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REPORT

EFFECTS OF PEFLOXACIN IN MULTI DRUG RESISTANT TYPHOID FEVER

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In 28 children, with bacteriologically and/or serologically diagnosed typhoid fever treated at CMH, Rawalpindi in 2003, first one of the three recommended drugs (viz. chloramphenicol, amoxycillin or co-trimoxazole) was given for 7 days for defervescence to occur. In those who failed to respond a second trial of therapy with one of the other two drugs was initiated, after excluding the first drug. A second failure of therapy was taken as an indication to use pefloxacin singly. Finally, 18 (64.3%) cases responded to chloramphenicol or amoxycillin or co-trimoxazole. Pefloxacin was used in 10(35.7%) cases. The failure rate of treatment with chloramphenicol was 50%, with amoxycillin 71.4% with co-trimoxazole 75% and 0% with pefloxacin. An analysis of the 28 cases revealed that apart from fever (in 100%), splenomegaly (in 82.1%) was the most important clinical indicator to diagnosis. along with absolute eosinopenia (in 71.4%). There were no major complications, except 2 cases with typhoid hepatitis that responded to choramphenicol and co-trimoxazole, respectively. Blood culture grew *Salmonella typhi* in 7 cases of which 5 (72%) were multi drug resistant *S. typhi.*

Keywords: Chloramphenicol, typhoid fever, cotrimoxazole, Pefloxacin.

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INTRODUCTION

Typhoid fever is a major endemic health problem among children in developing countries of the world. In addition to this, since 1990 there has been an emergence of multi-drug resistant typhoid fever in various parts of Pakistan (Osler, 1912; Lin *et al.,* 2000; Thong *et al.,* 2000; Luby *et al.,* 1998 and Bhutto *et al.,* 1997). In this study, we have compared the clinical features and laboratory findings in children with typhoid fever who responded to treatment with one of the three recommended drugs (5) viz. chloramphenicol, amoxycillin or cotrimoxazole, with those who at the end required pefloxacin therapy.

MATERIALS AND METHODS

In 2003, 100 children with a clinical diagnosis of typhoid fever were admitted to three different units with multiple pediatricians treating them. The clinical diagnosis of typhoid fever based on the progressive development of listlessness and a persistent fever, lasting longer than 4 days was confirmed by, (i) isolation of *S. typhi* by blood culture, or (ii) Widal agglutination titres of 1:160 or greater for *S. typhi* O antigen, or (iii) a positive countercurrent immunoelectrophoresis test to detect serum *S. typhi* antigen (Jesudason *et al*., 1996; WHO Report and Tsang & Chau 1981) whenever Widal's test was not being done in the laboratory. The diagnosis was bacteriologically and/or serologically confirmed in only 48. Of these 48 proven cases, 20 had received either an unreasonable and random treatment before admission, such as using Pefloxacin or norfloxacin or a combination of two recommended drugs without any laboratory evidence of typhoid fever or had received inadequate dosages of one of the recommended drug or it was changed unwisely to another drug without even 5 days trial. Excluding these patients, data of only 28 patients who were initially treated with either chloramphenicol or amoxycillin or co-trimoxazole in recommended dosages (Feigin, 1992 and Luby *et al*., 1998) for a minimum period of 5 to 7 days, awaiting both

Table 1
Clinical features of children with typhoid fever

Feature	Group A (n=18)	Group B (n= 10)	P value
Age (yr)	7.58 ± 1.83 (4.5-11.5)	7.4 ± 2.3(4-12)	NS
Duration of fever at admission (days)	12.74 ± 4.70 (7-25)	20.4 ± 14.98 (8-57)	NS
Defervescence (days)	327 ± 1.71 (1-6)	4.5 ± 1.70 (2-7)	NS

Values are mean SD, Range is parenhesis, student's 't' test: not significant.

