Erythromycin versus tetracycline for treatment of Mediterranean spotted fever

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SUMMARY Eighty one children aged between 1 and 13 years participated in a randomised comparative trial of tetracycline hydrochloride and erythromycin stearate for treatment of Mediterranean spotted fever. Both therapeutic regimens proved effective, but in patients treated with tetracycline both clinical symptoms and fever disappeared significantly more quickly. Likewise, when those patients who began treatment within the first 72 hours of illness are considered the febrile period had a significantly shorter duration in the group treated with tetracycline. One patient was switched to tetracycline because there was no improvement of clinical manifestations, with persistence of fever, myalgias, and prostration, after receiving eight days of treatment with erythromycin. These results suggest that tetracyclines are superior to erythromycin in the treatment of Mediterranean spotted fever.

Mediterranean spotted fever is an acute infectious disease caused by *Rickettsia conorii*. During the last few years there has been a resurgence of this disease in Mediterranean countries.¹ Likewise, acquired sporadic cases have recently been reported in northern Europe^{2,3} and the United States.⁴ Treatment with tetracyclines or chloramphenicol is effective, but tetracyclines can cause undesirable side effects, especially in children under the age of 8 years, and with chloramphenicol there is a risk of bone marrow toxicity.

Some cell culture studies have shown that erythromycin is an effective in vitro agent against various species of rickettsiae.^{5,6} We undertook a randomised clinical trial comparing tetracycline hydrochloride with erythromycin stearate to see if erythromycin could constitute a useful and less toxic therapeutic alternative in children with Mediterranean spotted fever.

Patients and methods

We included in the study all children diagnosed as having Mediterranean spotted fever and admitted during 1983 and 1984 to the Hospital de Sant Llätzer, Terrassa, and Clínica Infantil del Nen Jesús, Sabadell (Spain). Eight patients, who in the week preceding the study had received antibiotics,

were not included in the trial; neither were those with a history of allergy to tetracyclines and erythromycin.

The diagnostic criteria of Mediterranean spotted fever were as follows: presence of typical clinical manifestations plus tache noire and/or a positive serologic result by means of indirect immunofluorescence against *R. conorii* (a fourfold increase in the titre of acute serum over convalescent serum or a titre over 1:40 in those few cases in whom only one test was possible).

Eighty one children fulfilled the conditions for inclusion in the study; 12 who did not were excluded. Patients were treated at random with either erythromycin stearate or tetracycline hydrochloride according to a set of computer generated aleatory numbers. Over a period of 10 days patients received daily doses of either erythromycin 50 mg/kg (12.5 mg/kg four times a day) or tetracycline 40 mg/kg (10 mg/kg four times a day). Temperature was taken at least every six hours by nursing personnel not related to the study, and symptoms were evaluated daily until disappearance.

On admission the following laboratory studies were carried out: haemogram, erythrocyte sedimentation rate, urea, creatinine, total bilirubin, and electrolyte concentrations, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transami-

mase, alkaline phosphatase, creatine kinase, and lactate dehydrogenase activities, prothrombin time, total protein and protein electrophoresis, urinalysis, Weil-Felix reaction, indirect immunofluorescence against *R. conorii*, and blood cultures. Electrocardiograms and chest x ray films were also obtained. At the end of three weeks a clinical revision and new serological, haematological, and biochemical determinations were made. Apyrexia was defined as a temperature of less than 37°C taken in the armpit. Student's *t* test was used for statistical analysis.

Results

Of the 81 patients studied, 50 were boys and 31 girls. Ages ranged between 1 and 13 years. Thirty four patients received tetracycline hydrochloride and 46 erythromycin. One patient began treatment with erythromycin but was later switched to tetracycline. This 7 year old boy presented with fever, headache, and myalgias of 24 hours' duration. On physical examination a tache noire was noticed on the scalp accompanied by enlarged lymph nodes and maculopapular rash affecting the palms of the hands and the soles of the feet. There was no improvement of clinical manifestations, with persistence of high fever (39–40°C), headache, myalgias, and prostration on the eighth day of treatment with erythromycin. After two days of treatment with tetracycline fever subsided and clinical symptoms markedly improved. As the patient had not completed the prescribed 10 day course of antibiotic regimen this case was not evaluated in the results, and we think that this must be considered as an example of erythromycin proving ineffective.

