

Typhoid Fevers: Treatment with Lomefloxacin

Pages with reference to book, From 168 To 170

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Abstract

Typhoid group of fevers pose a major threat and are a cause of high morbidity and mortality in the tropical countries. Over the last decade there has been a steady increase in the development of multiresistant strains of *Salmonellae* all over the world. Multiresistance ranges between 5% to 86%. In a recent study in Pakistan multidrug resistance in *Salmonellae* has increased to over 39%. Hence alternative therapy is needed. Fluroquinolones are an effective alternative requiring a shorter course of treatment than conventional antimicrobial agents. Lomefloxacin because of its longer half life and convenient BD dose was used in a multicentre study to treat cases of typhoid group of fevers including cases due to multiresistant isolates. In order to overcome the challenge presented by the multiresistant *salmonellae*, a dual purpose multicentre study was conducted in two stages. The first stage included a *vitro* study and the second *in vivo* study. Two hundred local *salmonellae* isolates were collected and their sensitivity and minimum inhibitory concentrations were determined by standard methods. Two hundred and fourteen patients clinically suspected of suffering from typhoid groups of fevers were given Lomefloxacin 200 mg. BD for 14 days. Forty percent of *Salmonellae* isolates were found to be multiresistant while only 2% were found to be resistant to Fluroquinolones. The mean MIC 90 was found to be 0.06 mg/L Lomefloxacin was found to be effective in over 97% cases for treating typhoid group fevers including the ones due to multiresistant isolates. The side effects were found to be minimal and transient (JPMA 48: 168, 1998).

Introduction

Typhoid is a very important disease in the developing countries where potable water which plays a major role in the spread of enteric diseases is still a rare commodity¹. Typhoid fever is a severe, debilitating and potentially life threatening illness. *Salmonella typhi*, *S. paratyphi A* and *B* are important because of their frequent association with severe disease and bacteremia²⁻⁴. These serotypes are endemic in developing countries and results in high morbidity and mortality. The organisms invade the bowel mucosa and multiply in the submucosa and depending upon the virulence of the strain and the host response, they may invade the blood stream, lymphatic tissue or both⁵⁻⁷. The situation is more complicated by the fact that a high percentage of the isolates are resistant to the three commonly used antibiotics i.e. Cotrimoxazole, Ampicillin and Chloramphenicol⁸. As multiresistance is increasing, there is great room for the use of alternative therapy.

To overcome the challenge presented by the multiresistant *salmonellae*, a dual purpose multicentre study was conducted in two stages. The first stage included *in vitro* study and the second stage was *in vivo* study.

Methods and Subjects

In Vitro Study

Two hundred local *Salmonellae* isolates were obtained from Karachi, Lahore and Rawalpindi/Islamabad. These were consecutively collected routine isolated from the blood of patients

with Typhoid group of fevers confirmed by API and Serological tests. Their sensitivity and minimum inhibitory concentration was determined by sensitivity discs and agar dilution method⁶ using Brain Heart infusion agar. The Discs were standard discs manufactured by DIFCO USA⁹. The in-vitro study was conducted at one centre. Isolates from the other centres were isolated, identified and transported to Karachi on agar slopes where they were reconfirmed and all tests performed for sensitivity and MIC. Fifty isolates of *Salmonella* included *Salmonella typhi* 30, *Salmonella paratyphi A* 10 and *Salmonella paratyphi B* 10. There were taken randomly from the 200 isolates and minimum inhibitory concentration to Lomefloxacin was carried out at Karachi centre by incorporating the antibiotic in Brain Heart infusion agar and inoculating by multipoint inoculator (Denley).

In Vivo Study

An open multicentre trial was conducted to evaluate the safety and efficacy of Lomefloxacin (2x200 mg for 14 days). In all 214 patients clinically suspected of suffering from typhoid group of fevers were asked for their consent and detailed history was taken. Blood was collected for Haematology, Biochemistry and Microbiological tests including serological tests. Then the patients were given Lomefloxacin 200 mg BD for 14 days after which blood cultures were taken and after 21 days three consecutive stool samples were collected to evaluate the eradication of *Salmonella* species. The in-vivo study was conducted at Karachi, and Faisalabad.

Results

Table I. In Vitro susceptibility' resistance pattern of lomefloxacin to routine salmonella isolates from cases of gastrointestinal infections and septicemia.

Organism	Total antibiotic sensitivity in %								
	Isol.	Amp	Chl	Sxt	Amc	Cfm	Ctx	Lom	Ofx
Sal.typhi	100	32	66	30	92	90	92	98	98
Sal.paratyphi A	50	74	90	64	90	84	84	98	98
Sal.paratyphi B	50	60	70	60	100	90	90	100	100
Total	200	55	75	51	94	88	89	99	99

Isol: Number of isolates, Amp: Ampicillin, Chl: Chloramphenicol, Sxt: Cotrimoxazole. Amc: Amoxicillin/ Clavulanic acid, Cfm: Cefixime, Ctx: Cefatoxime, Lom: Lomefloxacin, Ofx: Ofloxacin.

Table I gives the results of in vitro study. In all 140 salmonella isolates were tested with the antibiotic routinely used for treating Salmonellosis and compared with Lomefloxacin. It is interesting to note that 99% isolates were found to be sensitive to the drug with the MIC range being 0.03-4.0 ug/ml while MIC 90 was found to be 0.5 ug/ml (Table II).

