PAPERS AND ORIGINALS

Further experience with amoxycillin in typhoid fever in children

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Summary

A study of 155 children with typhoid fever proved by blood culture showed that amoxycillin was superior to chloramphenicol with regard to clinical and temperature response and relapse and carrier rates. This confirmed the findings of a randomised clinical trial on 200 children with typhoid fever and lends support to the value of amoxycillin in this disease.

Introduction

Chloramphenicol has long been regarded as the treatment of choice for typhoid fever. Our policy of continuing chloramphenicol treatment in full dose for 21 days irrespective of the period of temperature response^{1,2} resulted in low rates of relapse (2-5%) and convalescent carriers (2-3%). In Durban, however, the response to chloramphenicol recently has not been as satisfactory as formerly, despite the fact that we have not encountered resistant strains of *Salmonella typhi* in this area. From elsewhere there are reports on the emergence of strains of *S typhi* resistant to chloramphenicol,³⁻⁸ and this has highlighted the need for an alternative drug for typhoid fever.

We have recently compared amoxycillin and chloramphenicol in a randomised trial in 200 children with typhoid.⁹ We found that both the relapse and the carrier rate in the 100 children treated with chloramphenicol was 5%. Only 2% relapsed after amoxycillin, and there were no carriers among those initially treated with this drug. Amoxycillin was also found to be significantly better than chloramphenicol with regard to clinical and temperature response. In a study in adults¹⁰ with typhoid fever from the same endemic areas amoxycillin produced satisfactory results.

Since the completion of the first therapeutic trial, a further 155 children with proved typhoid have been studied. This paper reports the outcome in these patients.

Patients and methods

The 155 African children were not randomly allotted to treatment with either amoxycillin or chloramphenicol. Because of the findings in the previous randomised trial of 200 patients this was thought to be unnecessary. The choice of drug was left to the paediatrician under whom patients were initially admitted. Every case came under my personal care, however, and all were submitted to the same dosage schedules, investigations, and follow-up study.

Investigations—On admission, cultures of blood, stool, and urine were done. In addition to positive blood cultures, 24 children had positive stool cultures, two positive urine cultures, and three a positive culture for both stool and urine. Agglutination titres were significant ($\geq 1/320$) on admission or became so thereafter in 74%. Blood cultures were repeated if fever was sustained or recurred after an afebrile period. Stool and urine samples were recultured after treatment ended until at least three successive negative cultures were obtained. Before treatment started blood urea levels were measured, urine was examined chemically and microscopically, and liver function tests were performed. These investigations were repeated on the 14th and 21st days of treatment, and more often when indicated. Full blood counts were done before treatment started and were repeated at least weekly during treatment and more often if indicated. In-vitro sensitivity tests and phage typing were done in all cases.

Dosage—The 85 children who were given amoxycillin 100 mg/kg/day formed group 1, and the 70 who were given chloramphenicol (Parke Davies) 50 mg/kg/day formed group 2. Both drugs were given in four divided doses daily for 21 days. Four gravely ill children, three in group 1, and one in group 2, received a three-day course of prednisolone.

Clinical details—The age distribution was similar in the two treatment groups. Fifty were aged 2 to 6 years and 105 were aged 7 to 11 years. The median for both groups was 8 years.

Nutrition—The nutritional status of both groups was comparable.

Length of history—The length of illness before admission was known in all but five cases. This ranged from one to 30 days, with a median of seven days in both treatment groups.

Severity—On the basis of toxæmia, delirium, signs of meningeal irritation, the presence of complications, etc, the two groups were comparable. Eighty-nine per cent of group 1 and 86% of group 2 were seriously ill.

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Complications present on admission—There was a similar incidence of complications in the two groups (table I).

TABLE I—Complications present on admission in 155 children with typhoid fever

Complications	Amoxycillin (group 1)	Chloramphenicol (group 2)
Bronchopneumonia ..	18	19
Lobar pneumonia ..	1	1
Neurological ..	10	12*
Hepatitis ..	5	4
Nephritis ..	1	0
Myocarditis ..	1	0
Intestinal haemorrhage ..	2	2

*Includes one case of typhoid meningitis.

Results

Clinical response was judged by relief of toxæmia, improvement in wellbeing, and return of appetite. There was a satisfactory clinical response within five days in 89% of group 1, while only 54% of group 2 responded satisfactorily within this same period. This difference was highly significant ($P < 0.001$). In neither group could the clinical response be correlated with the severity of illness or length of history. In both groups the clinical response often preceded the temperature response by many days.

The response of temperature is shown in table II. The number who responded satisfactorily without return of fever was also significantly better ($P < 0.001$) in group 1. The median was seven days in group 1 and eight days in group 2.

