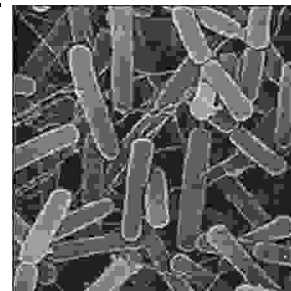


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TYPHOID FEVER; CLINICAL EXPERIENCE WITH LEVOFLOXACIN, ITS EFFICACY AND SAFETY.



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ABSTRACT... dr_maqsoodahmadd@yahoo.com **Objectives:** To find out the efficacy and safety of Levofloxacin in patients suffering from typhoid fever. **Design:** Non-comparative and prospective study. **Setting:** Medical Units of Allied & DHQ Hospital (PMC) Faisalabad. **Period:** From May 2002 to July 2004. **Material & Methods:** All suspected febrile patients were examined and provisionally diagnosed to have typhoid fever were admitted for the purpose of study till they were satisfactorily discharged. **Results:** This clinical study was conducted on 70 patients of Enteric Fever. Fifty-two patients were male and 18 were female. The mean age for male patients in the study sample was 37.58 ± 8.13 while the mean age of females was 21.92 ± 4.73 years. Fever as a symptom was present in all 70(100%) of the patients. Anorexia was there in 61(85.5%) patients and abdominal pain in 49(70%) patients. Twenty-seven (38.5%) patients had constipation along with other features. Diarrhea was present in 6 (8.5%) patients. Relative bradycardia was present in 20(28.5%) patients. Hepatomegaly was there in 31(44.3%) and Splenomegaly in 24(34.3%). Elevated liver enzymes were found in 29 (41.4%) of the patients and blood cultures positive for Salmonella typhi was seen in 19(27.1%) patients. Widal test was positive at dilution of 1:160 in almost all of the cases and at 1:320 dilution in 18% of cases in current study. The success rate of Levofloxacin in our study was 100% in the form of settlement of fever and other symptoms and signs. The side effects were seen in 17(24.2%) patients. **Conclusions:** In conclusion levofloxacin is effective in treatment of typhoid fever and its use in this indication is safe.

Key words Typhoid Fever, Levofloxacin, Efficacy, Safety.

INTRODUCTION

Typhoid fever occurs in all parts of the world where there is substandard water supply and sanitation. Typhoid fever has almost been eliminated from developed countries because of sewage and water treatment facilities but remains a common disease and a major cause of morbidity and mortality in the third world countries. Exposure of the individual to contaminated food or water closely correlate with the risk for enteric fever^{1,2,3}.

Salmonella typhi infects only humans. Typhoid fever is known to mankind since Greek ancient era. It was Thomas Willis in 1959 who gave the first classical description of typhoid fever and also differentiated it from other forms of fever⁴. Typhoid (Enteric) fever is an acute infection of the reticuloendothelial system, intestinal lymphoid tissues, and gall bladder caused by *Salmonella typhi* and Para typhi A, B & C. *Salmonella* infection remains prevalent in many parts of the world. The World Health Organization has estimated that 12.5 million cases of enteric fever occur annually worldwide (excluding China). Since the last decade emergence of drug resistance has become a major problem around the world⁵.

Typhoid fever is a febrile illness of prolonged duration marked by step-ladder fever, diffuse abdominal pain, frontal headache, delirium, splenomegaly, hepatomegaly and many other systemic manifestations due to bacteremia and septicemia. Typhoid fever is a common disease encountered in Pakistan. A major concern is the emergence of multi-drug resistant strains of *Salmonella typhi*, which was first reported in 1987 in Pakistan^{6,7}.

The continuing emergence of antibiotic resistance among *Salmonella* species has made the treatment difficult. A good number of *Salmonella* showed resistance to first-line drugs i.e Chloromphenicol (54%), Co-trimoxazol(56%) and Ampicillin (50%)^{8,9}.

Organisms causing complicated infections are much more likely to be resistant to one or more conventional oral anti-microbial agents. The quinolone group of drugs has emerged as useful drugs for the treatment of

multiple drug resistant cases of S-typhoid. But resistance to ciprofloxacin is now being reported both from the Indian subcontinent and West^{3,10,11}. *Salmonella typhi* including other organisms is susceptible to treatment with Levofloxacin^{12,13}.

OBJECTIVES

To find out the efficacy and safety of Levofloxacin in patients suffering from typhoid fever.

