

Ciprofloxacin in the Management of Multiple Drug Resistant Typhoid Fever

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Typhoid fever and systemic Salmonellosis continue to be important health problems all over the world, especially in India, causing considerable morbidity(1). Since the first report of its successful use in 1948(2), chloramphenicol has been the mainstay in the therapy of typhoid fever, and was the 'Golden Standard' against which other drugs were compared. It was in the early 1970s that *S. typhi* strains resistant to chloramphenicol were reported from different parts of the world(3), including India(4). Consequently, other drugs like ampicillin, amoxycillin and trimethoprim-sulfamethoxazole (TMP-SMZ) were evaluated for the treatment of chloramphenicol resistant strains(5). With the emergence of multiple drug resistant (MDR) strains of *S. typhi*(6), treatment of typhoid fever in children has become an increasingly difficult problem. This paper describes the treatment of MDR typhoid fever with ciprofloxacin, a newer quinolone antibiotic.

Material and Methods

The New Delhi Municipal Committee (NDMC) Hospital at Moti Bagh, New Delhi, is a 150 bedded General Hospital with 20 Pediatric beds. It caters to the middle and lower-middle class of South-Central Delhi. During the period July to October, 1990, 19 cases of typhoid fever were diagnosed in the Pediatric age group.

All cases were hospitalized, and besides detailed history and thorough physical examination, routine investigations, i.e., hemoglobin, total and differential counts, ESR, peripheral smear, urine routine and microscopy, stool microscopic, and X-ray chest (where indicated), were done. In all cases, blood culture and Widal were done before the start of therapy. The diagnosis of typhoid fever was made on the basis of clinical suspicion supported by either a positive blood culture for *S. typhi* or a Widal agglutination titre of 'O' and 'H' of 1:160 or more. Antibiotic sensitivities were determined by the disc inhibition method.

All suspected cases were started on chloramphenicol, 100 mg/kg/day which was either continued or replaced by TMP-SMZ, ampicillin, amoxycillin, furazolidone or ciprofloxacin depending either on sensitivity reports or the clinical response. Ciprofloxacin was given in a dose of 15 mg/kg/day orally in two divided doses for 7 to 10 days. All children given this drug were evaluated daily for joint symptoms till the time the drug was given and weekly thereafter for at least 2 months. Hematological, renal and hepatic parameters were monitored weekly for 2 weeks after discontinuation of therapy. Side effects, if any, of the drug were specifically looked for.

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Results

A total of 19 cases of typhoid fever were diagnosed, of which 12 were confirmed by blood culture and the remaining by positive Widal agglutination titres. There were 11 males and 8 females and the ages ranged from 2.5 to 13 years (7.68 ± 3.47 years). Eight children presented with fever of less than 7 days duration and 11 with more than 7 days. The only apparent clinical differences between the 'sensitive' group and the 'resistant' group were that the latter children appeared 'less toxic' and 7/8 of these children exhibited 'high grade intermittent' fever with solitary nocturnal spikes, after initial periods of typical continuous fever. The hematological parameters were not significantly different. Two children had encephalopathy, and both these were sensitive to chloramphenicol.

The antibiotic sensitivity pattern of *S. typhi* in the 12 culture proven cases were as follows: 1 to ampicillin, 2 to amoxycillin, 7 to chloramphenicol, 3 to cephalexin, 4 to furazolidone, 2 to TMP-SMZ, 10 to gentamicin, 9 to kanamycin, 6 to nalidixic acid, 2 to streptomycin and all 12 to both norfloxacin and ciprofloxacin. There were 5 cases resistant to ampicillin, amoxycillin and TMP-SMZ and 5 other cases resistant to all the above plus chloramphenicol.

Eight children responded to chloramphenicol with defervescence of fever between 3 to 7 days (mean 5.2 days), 8 to ciprofloxacin (2 to 5 days, mean 3.6 days); and 1 each to TMP-SMZ (6 days); amoxycillin (5 days), and amoxycillin plus furazolidone (5 days). Ciprofloxacin was started in 5 children on the basis of sensitivity reports, and in 3 others after succes-

sive trials of chloramphenicol, TMP-SMZ and amoxycillin plus furazolidone each given for at least 6 days, failed to resolve clinical symptoms. All 19 children finally recovered fully, and there were no relapses.

The youngest child given ciprofloxacin was 2.5 years, and the longest duration this drug was given was for 10 days. No adverse effects, either clinical or hematological/biochemical, were noted in any of the children given this drug.

Discussion

Multiple drug resistance of *S. typhi* is mediated by R-factor, and this resistance is transmissible. The combination of highly endemic areas for typhoid and the indiscriminate use of drugs such as chloramphenicol and tetracyclines are the ideal conditions predisposing for the selection of R-factors from coliform populations(6). Since such a situation is likely to continue, the problem of MDR is likely to assume alarming proportions in years to come.

The newer quinolones have been shown in adults to have very favorable results in the treatment of resistant typhoid(7). These drugs are, however, not recommended as yet for Pediatric use. This is because experiments have shown that large doses of quinolones can cause irreversible cartilage damage in strained joints of young animals(8). However, the first quinolone compound nalidixic acid, causes identical or even more extensive damage in experimental animals(9). There are no reports in literature of joint or bone defects attributable to the use of nalidixic acid, despite the use of this drug in children for the last 20 years. These facts raise the hypo-

thesis that interspecies differences might be relevant factors in the arthropathic potential of the quinolones(8). Small trials done so far in children have not been able to document skeletal toxicity related to these drugs(10). The outstanding features of the newer quinolones are their marked bactericidal activity, a broad antibacterial spectrum and favourable pharmacokinetics after oral and parenteral use. These agents act by inhibiting the A-subunit of the enzyme DNA-gyrase and thus interfere with DNA replication(11).

Our study showed that 8/19 (42%) cases of typhoid fever were resistant to the commonly used drugs, and 5/12 (41.6%) isolates were MDR strains. These figures are worrisome especially since they are likely to increase in the coming years. We have found ciprofloxacin a safe and effective alternative in the treatment of MDR typhoid fever. The safety of this drug in children can only be unequivocally established after long term epidemiological studies, but preliminary data from ongoing trials suggests that the newer quinolones are safe for use in children(12). Effective vaccination against typhoid fever will, however remain a far more cost-effective means to combat the disease.

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