Table II. Minimum inhibitory concentration (MIC) of lomefloxacin in uG/ml

Organism	No. of strains	No. of lactamase producer	MIC in ug/ML range	MIC 50%
<i>Salmonella typhi</i>	30	6	0.03-4.0	0.25
<i>Salmonella paratyphi A</i>	10	3	0.03-4.0	0.5
<i>Salmonella paratyphi B</i>	10	1	0.03-4.0	0.12
All <i>Salmonella</i> spp.	50	10	0.03-4.0	0.25

The in vivo study was carried out in 214 patients including 139 males (65%) and 75 females (35%).

The age range was 18- 80 years. The most susceptible group was 20-30 years of age (Table III).

Table III. Age and sex distribution in typhoid fever.

Age Group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
Upto 19	26	18.7	11	14.7	37	17.3
20-29	54	38.8	24	32.0	78	36.4
30-39	24	17.3	16	21.3	40	18.7
40-49	24	17.3	13	17.3	37	17.3
>49	11	7.9	11	14.7	22	10.3
Total	139	100	75	100	214	100

The clinical history revealed that only 9.3% of the patients had not taken any medication, during the 2 weeks prior to investigations (Table IV).

Table IV. List of medication taken or being taken by the patient in the past two weeks.

No. drugs	20	9.3%
Antimalarial	37	17.3%
Antibiotics	77	36.0%
Antimalarial + antibiotics	20	9.3%
Miscellaneous	39	18.2%
Not known	21	9.8%

The most common presenting symptom was Gastrointestinal which was seen in 56% of case (Table V).

Table V. Medical history on presentation

C.N.S.	28	13.1%
C.V.S.	12	5.6%
Respiratory	47	22.0%
Gastrointestinal	122	56.4%
Urogenital	19	8.9%
Skeletal	57	26.6%
Dermatological	14	6.5%
Haematological	12	5.6%
Hepatic	40	18.7%
Reticuloendothelial	31	14.5%
Known allergies	7	3.3%
Others	5	2.35

Enteric fevers were diagnosed on the basis of Widal test which was positive in 137 cases (64.0) while culture was positive in only 100 patients (46.7). Twenty three patients with a positive culture showed a significant rise in antibodies level while in the other 77 patients widal titre was insignificant. This illustrates the fact that culture for enteric pathogens specially blood culture should be carried out during the first seven days of onset of fever, otherwise it becomes negative as the antibodies levels rise. The laboratory findings are listed in Table VI.

Table VI. Laboratory evaluation.

Tests	No.	Range	Mean $\pm$ SD
Hb	193	6.0-15.2	11.5 $\pm$ 18.5
TLC	194	2200-75000	7900 $\pm$ 7434
ESR	188	2-170	35.6 $\pm$ 23.6
Lymphocytes	172	6-170	35.2 $\pm$ 11.0
Platelet	88	25000-480000	280000 $\pm$ 107000
Neut	178	30-89	61.0 $\pm$ 10.8
Basophil	92	0-6	1.0 $\pm$ 1.2
Monocytes	142	0-10	2.4 $\pm$ 1.8
Eosinophil	127	0-9	1.9 $\pm$ 1.6
Creatinine	91	0.3-2.1	0.9 $\pm$ 0.27

The TLC count either was within normal range or showed leucopenia ESR was raised while platelets were within normal range (Table VI).

Table VII. Frequency of side effects seen in 214 patients on lomefloxacin.

No side effect	158	74%
Side effect	56	26%
Side effect	No.	%
Nausea	19	34.0
Vomiting	10	17.9
Restlessness	8	14.3
Loose motions/diarrhoea	5	8.9
Headache	4	7.1
Irritability	4	7.1
Bad taste	4	7.1
Skin reactive occurs	4	7.1
Photosensitivity	2	3.5
Confusion	2	3.5
Decreased concentration	2	3.5

Table VII records the side effects of Lomefloxacin therapy. No adverse symptoms were reported of 74% of patients, while 26% experienced some side effects the commonest being nausea in 19(9%) and Photosensitivity and confusion in two individuals each.

Of the 100 culture positive patients, 11 were lost to follow up after stopping of the therapy. Only 89 subjects could be evaluated of which 88 (98%) achieved complete eradication of the pathogens as confirmed by a negative stool culture. The pathogen persisted in one case. Of the 214 patients on Lomefloxacin, 209 (97.6%) responded satisfactorily. 5 (2.3%) failed to respond and were classed as treatment failure.

Discussion

Typhoid fever is a very common disease seen in the developing countries, the main promoting factor being contaminated water. Typhoid is endemic in Pakistan and usually a higher frequency is seen in the warmer months. There is a gradual increase in the multiresistant strains in the community⁶ thus causing tremendous difficulties in the treatment of typhoid fevers.

The in-vitro study suggested that 99% of the isolates are sensitive to Lomefloxacin hence a in-vivo study was conducted. It is interesting to note that of the 220 patients included in the study, only 9.5% had received no medication before presentation. This is quite common in countries where medicines are available over the counter leading to self medication. The most vulnerable age group was found to be 20-29 years. This could be due to the fact that individuals in this age group are adventurous and consume food which is exposed to contamination. The most common clinical symptom was found to be gastrointestinal upset. The culture was positive only in 100 (46.8%) cases this could be due to the fact that the Laboratory standards are not the same or because most of the patients had taken some medication prior to presentation. Widal test was positive in 137 patients and is probably the test which is relied on by most of the local physicians.

Lomefloxacin (2x200 mg) was found to be effective in treating Typhoid group of fevers in 97.6% of patients which included patients who had multiresistant salmonella isolates. The mean MIC of Salmonella isolates was found to be 0.5 µg/ML, which is generally achievable at all body sites. The pathogen was eradicated in 98% cases hence the drug was found to be effective in eliminating the possibility of conversion of patients into the carrier state. This would help in the Epidemiological control of the disease.

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