MATERIAL AND METHODS

This is a non-comparative and prospective case series conducted in medical units of Allied Hospital and Divisional Headquarter Hospital, Faisalabad from May 2002 to July 2004. All suspected febrile patients with symptoms and signs (Remittent fever (Step ladder pattern), Relative bradycardia, Abdominal pain, Constipation / Diarrhea, Headache, Rose Spots & Hepato-splenomegaly) were examined and when a provisional diagnosis of typhoid fever was made, following investigations were carried out before recruiting them in the study and during study period they were kept admitted in the wards.

- * Rising titers of anti-bodies against somatic antigen of *Salmonella Typhi* (Four fold increase).
- * Blood Culture
- * Stool Culture.
- * Typhidot test (1gM).
- * Complete blood count
- * Bone marrow aspiration and culture (If pyrexia of unknown origin and not treated with Quinolones in recent weeks)
- * X-ray chest (PA view).

INCLUSION CRITERIA

Patients eligible for the study include:

- Patients 18 years and above,
- Both males and females.
- Patients presenting with symptoms, signs and laboratory investigations diagnostic of enteric fever.

EXCLUSION CRITERIA

Patients who cannot be included in the study;

- Pregnant and lactating mothers.
- Children.
- Known hypersensitivity to Levofloxacin or any other Quinolones.
- History of epilepsy.
- Tendon disorders (Patients suffering from bone, cartilage and tendon related diseases)
- Suffering from colitis or severe gastrointestinal disorders (Clostridium difficile associated diseases e.g. pseudo-membranous colitis, bleeding ulcers, SBP etc.).
- With moderate to severe renal impairment (Serum Creatinine > 2.5 mg/dl) and patient on renal replacement therapy.
- Hepatic impairment e.g. cirrhosis of liver, hepatic encephalopathy.
- Immuno-compromised immuno suppressed and on cytotoxic drugs.
- Known to be tuberculous.

DOSAGE

The dose of Levofloxacin in Enteric fever used was as follows;

500 mg twice daily for initial 3 days then followed by 250 mg B.I.D. orally.

The therapy in patients of enteric fever was continued for 7 days after settlement of fever.

DURATION OF OBSERVATION

Each patient was observed during the course of therapy with Levofloxacin daily till the end of a clinical evaluation of the patient.

Safety /side Effect of Levofloxacin

Patients at the start of treatment were advised to be vigilant about new symptoms and additionally they were inquired about the side effects during the treatment through leading questions repeatedly. The side effects were graded as mild when they needed re-assurance and/or oral based treatment and moderate when these

were to be managed with some parenteral therapy and severe when these would need discontinuation of therapy.

STATISTICAL ANALYSIS

Data was recorded on the forms and fed to the computerized data base in SPSS for windows® version 10.01 for analysis. Analysis of Variance and paired T-test was used to compare the mean of quantitative variables for their possible significance. Chi-square was worked out among different parameters. Values have been presented in Mean ± standard deviation format.

RESULTS

Out of a total number of 70 patients, 52 were male and 18 were female. The youngest patient in the study was of 19 years of age and of the maximum age of the recruited patient in trial was 62 years. The mean age for male patients in the study sample was 37.58± 8.13 while the mean age of females was 21.92± 4.73 years.

The average weight of male patients were 63.15±5.26 Kg and for females patients were 47.45± 4.65 Kgs (Table I).

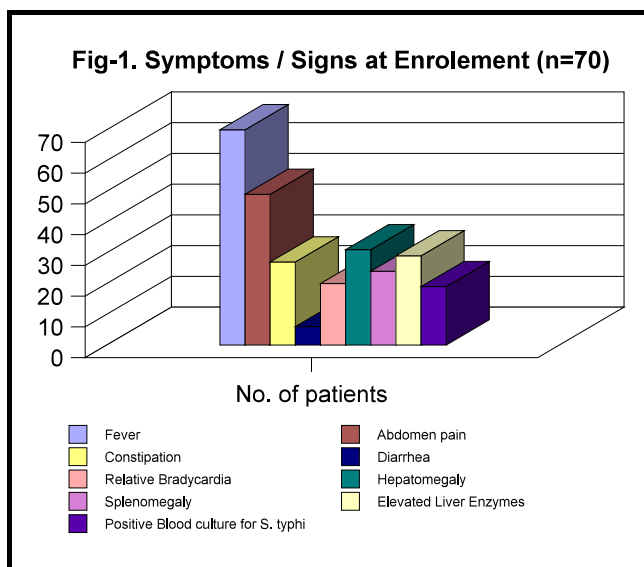
| Table-I. Patient Demography (n=70) | | |
|------------------------------------|------------|------------|
| Parameters | Male | Female |
| Number of patients | 52 | 18 |
| Mean age (years) | 37.58±8.13 | 21.92±4.73 |
| Mean weight (Kg) | 63.15±5.26 | 47.45±4.65 |

The patients had presented with a variable combination of symptoms and fever as a symptom was present in all 70(100%) of the patients. In the order of frequency next most common symptom was anorexia, which was there in 61(85.5%)patients and third common symptom being abdominal pain was present in 49(70%) patients. Twenty-seven (38.5%) patients had a complaint of constipation along with other features. Diarrhea was present in 6(8.5%) patients.

