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Problems and new developments in the treatment of acute and chronic brucellosis in man

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The aim of this communication is to illustrate the main difficulties in the treatment of human brucellosis and to point out some new developments in this field.

In spite of improvements in the control of animal brucellosis in some developed countries, human brucellosis is still one of the most important and frequent zoonoses. Information from the WHO indicates that there occur half a million cases per year. The disease can be imported in non-endemic areas by immigrant workers and tourists.

The active human brucellosis (isolation of *Brucella* sp., high titers of antibody, clinical symptoms, local infection or complication) must be treated with antibacterial chemotherapeutic agents. Without such a specific therapy the mortality rate reaches 1–6%.

Unfortunately many antibiotics are practically ineffective in brucellosis. Based on recommendation of the WHO, a combination of tetracyclines with streptomycin and occasionally with sulfonamides – for 3–6 weeks – was used as the basic therapeutic scheme for human brucellosis. Though this treatment was frequently successful in the acute form, relapse rates of 15–70% with occasional transition to the chronic form were observed. Patients compliance with such a long term ad hoc combination was in many cases unsatisfactory, side effects were not uncommon. Furthermore tetracyclines are contra-indicated in childhood.

In the chronic form, which is a much less defined entity, and where immunological components play an important role, the relevance of specific therapy is not yet clearly established.

In view of these therapeutic problems, alternative treatment forms were sought.

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In place of the older tetracyclines newer ones (doxycycline, minocycline) have been tried which can be administrated in relatively low doses and must be given only once or twice per day. Unfortunately, with longer administration of doxycycline, an increased number of photodermatoses have been observed (Rey et al., 1977). The first results with minocycline were encouraging, but they must be confirmed in more cases (Grasso, 1978). The possibility of vestibular dysfunction must also be borne in mind with this drug.

Recently, in a limited number of cases, streptomycin has been replaced by rifampicin alone or in combination with tetracycline for the treatment of acute brucellosis. The dosage was relatively high (900 mg daily) and the therapeutic results encouraging (Frottier, 1979). Though, the danger of quick development of bacterial resistance is well known with the administration of rifampicin alone.

In the last ten years, the fixed combination of trimethoprim plus sulfamethoxazole in a ratio of 1 : 5, co-trimoxazole[1] has been tested experimentally and clinically in human brucellosis. On the basis of a literature survey, the most important results of these trials are presented here.

In an in-vitro sensitivity test, Robertson et al. (1973) investigated the synergistic effect of sulfamethoxazole and trimethoprim. For 25 *Br. abortus* strains, the MIC of sulfamethoxazole was 2 μg/ml and that of trimethoprim 32 μg/ml. When the two agents were used in combination in the same ratio as their MIC values, a 16-fold potentiation between them was found, all strains being inhibited by a combination of 0.125 μg/ml of sulfamethoxazole and 2 μg/ml of trimethoprim.

Roux et al. (1974) investigated the sensitivity of 24 *Brucella* sp. strains to the combination of sulfamethoxazole + trimethoprim. 18 of the 24 tested strains were sensitive to the combination.

These results of in-vitro sensitivity tests proved a mutual synergism of the two components and a high efficacy of the combination.

The therapeutic results of 500 patients, who received the preparation for the treatment of brucellosis, could be analysed from 30 papers. In all patients the diagnosis was made clinically and serologically, and in many cases it was supported bacteriologically (positive culture). In most of the cases the daily dosage was 4–6 tablets or ampoules, respectively, and the duration of therapy 3–6 weeks. The therapeutic result was considered as successful, if the patient was cured by the first treatment course without relapse (very good result) or by a second course with the combination after a relapse (good result). The therapeutic result was considered as moderate, if the patient showed a relapse after a successful treatment with the combination and needed a treatment with another antibacterial agent. The therapeutic result was bad, if the treatment with the combination failed totally.

[1] e.g. Bactrim, Septrin. 1 tablet or ampoule for i.v. infusion = 80 mg trimethoprim + 400 mg sulfamethoxazole

365 patients (described in 22 papers) received co-trimoxazole in open non-comparative trials for the treatment of acute brucellosis (Table 1). Defervescence was obtained in an average of 4–5 days. The success rate (very good and good results) amounted to 88.8%.

The results of 8 patients, published in the paper of Antoniello et al. (1975), are particularly worth mentioning: these patients received the combination, as a second therapy after unsuccessful treatment with tetracycline + streptomycin. All patients could be immediately cured with the combination.

Twenty-five patients with symptomatic subacute or chronic brucellosis (described in 5 papers) were treated with the combination (Table 2). Defervescence was obtained in an average of 3.6 days (in 20 patients) and the success rate of the 25 treated patients was 88%.

In 4 studies, 110 further patients received co-trimoxazole in comparative trials versus tetracycline alone or tetracycline + streptomycin, respectively, for the treatment of acute brucellosis.

In Brescia (Italy) Sueri and Colonello (Sueri, 1972; Sueri, 1973; Sueri et al., 1974; Colonello, 1973) tested the efficacy of co-trimoxazole versus tetracycline in two studies after two different dosage schemes. In the first study 30 patients received co-trimoxazole 4 tablets per day and 32 patients tetracycline 2 g per day for 15–25 days. The relapse rate was 37% in the low-dose co-trimoxazole group and 19% in the tetracycline group, respectively. In a second study co-trimoxazole was given in a daily dosage of 4 tablets + 4 ampoules and tetracycline in a dosage of 3–4 g per day for 15 days. The relapse rate was 5% in the high-dose co-trimoxazole group and 11% in the tetracycline group, respectively. These studies demonstrated, that the response to co-trimoxazole was clearly dose-related.

