OPEN STUDY ON EFFICACY AND SAFETY OF LEVOFLOXACIN IN TREATMENT OF UNCOMPLICATED TYPHOID FEVER

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Abstract. The main objective of this study was to determine the clinical efficacy and safety of levofloxacin in an open setting for typhoid fever cases. Patients with clinical signs and symptoms of typhoid fever without previous antimicrobial treatment admitted to affiliated hospitals of the Faculty of Medicine, University Indonesia were included in this study. Adults, 18 years or above, were screened for any serious underlying conditions, pregnancy or possible complications of typhoid fever before final enrollment. Fifty-three subjects were screened, 48 were enrolled. The final diagnosis of enteric fever was made by positive blood culture, polymerase chain reaction or serology, was obtained in 31 cases, in whom one had a concomitant sinus infection and had to be excluded. Thirty patients (11 males, 19 females) aged between 18-58 years (mean 31.7 years) with a history of fever between 1 and 10 days (mean 6.1 days) showed excellent clinical response, becoming afebrile at an average of 2.43 days (range 1-5 days). Adverse effects noted were nausea in 4 patients, vomiting in one and meteorism in another one, which were all difficult to distinguish from the enteric infection. A pruritic rash occurring in two patients may be related to levofloxacin, and insomnia in another patient may be related. Microbiological clearance was obtained both immediately after treatment and at one month. No carrier states were detected in the cases positive for *Salmonella typhi* or *paratyphi*. None of the treated typhoid fever cases experienced a clinical relapse. In this open study of levofloxacin 500 mg/day for one week in treatment of uncomplicated typhoid fever, a 100% clinical efficacy was obtained in 30 patients with minimal adverse reactions warranting more intensive studies for this new indication of an old but well known disease in the developing world.

INTRODUCTION

Typhoid fever is an acute systemic infection caused by *Salmonella enterica* serotype Typhi or Paratyphi. This disease is endemic in most developing countries, including South and Southeast Asia (including Indonesia), Central America and other countries which are populous, have high urbanization and a lack of proper hygiene and sanitation (Parry *et al,* 2002). The worldwide incidence of typhoid fever is estimated to be approximately 16 million cases annually, of which 7 million cases occur in Southeast Asia. More than 600,000 people die due to this disease each year (Ivanoff, 1995).

The main symptom of this disease is fever with a step ladder pattern, followed by headache, malaise, anorexia, nausea, generalized aches and abdominal disturbances like discomfort, constipation or diarrhea. In severe cases intestinal bleeding and perforation can occur which may potentially be fatal. Disturbance in consciousness from apathy, delirium or coma may be present. Other symptoms, such as a coated tongue, enlargement of the liver and spleen, relative bradycardia and rose spots definitely support the diagnosis (Gill and Beeching, 2004).

Sometimes the symptoms of typhoid fever are not typical and are misinterpreted. Other common infectious diseases, like malaria, dengue fever, pneumonia, tuberculosis or meningi-

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tis, sometimes mimic typhoid fever and may be difficult to distinguish in the early course of the disease. Early recognition and management of typhoid fever is needed to avoid the severe complications and possible fatality (Khosla, 1992).

Chloramphenicol, ampicillin, cotrimoxazole and fluoroquinolones are potent and commonly used drugs in the treatment of typhoid fever. Presently some *S. typhi* strains are known to be resistant to conventional drug treatment. (Mirza *et al* 1996). As levofloxacin is an optically pure levorotatory isomer of ofloxacin, it may be assumed that successful treatment of typhoid fever with ofloxacin may extend to this isomer. As is the case with ofloxacin, levofloxacin has a broad spectrum of antimicrobial activity, and is effective against gram-positive and gram-negative bacteria (Goto *et al,* 1992). Data regarding the efficacy of levofloxacin in the treatment of typhoid fever is at present not available. This open pilot study regarding the efficacy and safety of levofloxacin in the treatment of typhoid fever was initiated by the Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, University of Indonesia in Jakarta.

PATIENTS AND METHODS

An open study was conducted in the hospitals affiliated with the University of Indonesia, Department of Internal Medicine, Dr Cipto Mangunkusumo National General Hospital between August 2003 and May 2004.