Table 2
Clinical features of children with typhoid fever

Symptom/Sign	All patients N =28 N/(%)	Group A N=18 N/(%)	Group 13* N=10 N/(%)
Fever with chills	14 (50)	10 (55.5)	4 (40)
Toxic look	9 (32.2)	5 (27.9)	4 (40)
Headache	4 (14.4)	3 (16.6)	1 (10)
Vomiting	8 (28.7)	4 (22.2)	4 (40)
Diarrhea	8 (28.7)	6 (33.5)	2 (20)
Abdominal pain	9 (32.2)	3 (16.7)	6 (60)
Hepatomegaly>2cm	9 (32.2)	8 (44.5)	1 (10)
Tender hepatomeg	2 (7. 2)	2 (11.2)	0 (0)
Splenomegaly	23 (82.4)	15 (83.3)	8 (80)
Convulsions	1 (3.6)	1 (5.5)	0 (0)
Meningitis	1 (3.6)	1 (5.5)	0 (0)
Respiratory (cough)	6 (21.5)	5 (27.9)	1 (10)

defervescence and the antibiotic sensitivity report were analysed. Sensitivity of antibiotic discs was tested by the Kirby-Bauer disk diffusion technique (Mitchell, 1997). In the 7 bacteriologically confirmed patients, this report was used as a guideline for deciding the drug to be used. In the remaining 21 patients whose diagnosis was confirmed by only serological methods, if defervescence, reduction in lever peak and decrease in spleen and liver size did not occur within 7 days the drug was omitted. The child was now treated with one of the other two recommended drugs, for another 7 days. A second failure of therapy led to omitting the drug, and was taken as an indication for using Pefloxacin. Pefloxacin was given initially intravenously (5-10 mg/kg/day in b.d. doses), and once defervescence occurred, therapy was changed to oral rout (7.5-15 mg/kg/day in b.d. doses), for a total 10-days period (Murdoch *et al*., 1998).

A complete hemogram and liver function tests were done in all the patients, and were interpreted as per age related values (Parry *et al*., 1998). Chest radiograph, ECG and CSF examination were done when indicated. Statistical comparison between the two groups viz. those who responded to a recommended drug (Group A) and those who required Pefloxacin (Group B) was performed using student's 't' test ($p < 0.05$ was considered significant) and X2 test (X2 value representing 95% confidence level was considered significant).

RESULTS

Of the 28 patients, 18 (Group A) responded to chloramphenicol, amoxycillin or cotrimoxazole, and 10 (Group B) to Pefloxacin. There were no clinical features to differentiate these 2 groups (Tables 1 and 2). As the first line drug, chloramphenicol was successful in 12/21 (57.1%) cases, amoxycillin in 1/4 (25%) and co-trimoxazole in 0/2 (0%). As the second line drug, chloramphenicol was successful in 2/3 (66.7%) cases, amoxycillin in 1/2 (33.3%), and co-trimoxazole in 2/5 (40%). The overall success rate of treatment with chloramphenicol was 50%, with amoxycillin 28.6% with co-trimoxazole 25%. All the 10 patients eventually treated with Pefloxacin responded well. In 4, Pefloxacin was used after first line treatment (with chloramphenicol in 3 and co-trimoxazole in 1) failed, with deterioration of the toxic look of the child. Only in 1 of these 4 cases, antibiotic sensitivity report confirmed multi-drug resistant *S. typhi*. In another 6 cases Pefloxacin was used as the third line drug. Even though antibiotic sensitivity report in 4 of these 6 cases confirmed multi-drug resistant *S. typhi*, the clinical status of the child did not discourage a second trial with another recommended drug. But eventually in all the 4 patients, need for Pefloxacin became obvious. Two patients had hepatitis and they responded to chloramphenicol and co-trimoxazole, respectively. No other complications were observed.