Among the signs in these patients relative bradycardia

was present in 20(28.5%) patients. Hepatomegaly was there in 31(44.3%) and Splenomegaly in 24(34.3%). Elevated liver enzymes were found in 29(41.4%) of the patients and blood cultures positive for Salmonella typhi was seen in only 19(27.1%) patients (Table II).

| Symptoms/signs | No. of pts | %age |
|-------------------------------------|------------|-------|
| Fever | 70 | 100 |
| Abdomen pain | 49 | 70 |
| Constipation | 27 | 38.5% |
| Diarrhea | 6 | 8.5 |
| Relative Bradycardia | 20 | 28.5 |
| Hepatomegaly | 31 | 44.3 |
| Splenomegaly | 24 | 34.3 |
| Elevated Liver Enzymes | 29 | 41.4 |
| Positive Blood culture for S. typhi | 19 | 27.1 |



Blood complete examination was done at the enrolment and at the end of observation period. Mean hemoglobin level before and after treatment was 12.56±2.02 g/dl and 12.68±1.84 g/dl respectively with non significant difference (P=0.63). WBC counts had shown a mean

value of 8715.70±1257.20/Cubic mm. before the commencement of therapy and 9112.35±987.45/ Cubic mm. at the end of treatment with non significant change (P=0.16). The mean neutrophil count at the start and at the end of treatment was 67.75±4.32 versus 74.75±6.12 respectively, with a statistically significant difference (p=0.00). The lymphocyte count also had changed significantly from baseline to end of treatment with p value 0.00. The figures were 29.25±4.214 and 23.00±6.11 (Table III). Widal test was positive at dilution of 1:160 in almost all of the cases and at 1:320 dilution in 18% of cases in current study.

The average number of days with fever at presentation was 8.92±2.99 and it settled in 5.21±2.91 days of start of therapy. Abdominal pain took 5.38±1.94 days to settle. Constipation settled in 6.45±3.17 days after the start of therapy and diarrhea was settled in 4.65±1.8 days (Table IV).

| Parameters | Baseline | End of treatment | P value |
|------------------|---------------|------------------|---------|
| Hemoglobin | 12.56±2.02 | 12.68±1.84 | 0.63 |
| White cell count | 8715.7±1257.2 | 9112.35±987.45 | 0.16 |
| Polymorphs | 67.75±4.32 | 74.75±6.12 | 0.00 |
| Lymphocytes | 29.250±4.214 | 23.00±6.11 | 0.00 |

| Symptoms | Days to resolve |
|----------------|-----------------|
| Fever | 5.21±2.91 |
| Abdominal pain | 5.38±1.94 |
| Constipation | 6.45±3.17 |
| Diarrhea | 4.65±1.8 |

The success rate of Levofloxacin in our study was 100% in the form of clinical improvement resulting in settlement of fever and other symptoms and signs. No follow up was

planned in the study design.

The side effect profile is given in Table V and side effects were graded as mild when they needed re-assurance and/or oral based treatment and moderate when these were to be managed with some parenteral therapy and severe when these would need discontinuation of therapy.

| Side effects | No of patients | Severity |
|-------------------|----------------|----------|
| Nausea | 9 | Mild |
| Distaste in mouth | 6 | Mild |
| Light headed ness | 5 | Mild |
| Irritability | 1 | Moderate |
| Skin rash | 2 | Mild |

In our study side effects were seen in 17(24.2%) patients and they were of mild category except for one patient who developed irritability of moderate degree and managed with I/V benzodiazepines for one day. The most common side effect was nausea, seen in 9(12.8%) patients followed by distaste in mouth present in 6(8.5%) patients and light-headed ness was reported by 5(7.1%) patients.

DISCUSSION

Typhoid and Para-typhoid fever is endemic in Indo Pakistan Subcontinent, South and Far East Asia, Middle East, Africa and Central and South Africa. Its prevalence is high during the months of May to August in Sub Continent. Epidemiology of Salmonella infection is related to ingestion of food and water contamination by human and animal wastes. Lack of chlorination, equipment failure and back siphonage in the water distribution system leads to contamination of drinking water¹⁴.

