

THERAPEUTIC IMPLICATIONS OF OFLOXACIN IN THE TREATMENT OF TYPHOID FEVER CAUSED BY MULTIPLY RESISTANT SALMONELLA TYPHI

Pages with reference to book, From 176 To 178

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ABSTRACT

The antibiotics of choice for the treatment of typhoid fever in most parts of the world is still chloramphenicol. Ampicillin and cotrimoxazole have been used in recent years. Selection of antimicrobials for therapy has been complicated by the emergence of *Salmonella typhi* strains resistant to the above mentioned antibiotics. Blood and/or bone marrow cultures of 30 adult patients grew *S. typhi* that was resistant to chloramphenicol, ampicillin and cotrimoxazole. However, these strains were sensitive to cefotaxime, ceftriaxone, aztreonam and ofloxacin. Ofloxacin 400mg twice a day was given orally to these patients for 14 days. All patients recovered with no untoward side effect. We concluded that ofloxacin can be used as a drug of choice for typhoid fever, in those adult patients who are infected with *S. typhi* resistant to chloramphenicol, ampicillin and cotrimoxazole (JPMA 40: 176, 1990).

INTRODUCTION

Typhoid fever is an acute and systemic illness. Although the incidence has decreased in the West, typhoid fever is still endemic in Karachi, as it is in other parts of the world with poor sanitation¹⁻³. The commonest organism which causes typhoid fever is *Salmonella typhi* and less so are *Salmonella paratyphi A*, *Salmonella paratyphi B*, and *Salmonella paratyphi C*⁴. The diagnosis of typhoid fever is usually suspected on clinical ground and confirmed on the basis of isolation of the organism from blood⁵. In the absence of antimicrobial therapy, blood cultures are positive in over 80% of patients seen in the first week of illness⁶. Antimicrobial therapy diminishes possibility of recovery of the causative agents from blood. In these patients cultures of supplementary site such as bone marrow is a better source of organism than blood⁷. The antimicrobial of choice for typhoid fever in most areas of the world is still chloramphenicol^{8,9}. Ampicillin is also effective in the treatment of typhoid fever¹⁰. Several studies have demonstrated a slower response rate to ampicillin than chloramphenicol^{10,11}. Trimethoprim-sulfamethoxazole has been used in recent years in the treatment of typhoid fever¹². Strains of *Salmonella typhi* resistant to chloramphenicol have been reported in recent years from Mexico, Vietnam and India¹³. Ampicillin is recommended as an alternative to chloramphenicol as antibiotic therapy for typhoid fever caused by chloramphenicol resistant strains of *Salmonella typhi*¹⁴. Only occasional strains of *Salmonella typhi* are known to be resistant to both chloramphenicol and ampicillin¹⁵. Trimethoprim-sulfamethoxazole is the drug of choice for typhoid fever caused by chloramphenicol or ampicillin resistant strains of *Salmonella typhi*¹⁶. Over a period of three years 3224 patients attended emergency room and consulting clinic of the Aga Khan University Hospital Karachi, for pyrexia of unknown origin. Blood cultures from all of these patients and bone marrow from selective patients were collected and sent to Microbiology laboratory of The Aga Khan University Hospital for culture. Total positive isolated were 13% out of which 3 1.5% were *Salmonella* species. Further sub typing of species showed *Salmonella typhi* in 83%. Antibiotic sensitivities result of these

strains showed that approximately 30% were resistant to ampicillin, chloramphenicol and cotrimoxazole. We report management of 30 such patients suffering from typhoid fever caused by *Salmonella typhi* resistant to the first line antibiotics (chloramphenicol, ampicillin and cotrimoxazole). The aim of this study was to determine the effectiveness of ofloxacin in the treatment of such patients.

MATERIALS AND METHODS

Samples of blood and/or bone marrow were collected from 30 patients suspected for typhoid fever. Each blood sample (4-5 mls) or bone marrow sample (0.5 — 1.0ml) was collected in each of the 2 blood culture bottles containing 45ml of aerobic medium (brain heart infusion broth) and anaerobic medium (thioglycolate broth). Bottles were immediately transported to the laboratory and incubated at 37°C for 7 days. Gram stain film was made from each bottle daily for 7 days. All bottles were subcultured after 24, 48, 72 hours and 7th day of incubation on to blood agar and MacConkey's media. Non lactose fermenting colonies from MacConkey's plate were biochemically speciated using API 20E* strips. Serological confirmation was done by type specific sera. Antibiotic sensitivity testing of all isolates was performed by the method described earlier¹⁷. The antibiotic discs used were ampicillin (10mcg), cotrimoxazole (25mcg), chloramphenicol (30mcg), cefotaxime (30mcg), aztreonam (30mcg), ceftriaxone (30mcg) and ofloxacin (5mg).

