). The Duncan test showed no significant difference between any two groups (*P* > 0.05).

DISCUSSION

The tetracycline plus streptomycin combination has been considered as the classic treatment for human brucellosis.⁷ Recently, the World Health Organization has recommended the use of a six-week course of doxycycline plus rifampicin therapy as the treatment of choice.⁸ Debate still continues regarding the best antibiotic combination for treating human brucellosis.⁹ Many factors are likely to govern the choice of antibiotics, including preference of the treating physician, age of the patient, availability of the drug, patient's tolerance, and appearance of side effects.

In this retrospective study, we compared the early clinical response to different drug combinations in relation to defervescence and hospital stay. The drug combinations used had been chosen by the treating physicians independently according to their clinical judgment. We did not find any significant difference among all the groups compared in relation to defervescence or hospital stay. However, lack of statistical significance could also be due to the low power of comparison since some of the groups had few patients. Prospective studies with larger number of patients in each group are needed to confirm this finding. When individual pairs of groups were compared, there was no significant difference between any two groups regarding hospital stay. However, the combination of rifampicin plus doxycycline was better than streptomycin plus doxycycline in relation to defervescence (3.33 days versus 5.38 days) (*P* < 0.05, by the Duncan test). A previous study showed no significant difference in the cure rate between rifampicin plus doxycycline and streptomycin plus doxycycline,⁹ and the fever response was

TABLE 1

Fever response to different therapeutic regimens in human brucellosis*

Drug combination†	No. of patients	Mean time to defervescence (days)	95% confidence interval (days)
GTC + CXZ	16	4.31	3.52–5.11
RFC + DXC	9	3.33	2.95–3.72‡
RFC + CXZ	10	4.4	2.92–5.68
RFC + TTC	11	4.56	3.45–5.64
STC + DXC	8	5.38	4.20–6.55‡
DXC + CXZ	3	4	1.52–6.48
TTC + CXZ	3	4	1.52–6.48
TTC + STC	13	4.23	3.48–5.00
Total	73	4.32	3.97–4.66

* One-way analysis of variance: degrees of freedom = 7, F ratio = 1.29, $P = 0.27$.

† GTC = gentamicin; CXZ = cotrimoxazole; RFC = rifampicin; DXC = doxycycline; TTC = tetracycline; STC = streptomycin.

‡ $P < 0.05$, by Duncan test.

slightly better in the group receiving streptomycin plus doxycycline (3.2 days versus 4.2 days), but the difference was not significant ($P > 0.2$). Other studies favored the streptomycin plus doxycycline combination in the over all cure rates without comparing the defervescence time.^{10,11} Our study was a retrospective analysis that explored the early clinical response to treatment, and it is difficult to compare the cure rates since compliance and continuation of therapy after discharge from the hospital is difficult to ascertain. After reviewing the medical charts, relapse was documented in five cases (6.8%). Three were in the group receiving gentamicin plus cotrimoxazole, one in the group receiving tetracycline plus streptomycin, and one in the group receiving doxycycline plus cotrimoxazole. In all five cases the patients stopped taking their medication after feeling better and they responded to a second course of treatment with the same drugs.

In conclusion, it appears that all of the drug combinations analyzed are equally effective in the treatment of *Brucella* infection. The choice of the drug combinations is likely to depend upon the age and sex of the patient (tetracyclines are contraindicated in children and pregnant women), as well as drug availability, presence of side effects, and patient's tolerance. Prospective studies will be needed for the proper evaluation of any differences in the final cure rates observed with these therapeutic regimens. This will entail recruiting large number of patients that will require multicenter collaboration.

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TABLE 2

Time to discharge using different therapeutic regimens in human brucellosis*

Drug combination†	No. of patients	Mean time to discharge (days)	95% confidence interval (days)
GTC + CXZ	16	7.69	6.61–8.77
RFC + DXC	9	7	5.37–8.63
RFC + CXZ	10	8	5.89–10.11
RFC + TTC	11	8.18	7.15–9.21
STC + DXC	8	8	5.51–10.49
DXC + CXZ	3	8.67	4.87–12.46
TTC + CXZ	3	7.67	1.42–13.92
TTC + STC	13	7.46	6.46–8.47
Total	73	7.75	7.26–8.25

* One-way analysis of variance: degrees of freedom = 7, F ratio = 0.355, $P = 0.925$. No two groups were significantly different ($P > 0.05$, by the Duncan test).

† For definitions of abbreviations, see Table 1.

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