Porto et al. (1974), Coimbra (Portugal) tested in a prospective, comparative trial the efficacy of co-trimoxazole (25 patients) versus tetracycline + streptomycin (27 patients). The treatment lasted in both groups 60 days. There was no significant difference between the two trial groups considering the relapse rate (28% versus 22%) and average time until defervescence (2.40 ± 1.07 days versus 2.96 ± 1.07 days).

Antoniello et al. (1975), Naples (Italy) compared the efficacy of co-trimoxazole versus tetracycline + streptomycin. 35 patients received co-trimoxazole and 10 patients were given the combination of tetracycline + streptomycin, in both groups for 21 days. In this trial the results obtained with co-trimoxazole were superior to those obtained with the combination of tetracycline + streptomycin, when the following parameters are considered: average days until defervescence (4 versus 9 days) and normalization of hepatomegaly (12 versus 16 days), splenomegaly (7 versus 13 days), blood sedimentation (5 versus 9 days) and haemoculture (3 versus 6 days).

In conclusion, co-trimoxazole proved to be at least equal to the control drugs in these comparative trials.

TREATMENT OF ACUTE BRUCELLOSIS WITH CO-TRIMOXAZOLE / THERAPEUTIC RESULTS

No. of paper	Author	Year	Country	Pathogen	Dosage per day		Duration of treatment in days	Bacteriology: culture from			No. of evaluable cases	Therapeutic result				No. of days until defervescence (average)
					tabl.	amp.		blood	bone marrow	stool		very good	good	moderate	bad	
1	Antoniello et al.	1975	Italy	Br. melitensis	3x2		21	X	X		8 *	8				
2	Ariza et al.	1977	Spain	Br. melitensis	2x3 2x2		15 30	X			31	21		9	1	1-20 (8)
3	Barba et al.	1972	Italy	"	2x1-2		10-40				7	7				1-3 (2,5)
4	Billi et al.	1971	Italy	?	4		10				3	3				1-4
5	Cantalamessa	1972	Italy	?	2x2		14-28	X			14	12	2			3-7 (5,1)
6	Casanova et al.	1975	France	?	3-6		10-42	X			28	23			5	3-7
7	Daikos et al.	1973	Greece	Br. melitensis	 4-8	2x2	10 (6 pat.) 15-30	X			86	76	2		8	2-8
8	D'Alessandro et al.	1973	Italy	?	3x2		20				20	18		2		1-9 (4,7)
9	Farid et al.	1970	Egypt	Br. abortus	2x1		10				1	1				4
10	Fiori et al.	1978	Italy	9 Br. abortus 3 Br. suis	3x2		4-26	X	X		47	45		2		1-10 (3,9)
11	Giunchi et al.	1972	Italy	Br. melitensis	4-6		21-28	X	X		27	24		2	1	1-11 (3,9)
12	Guevara	1974	Peru	Br. melitensis	2x1-2 spoon 2x½-1 " 2x¼-½ "		30 30 30	X			3	3				
13	Hassan et al.	1971	Egypt	Br. melitensis	2x2-4		21-42	X			8	5	2	1		2-7 (4)
14	Lal et al.	1970	England	Br. abortus	2-3x2		84-140 (in intervals)		X		4	3			1	1-2
15	Minoprio	1975	Argentina	Br. melitensis	2x4 2x2		5 25	X	X		14	14				(6,4)
16	Niutta et al.	1974	Italy	?	?		10-15				13	12	1			2-9 (3,8)
17	O'Brien et al.	1974	England	Br. abortus	?		10				1				1	
18	O'Meara et al.	1974	England	Br. melitensis	3x2 2x2		60 305	X			1	1				
19	Paschetta	1972	Italy	?	4		30	X		X	14	14				2-12 (5,6)
20	Rigatos et al.	1975	Greece	Br. melitensis	3x1-2		at least 21				30	24		4	2	1-18 (5)
21	Siasoco et al.	1972	Philippines	Br. abortus	 2x2	2x2	2 12	?			1	1				2,5
22	Visco et al.	1975	Italy	?		6-8	8-25				4	2			2	6-9
TOTAL 22 PAPERS DESCRIBING CASES:											365	317	7	20	21	
SUCCESS RATE:												88,8 %				

* SECOND THERAPY AFTER UNSUCCESSFUL TREATMENT WITH TETRACYCLINE + STREPTOMYCIN

TABLE 2

TREATMENT OF SUBACUTE AND CHRONIC BRUCELLOSIS WITH CO-TRIMOXAZOLE

No. of paper	Author	Year	Country	Pathogen	Dosage per day (tabl.)	Duration of treatment in days	No. of evaluable cases	Therapeutic result			No. of days until defervescence (average)
								very good	good	moderate	
1	Barba et al.	1972	Italy	Br. melitensis	2x2 then 3 then 1	20 10 30	1	1			
2	Ciaccheri et al.	1973	Italy	Br. melitensis	6	42	1	1			
3	Guevara	1974	Peru	Br. melitensis	2x2 spoons 2x1 " 2x½ "	30 30 30	2			2	
4	Hyman	1970	South Africa	Br. melitensis + abortus	2x2 then 2x1	~120	1	1			
5	Kontoyannis	1975	Greece	Br. melitensis	2x3 then 2x2	2-7 ~ 60	20	7	11	2	2-7 (~3.6)
TOTAL 5 PAPERS DESCRIBING CASES: SUCCESS RATE:							25	10	11	4	
								88 %			

The tolerance of co-trimoxazole was satisfactory, no severe adverse reactions were noticed. Skin reactions occurred in 4.2% and gastrointestinal side effects in 2.6% of the cases.

These results indicate that co-trimoxazole can be recommended as an effective and safe drug for the treatment of acute brucellosis. In subacute and chronic brucellosis, the findings available so far are encouraging and suggest further trials for confirmation.

References may be requested from the author.