RESULTS

A wide variety of clinical presentations were observed in these 30 patients (Table 1).

TABLE I. Clinical features at admission.

| Clinical features | No. of patients |
|-------------------|------------------------------|
| Fever | 30 |
| Sore throat | 25 |
| Nausea | 30 |
| Vomiting | 15 |
| Headache | 30 |
| Constipation | 05 |
| Diarrhoea | 12 |
| Abdominal pain | 20 |
| Hepatomegaly | 19 |
| Splenomegaly | 10 |
| Total WBC | 30 (6,900 – 12,200 per cmm). |

The blood and/or bone marrow* cultures from all the 30 patients grew *S. typhi* at varied times after incubation (Table II).

TABLE II. Duration after incubation at which *S. typhi* was isolated from blood and/or bone marrow cultures.

| Day post incubation | No. of positive samples | % |
|---------------------|-------------------------|------|
| 1 | 02 | 6.7 |
| 2 | 16 | 53.3 |
| 3 | 08 | 26.7 |
| 4 | 02 | 6.7 |
| 5 | 02 | 6.7 |
| 6 | 0 | — |
| 7 | 0 | — |

Approximately 7% of the samples grew typhi on either day 1, 4 or 5 post incubation. However, 53.3% and 26.7% of the samples grew *S. typhi* on day 2 and 3 post incubation, respectively. The antibiotic sensitivity test showed all the isolates of *S. typhi* were resistant to ampicillin, cotrimoxazole and chloramphenicol, however they were sensitive to cefotaxime, aztreonam, ceftriaxone and ofloxacin. All patients were initially treated with the first line antibiotic therapy (ampicillin, cotrimoxazole or chloramphenicol), Eleven patients were prescribed ampicillin 1gm 8 hourly, 7 patients received cotrimoxazole D.S. 12 hourly and 12 patients were given chloramphenicol 1gm 6 hourly. Treatment was reviewed after the antibiotic sensitivity results were obtained. All patients were then given ofloxacin, 400mg twice a day, orally for 10 to 14 days. Temperature of all these patients settled within 48 to 72 hours after the ofloxacin therapy.

DISCUSSION

This study clearly shows that most common cause of typhoid fever in Karachi is *S. typhi* as all the blood and/or bone marrow cultures grew this organism within 5 days of incubation, with over 50% showing growth of the organism at 5 hours of incubation. The drugs of choice in typhoid fever are chloramphenicol, ampicillin and cotrimoxazole^{5,13,15}. All patients were initially treated with these antibiotics, but did not respond within 48 hours and in some cases even after 5 days of treatment. This observation indicated the infection with resistant *S. typhi* which was confirmed by microbiological results. At this point ofloxacin was administered to these patients. In the recent past ofloxacin had been tested in vitro for its efficacy against *S. typhi*. The minimum inhibitory concentration (MIC) ranged from 0.03 to 0.12 mcg^{16,17}. Similarly the mean MICs of cefotaxime, aztreonam, ceftriaxone for *S. typhi* has been shown to be less than 0.97 mcg¹⁸. The selection of ofloxacin for our patients was done because the drug is effective in vitro¹⁶, can be administered orally therefore eliminates the cost of hospitalization and is relatively less expensive than the other newer antibiotics. The recommended dose of ofloxacin in gram negative systemic infections is 200mg twice a day. As these patients are seriously ill, they were given 400mg twice a day. Fever subsided within 72 hours after administration of this therapy. The treatment was continued for 14 days. No untoward effects were observed. Ofloxacin is a good drug in *S. typhi* infection resistant to the first line antibiotics. However this drug should not be

used in children under 14 years of age and in pregnant women. Further studies with a larger group of patients are recommended to evaluate the dose and effectiveness of this drug to substantiate our conclusions.

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