TABLE II—Comparison of temperature response in two groups of children with typhoid fever treated with amoxycillin or chloramphenicol

Temperature response	Amoxycillin (group 1)	Chloramphenicol (group 2)
No return of fever ..	75 (88%)	46 (66%)
Range (days) ..	2-14	3-16
Median (days) ..	7	8 (5 became carriers)
Initial response, return of fever later ..	4 (5%)	11 (16%) (1 relapsed)
No response, fever throughout course ..	2 (2%)	7 (10%) (2 blood cultures repeatedly positive)
Low grade fever at start of drug	4 (5%)	6 (8%) (1 became carrier)

Haematological study—On admission anaemia of less than 10 g/dl was present in 43% of group 1 and 33% of group 2. Leucocyte counts ranged from $2.3 \times 10^9/l$ to $25.0 \times 10^9/l$ ($2300-25\,000/mm^3$) with a median of $7 \times 10^9/l$ ($7000/mm^3$) in both groups. A moderate thrombocytopenia was present in 16% of both groups, while severe thrombocytopenia was apparent in 5% of group 1 and 4% of group 2 before treatment.

Study of liver function—Five children in group 1 and four in group 2 were jaundiced; they had raised concentrations of serum bilirubin and transaminase on admission, which suggested a diagnosis of hepatitis. A further four in group 1 and three in group 2 had slightly raised serum bilirubin but normal transaminase levels. Reticulocyte counts in these children indicated that mild haemolysis was the probable cause. Serum transaminase levels before treatment were raised in 65% of group 1 and 63% of group 2. In most the concentrations returned to normal during treatment, and in the rest they did so during the period of observation after treatment.

Renal function study—Except in three children with schistosomiasis and one with acute nephritis urine examinations showed nothing abnormal in either group. Dehydration present on admission accounted for raised blood urea concentrations in eight of group 1 and seven of group 2. These all rapidly returned to normal once the patients were rehydrated. In all the remaining patients in both groups blood urea levels remained normal throughout.

Bacteriological study—Repeat blood cultures were performed in 111 patients (table III) because temperatures were increased beyond day three or there was return of fever after an afebrile period. *S. typhi* was recovered from five patients in group 1 at day 5 and from 14 in group 2 at days 4 to 17.

TABLE III—Repeat blood cultures in 111 children with typhoid fever during treatment with amoxycillin or chloramphenicol

Group	No of patients who had repeat cultures	Total positive	Positive								
			Day of treatment								
			4	5	6	7	8	12	16	17	
1 (Amoxycillin) ..	53	5		5							
2 (Chloramphenicol) ..	58	14	3	2	4	1	1	1	1*	1*	

*Febrile throughout. Treatment changed to amoxycillin. All subsequent cultures negative.

Outcome—All patients in both groups recovered. In group 1 no relapses occurred and no children became carriers. In group 2 one relapse occurred with reisolation of *S. typhi* from the blood 19, 20, and 22 days after treatment stopped. This child responded satisfactorily to a course of amoxycillin. There were six temporary convalescent carriers in group 2. After treatment stools were positive in four, urine in one, and both stool and urine in one. These six received a full 21-day course of amoxycillin. Thereafter all cultures remained negative over a long period of observation. Two further patients in group 2 failed to respond to chloramphenicol: they remained ill and febrile. Repeat blood cultures were positive on days 5, 13, 14, and 17 in one child and on days 10 and 16 in the other. Treatment was changed to amoxycillin and both responded promptly and recovered completely.

Phage typing—The predominant strain was A (88%). There was one example each of types 42 and 46, and 10 of degraded Vi. Seven were not typable.

In-vitro sensitivity—The *S. typhi* strains recovered from all patients before treatment were sensitive to both amoxycillin and chloramphenicol in disc diffusion. Some strains were also subjected to minimum inhibitory concentration tests, which showed them to be sensitive. The organisms reisolated during treatment and from the one patient who relapsed and the six carriers in group 2 were still sensitive to both drugs.

Adverse reactions—After nine days of amoxycillin treatment one child developed a maculoerythematous rash, which was probably a drug reaction. There were no other adverse reactions to either drug.

Discussion

In this trial amoxycillin gave better results than chloramphenicol. Clinical and temperature responses were significantly better than those obtained with chloramphenicol. Bacteriological response was also better. There were no relapses or cases of children becoming carriers after amoxycillin, whereas two children failed to respond to chloramphenicol, one relapsed, and six became carriers after treatment.

This study confirms our earlier findings.⁹ Amoxycillin has now been used to treat 185 children with proved typhoid fever, and there have been only two relapses (1%). The only case of the carrier state after amoxycillin occurred in a patient in the first study who initially received chloramphenicol and relapsed. After amoxycillin this patient had one positive urine culture. Thus no carriers were encountered among patients initially treated with amoxycillin.