DISCUSSION

Early diagnosis of multi-drug resistant *S. typhi* is a therapeutic challenge. Blood cultures were positive in only about 40% of children during the initial stage of typhoid fever (Feigin, 1992). Also, prior treatment with antibiotics is known to inhibit growth on blood cultures and depress Widal titres (Feigin, 1992; Thong *et al*., 2000 and WHO Expert Committee). Although a clinical diagnosis of typhoid fever was made in 124 children admitted in 1991 only 48 (38.7%) were bacteriologically and/or serologically confirmed 'Recent reports' (Osler, 1912; Lin *et al*., 2000; Sinha, 1999 and Brown *et al*., 1994) suggest a high percentage (64 to 82%) of multi-drug resistant typhoid fever cases. In our cases, only in 5 (17.8%) of 28 patients multi-drug resistant *S. typhi* were isolated. However, clinically multi-drug resistance was found in 11 (39.3%) of 28 patients treated with various drugs. Pefloxacin was used in 10 (35.7%) patients, and in 6 of them two trials with a recommended drug had failed to initiate defervescence. A third trial with another recommended drug was not considered practical in a child with fever of more than 2 weeks duration. We did not find any clinical feature to identify multi-drug resistant typhoid fever (Tables l and 2) or any increased incidence of complications. Bhutta ZA (Sinha *et al.,* 1999) has also found no increased incidence of complications. Other (Osler, 1912; Lin *et al*., 2000 and Brown *et al*., 1994) have reported increased incidence of complications in their multi-drug resistant cases such as encephalopathy, shock, gastrointestinal haemorrhage, meningitis, myocarditis and hepatitis. In our study, 2 patients of typhoid hepatitis, Group II (severe) according to the clinicobiochemical classification (Bauer *et al*., 1966), responded to chloramphenicol and co-trimoxazole, respectively. One interesting finding was in a 7-year-old boy with history of fever for 60 days and positive Widal's test on admission. Fever continued for a further 12-day period, during treatment with co-trimoxazole and later chloramphenicol. Use of Pefloxacin led to defervescence within 4 days. Adam (1989) has reported 12 cases with multi-drug resistant typhoid fever with history of fever for 6 to 7 weeks, till use of Pefloxacin led to defervescence. It seems that unlike in routine typhoid fever cases, natural defervescence does not occur after 3 to 4 weeks in multi-drug resistant cases. Eosinopenia, as seen in 71.4% patients in our study, may be useful tool in the diagnosis of typhoid fever in children with prolonged fever and hepatosplenomegaly (Rowe *et al*., 1995 and Luby *et al*., 1998).

Pefloxacin is not licenced for use in children because of its possible adverse effect on growing cartilage. Though a long-term follow-up is needed to detect such a complication, we did not encounter any other complications with Pefloxacin use. A survey done in Military Hospital, Rawalpindi (Shanahan *et al*., 2000 and WHO Tech Report) revealed that

147 pediatricians in Rawalpindi over a 2-month period had prescribed Pefloxacin or some other flouroquinolone in typhoid fever. There seems to be a swift trend to directly use Pefloxacin or jump to using it without a fair trial with at least 2 of the recommended drugs used singly. Also, a limited facility for culture and antibiotic sensitivity testing adds to the problem. Since ceftriaxone a recommended drug for multi-drug resistant typhoid fever (Feigin, 1992; WHO Expert Committee and Parry *et al*., 1999) is expensive, alternative drugs have been tried with moderate success viz. cephalexin (Osler, 1912 and Luby *et al*., 1998), gentamicin (Osler, 1912), cefotaxime (Thong *et al*., 2000) and cephalexin with furazolidine (Thong *et al*., 2000). Sinha *et al* (1999) have reported total failure with gentamicin and furazolidine. Indiscriminate use of chloramphenicol, amoxycillin and co-trimoxazole for trivial infections like gastroenteritis and common cold has led to the emergence of multi-drug resistant *S. typhi* strains. Proper sanitation, use of clean drinking water, mass immunization against typhoid fever, and a rational drug therapy will help control this problem. Pefloxacin has now been officially listed as an essential reserve drug for strains of *S. typhi* resistant to chloramphenicol, amoxycillin and co-trimoxazole (Luby *et al*., 1998 and Lanata *et al*., 1983). We recommend that Pefloxacin should be used after at least one trial with the standard antibiotic therapy has failed. In developed countries where self-medication is discouraged, the emergence of multi-drug resistance has been attributed to the use of antibiotics in the feed of farm animals and birds; these are important ingredients of growth promoters (Johnson *et al*., 1981).

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