The inclusion criteria were: male or female aged between 18 and 65 years old with clinical typhoid fever without signs of complications, agreeing to join this study after being properly informed of the objectives of study and after signing a consent form. The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Indonesia.

The exclusion criteria were as follows: age below 18 years, pregnant or lactating females, severe or moribund cases, immunocompromized conditions, renal insufficiency (blood creatinin >1.4 g/dl), history of allergy to fluoroquinolones, history of convulsions or photosensitive reactions, usage of drugs with potential interactions with levofloxacin, such as theophyllin or warfarin.

Subjects who took antimicrobial medication would be washed out for 2-3 days. Patients with fever persisting after the wash-out period would be treated with levofloxacin (Cravit, Daiichi) 500 mg once daily (oral or iv) for 7 days. Other concomitant treatments were recorded. Antipyretics were given if the body temperature reached 40°C or above.

The diagnosis of typhoid fever was performed by Widal serology test (Pang *et al*, 1983; Hardi *et al*, 1992), gall culture (from blood, feces and urine) and PCR for *Salmonella typhi* (Song *et al*, 1993; Prihatini *et al*, 1998). Hematology, biochemical and serological examination (white blood cells, differentiated count, C-reactive protein, bilirubin, ALT, AST, serum creatinin) were performed to asses the basic clinical condition.

Diagnostic criteria were classified into definite and probable cases. Definite cases were defined as positive gall cultures or PCR *Salmonella typhi* or Widal serology agglutinin O titer $\geq$1/640 or H liter >1/1280 or an elevated repeat O titer twice or more the initial titer. Probable cases were defined as Widal serology agglutinin O titer 1/320 or H titer 1/640. Clinical efficacy was defined as a successful response or failure. Time to defervescence was counted hourly from start of treatment until clearance of fever. Clinical side effects were classified as mild, moderate and severe.

RESULTS

Fifty-three subjects were screened for this study. Five subjects were excluded because of unfulfilled inclusion criteria (severe condition, pregnancy or spontaneous resolution of fever before treatment was started). From 48 subjects who received levofloxacin, 3 subjects withdrew because of vomiting (1 case) and skin rash/pruritus (2 cases), 5 subjects were excluded because of another diagnosis (dengue fever, gram-negative sepsis or streptococcal pneumonia) and 10 subjects were excluded because of not fulfilling microbiological or serological criteria set out in the study protocol.

Thirty subjects were analyzed, consisting of

Table 1
Subject characteristics (n=30).

	n	%
Sex		
Male	11	36.7
Female	19	63.3
Age (mean 31.7 years)		
<20	5	16.7
21-30	12	40.0
31-40	10	33.3
41-50	1	3.3
>51	2	6.7
Fever before treatment (mean 6.1 days)		
<4 days	3	10.0
4 days	5	16.7
5 days	6	20.0
6 days	3	10.0
7 days	4	13.3
8 days	6	20.0
9 days	1	3.3
10 days	2	6.7

Table 2
Distribution of subjects according to diagnostic criteria.

Diagnostic criteria	n	%
Definite (n= 21)		70
Positive microbiological blood culture	4	
Positive *Salmonella typhi* PCR	8	
Positive *S. typhi* PCR & blood culture	1	
Widal agglutinin O titer 1/640	1	
Widal agglutinin H titer 1/1280	1	
Increasing Widal agglutinin O titer ≥ 2 times	6	
Probable (n=9)		30
Widal agglutinin O titer 1 /320	7	
Widal agglutinin H titer 1/640	2	

Table 4
Adverse events experienced (n=48).

Adverse events	n	%
Mild		
Nausea[a]	4	8.3
Vomit[a]	1	2.1
Insomnia[a]	1	2.1
Rash /Pruritis[b]	2	4.2
Moderate		
Meteorism[c]	1	2.1
Severe		
None		

[a]probably related [b]definitely related [c]unlikely related

11 males and 19 females, age 18 to 58 years old (mean 31.7 years). Duration of fever before treatment was between 1 to 10 days (mean 6.1 days) (Table 1).

A definite diagnosis of typhoid fever was obtained in 21 subjects (70.0%) and probable cases in 9 subjects (30.0%). The distribution of subjects according to diagnostic criteria can be seen in Table 2.