Iqbal et al quoted male to female ratio as 4:1 in their case series of 52 typhoid patients. These findings are

also supported by Khosla who described that this male preponderance may be due to greater chances of exposure to male population who go out of the house much frequently than females for eating food from restaurants and Street vendors^{15,16}.

In our study the male to female ratio is 3.5:1 which is consistent with and comparable to the above cited studies and it is also relevant that we excluded pregnant and lactating females. The mean age in our study for males was 37.58 ± 8.13 while the mean age of females was 21.92 ± 4.73 .

Khan et al reported that main group of patients in their study was of younger age, where 18 out of 22 patients (64%) were below 32 years of age. Velema. JP and co-workers in a recent study from Indonesia regarding the high risk groups and high risk behaviors concluded that the median age of the cases was 22 years^{17,18}.

According to woodruff, the symptoms of typhoid fever in 975 patients were headache (74.9%), abdominal discomfort (60.7%), fever (92%), vomiting 24.5%, joint pains 54%, cough 21.7%, diarrhea without blood 29.6% backache 11.4% and chest pain 20.4%¹⁹.

Durrani described common clinical features as fever, abdominal pain, vomiting and diarrhea²⁰. This may be due to different set up and different inclusion criteria.

Y F Yap, described fever was present in 98%, abdominal pain 46.2%, diarrhea 44% constipation noted in only 22% of cases²¹. The results of present study are comparable with above cited studies. Fever, abdominal pain, diarrhea without blood headache and myalgia coincide with woodruff whereas the incidence of Nausea, vomiting constipation and anorexia was much more common in the patients under study. This difference may be due to different study sample.

Strum et al described that incidence of hepatomegaly was about 10%. Arif et al described 9 cases of clinical jaundice their study and most of them were suffering from anemia, malnutrition and poor health at the same

time^{22,23}.

Among 70 cases in our study only 19(27%) cases showed positive blood culture for salmonella Typhi and none yielded S. Paratyphi.

Farooqi et al showed that S.typhi is seen as isolate in 83%, S.paratyphi A 12.8% and S.paratyphi B is 4.1% of cases. Karamat et al in their study reported S. Typhi 80% and S. paratyphi A in 20% of their current proved cases^{24,25}. This difference of results is possibly due to that above mentioned studies are primarily laboratory data of salmonella isolates and from a large number of cultures.

This is in contrast to findings in developed countries. Gugnani HC and co-workers recorded a higher proportion of paratyphoid infection over typhoid infection and the major culprit was paratyphoid¹⁴.

Possible cause of high infection with paratyphoid organisms in Europe is that they use prepared food products more than people of underdeveloped countries and paratyphoid is mostly spread by meat, fish and other prepared foods. Widal test was positive at dilution of 1:160 in most of the cases and at dilution 1:320 in 18% of cases in current study. Hanif et al in their study conducted in Bangladesh described that Widal test was positive in 72% cases of their 150 bacteriologically proven cases²⁶.

The most common symptom in this study was the fever, present 100% of cases. Patients presented at an average of 8.92 ± 2.99 days of duration of fever. This is in accordance with Yap Y F, in which duration of symptoms before hospital admission ranged from 2 to 28 days with mean period of fever 13 days. The temperature subsided after the commencement of treatment and resolved in 4-6 days with mean value of 5.8 ± 2.7 days.

Reports from 20th International Congress of Chemotherapy, Sydney Australia stated that mean time period to disappearance of symptoms specially fever was

4.13 ± 1.31 days²⁷.

The publish data also suggest that fluoroquinolone are more rapidly effective and are associated with lower rates of stool carriage than traditional first line drugs (Chloromphenical and trimethoprim-sulfamethoxazole)²⁸. The results are highly comparable with the study under discussion as fever resolved within 5 days and all the patients responded to treatment well making cure rate 100% and lastly no relapse of infection was documented till the end of study period. So fluoroquinolone including levofloxacin are as effective as other traditional drugs for typhoid fever.

CONCLUSION

From our study it can be concluded that typhoid fever mainly affects the younger age group. Males are affected more with this febrile illness. Fever at the time of presentation is present in almost all the cases. Diagnosis is generally clinical but should be supported with relevant investigations. Elevated liver enzymes at the time of diagnosis may be present in one third of the cases. quinolones including Levofloxacin are highly effective and safe drugs in this condition.

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