Mean (SD) ages of the patients were similar in both groups (6.9 (2.2) years in the group treated with tetracycline *v* 5.9 (2.6) years in the group treated with erythromycin). Maximal temperatures recorded on admission were also similar (39.6 (0.6)°C *v* 39.5 (0.7)°C, respectively). The interval

Figure Accumulated percentage of afebrile patients on successive days after the beginning of treatment with tetracycline hydrochloride (solid line) or erythromycin stearate (broken line).

between first occurrence of symptoms and beginning of treatment was somewhat longer in the group treated with tetracycline (4.3 (1.8) days) than in the group treated with erythromycin (3.5 (1.7) days); this difference was significant ($p < 0.05$).

All patients recovered uneventfully. After the beginning of treatment fever and clinical symptoms disappeared significantly more quickly in the group treated with tetracycline (Table). Also the total duration of fever in this group was shorter, although the difference was not significant. When only the 38 patients who began treatment within the first three days of illness were considered the total duration of fever was significantly shorter ($p < 0.01$) in the 14 patients treated with tetracycline (5.0 (0.8) days) than in the 24 patients treated with erythromycin (6.3 (1.7) days). The Figure shows the accumulated percentage of afebrile patients in each group on successive days after the beginning of treatment. No relapses were observed. One patient had side effects (diarrhoea), which may be attributed to erythromycin, but in this single case suspension of the trial was not necessary.

Discussion

Mediterranean spotted fever is a benign disease,^{7 8} fatalities from which are rare (mortality of 0–2%).^{9 10} On the other hand, clinical manifestations are usually severe, with intense malaise. The natural duration of Mediterranean spotted fever is from 10 to 15 days.¹¹ Treatment with tetracyclines or chloramphenicol shortens this symptomatic period and avoids possible serious complications. The risk of bone marrow toxicity is an argument against the use

Table Results of a therapeutic trial, tetracycline *v* erythromycin, in children with Mediterranean spotted fever. Values are mean (SD)

	Treatment group		<i>p</i> Value
	Tetracycline	Erythromycin	
n=	34	46	
Apyrexia after treatment (days)	2.2 (1.0)	3.5 (1.5)	<0.0005
Disappearance of symptoms (days)	2.4 (1.0)	3.4 (1.4)	<0.0005
Duration of febrile period (days)	6.5 (2.1)	7.0 (1.6)	NS

of chloramphenicol in such a generally benign disease. Untoward effects of the tetracyclines in children aged under 8 include staining of the teeth, temporary retardation of bone growth, and hypoplastic enamel.¹² For this reason the use of tetracycline antibiotics in children has been restricted, except in some diseases, such as rickettsiosis, brucellosis, and psittacosis.¹³ In fact, staining of the teeth is related to the accumulative doses administered during childhood.¹⁴ Thus it is more important to suspend the use of tetracyclines in daily paediatric practice than to avoid administration of a single course of the drug.

This study shows that tetracycline hydrochloride is superior to erythromycin stearate in the treatment of Mediterranean spotted fever. Symptoms and fever disappeared significantly more rapidly in the group treated with tetracycline. Although the difference in the total duration of fever between the two groups was not significant, this is probably due to the fact that treatment was started more promptly in the group treated with erythromycin. In fact, when only those patients who began treatment within the first three days of illness are considered the total duration of the febrile period was significantly shorter in the group treated with tetracycline. Differences in the clinical point of view between patients on tetracycline and patients on erythromycin, however, were less apparent (delay of apyrexia of about 1.5 days), except in one case of unsuccessful treatment with erythromycin.

In conclusion, erythromycin could constitute an acceptable therapeutic alternative to tetracycline for children aged under 8 years with Mediterranean spotted fever, except those with severe symptoms or serious illness.

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