A good clinical response was obtained in all 30 subjects (100%). There was no failure of treatment. Defervescence was noted to occur in 1 to 5 days (mean 2.43 days) (Table 3).

Five subjects with *S. typhi* positive blood cultures were evaluated at the end of treatment with no growth on re-culture. All of these subjects also showed negative *S. typhi* stool and urine cultures on 4 weeks follow-up.

Adverse events were evaluated in 48 subjects who received levofloxacin treatment. Nau-

Table 3
Clinical results of treatment.

Treatment results	Definite cases		Probable cases	
	n	%	n	%
Clinical efficacy				
Response	21	100	9	100
Failure	0		0	
Defervescence on:				
1st day after treatment	4	19.0	1	11.1
2nd day after treatment	6	28.6	6	66.7
3rd day after treatment	10	47.6	1	11.1
4th day after treatment	0		1	11.1
5th day after treatment	1	4.8	0	
Mean (days)	2.43		2.22	

Table 5
Comparison of defervescence in typhoid fever in local studies.

Name of Drug	Dosage	Duration	Fever clearance	References
Ciprofloxacin	500 BID	6 days	3.6 days	Nelwan *et al,* 1995a
Ofloxacin	600 mg daily	7 days	3.4 days	Nelwan *et al,* 1995b
Pefloxacin	400 mg daily	7 days	3.1 days	Nelwan *et al,* 1992
Fleroxacin	400 mg daily	5 days	3.4 days	Nelwan *et al,* 1998
Levofloxacin	500 mg daily	7 days	2.4 days	This study 2003/4

sea was experienced by 4 patients, vomiting, meteorism and insomnia in one patient, respectively, and rash in two of the subjects. No one experienced severe or fatal adverse events.

All intestinal side effects were classified as probably related to typhoid fever (nausea, vomiting and meteorism). Pruritic rash was suspected due to an allergic reaction to levofloxacin, as these subjects did not receive other medications. One patient withdrew because of vomiting and 2 patients because of possible skin allergy (Table 4).

DISCUSSION

Various previous studies in foreign as well as in our own clinical setting showed excellent clinical and bacteriological efficacy for the treatment of typhoid fever with fluoroquinolones like ciprofloxacin (Ramirez *et al,* 1986; Nelwan *et al* 1995a), ofloxacin (Velmonte *et al,* 1989; Nelwan *et al,* 1995b), pefloxacin (Ait Khaled *et al,* 1990; Nelwan *et al,* 1992). Ofloxacin and pefloxacin were given as a single dose of 600 mg and 400 mg, respectively, in our local studies and ciprofloxacin was administered as 2 x 500 mg. Fleroxacin was given 400 mg daily. Fever clearence in uncomplicated typhoid fever patient is shown in Table 5 for each of the different fluoroquinolones. Levofloxacin in this study performed slightly better, with an average defervescence occurring within 2.5 days while in previous studies with other fluoroquinolones it took over 3 days before the patients became free from fever.

In this series of patient where medical care was sought earlier because of a huge dengue hemorrhagic fever outbreak in the capital city which occurred at the same time as the study, medical care was sought on the sixth day, which differs from previous studies where the average duration of fever before hospital admission was more than 10 days. This may explain the faster response to treatment in this study group (less than 3 days) compared to over 3 days in studies with previous generation of fluoroquinolones. One feature all these local studies had in common was that none became carriers of Salmonellae. This outstanding feature is significantly different from the chloramphenicol treated patient, where 16.8 % may become post-treatment carriers in the clinical setting, and therefore forms a threat to the family as well as the community (Nasir, 1989).

In this study out of 48 patients, one withdrew because of vomiting and two because of pruritic rash. Six cases had gastrointestinal adverse effects. It is difficult to asses the adverse effects because typhoid fever affects the gastrointestinal tract. Japanese data reports 2.3% of gastrointestinal side effects while US/European data report twice as many adverse reactions in their population, giving figures more reliable than those reported for typhoid fever in this series. Central nervous system and skin side effect in all the studies were minimal (around 0.5%) making levofloxacin one of the safest fluoroquinolones used (Ball *et al*, 1999).

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