Among 170 patients treated with chloramphenicol in this and the earlier trial two patients failed to respond, one relapsed, and 11 became carriers. This bacteriological failure rate of 11% supports our experience in Durban in the past few years that chloramphenicol is not as effective as formerly.

No correlation could be found between the bacteriological failure of chloramphenicol and length of history, nutritional state, or concurrent disease. There did not seem to be a relation between failures and white blood cell counts. The mean was $6.857 \times 10^9/l$ ($6857/mm^3$). At the start of treatment the mean neutrophil count was 68% and that of lymphocytes 27%. Serum protein levels did not seem to be a factor. The mean serum globulin level was 44 g/l. As electrophoretic studies were not routinely performed, however, the γ -fraction of the globulins was not known. The strains of organism in this area has not

changed and sensitivity to chloramphenicol is constant. There has been no change in the product used, the dose, or length of treatment. The reason why the response to chloramphenicol has become less satisfactory remains obscure.

Reports of treatment of typhoid carriers with amoxycillin cover few cases.^{11 12} So far nine of the 11 children who became carriers after chloramphenicol treatment have been given a single 21-day course of amoxycillin with success. This contrasts favourably with past experience, when ampicillin, in high doses over long periods, sometimes failed. In view of the success in treating these few carriers it seems worth while to evaluate amoxycillin in the management of the asymptomatic carrier state in different areas where typhoid fever is endemic.

Amoxycillin is undoubtedly safe and readily acceptable, and on the evidence of its success in symptomatic typhoid fever may well become the drug of first choice in this disease.

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Amoxycillin in treatment of typhoid fever in patients with haematological contraindications to chloramphenicol

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Summary

Thirty adults with proved typhoid fever were treated with amoxycillin 1 g six-hourly by mouth for an average of 14 days because of haematological contraindications to chloramphenicol. Eighteen patients were Egyptian men with the Mediterranean variety of glucose-6-phosphate dehydrogenase deficiency and an enzyme activity in the red cells ranging from 0 to 3%, and 12 patients had a history of severe but reversible myelosuppression after eight to 12 days' treatment with chloramphenicol 1.5-2 g daily. The clinical and bacteriological responses in this group of patients were compared with those of 30 haematologically normal patients of comparable age and sex treated with chloramphenicol.

The results showed that amoxycillin is an effective alternative to chloramphenicol for treating typhoid fever in patients with haematological contraindications to chloramphenicol.

Introduction

Although typhoid fever is not endemic in Egypt, it is a common cause of pyrexia of undetermined origin in adult Egyptians. This fact is overemphasised by general practitioners, who usually start treating patients with pyrexia of undetermined origin with chloramphenicol before the laboratory tests for the diagnosis of enterica have proved or disproved the presumptive diagnosis of typhoid fever. This, together with the prevailing practice by

many ear, nose, and throat specialists of using chloramphenicol as the drug of choice for upper respiratory tract and ear infections, has resulted in excessive use of chloramphenicol in medical practice in Egypt.

Among the many patients subjected to one or several courses of chloramphenicol some have shown definite but transient haematological toxicity characterised by a delayed clinical onset of moderate depression of bone marrow cellularity and a single reversible cytopenia or pancytopenia. This type of toxicity, described by Best¹ as intermediate between the irreversible aplasia of delayed onset and the dose-dependent transient erythroid depression, is the commonest form of chloramphenicol-induced blood dyscrasia observed by Egyptian haematologists. It is considered to be an idiosyncratic reaction to chloramphenicol of transient type which leads to a short-lived episode of bone marrow aplasia of either one or more of the three elements of haematopoiesis. In addition to the gradually increasing number of patients belonging to this category, a fixed percentage of Egyptian men suffer from the Mediterranean variety of glucose-6-phosphate dehydrogenase deficiency.² These patients may develop haemolysis and jaundice with fever, and their haemolysis may be aggravated by the administration of challenging agents such as chloramphenicol to the enzyme deficient red cells.

These two facts prompted us to carry out a clinical trial of an alternative drug that could replace chloramphenicol in the treatment of typhoid fever in these patients. Amoxycillin (D(-)- α -amino-p-hydroxybenzylpenicillin trihydrate) 1 g six-hourly was chosen for the trial in view of its safety and its considerably higher serum concentrations than ampicillin.³ Reports have shown the success of amoxycillin in treating typhoid fever in several groups of patients.⁴⁻⁶ We believed that running a clinical trial of amoxycillin in the treatment of typhoid fever in these two groups of patients was justifiable.

Patients and methods

Thirty adults suffering from typhoid fever and ranging in age from 16 to 38 years were included in the trial. Eighteen were men suffering from severe Mediterranean glucose-6-phosphate dehydro-

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