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Full Length Research Paper

Intravenous administration of ciprofloxacin alongside levofloxacin in patients with complicated typhoid fever

Susilo Ali Alatas[1]*, Nicholas Wahid[2], Pevita Kalla[3], Ahmadun Herfanda[4], Aburizal Hidayat[1], Jusuf Pearce[2], Afgansyah Aburizal[5], Taufik Bakrie[5], Christine Alexander [6] and A. Syahputra[6]

[1]Division of Tropical and Infectious Disease, Department of Internal Medicine, University of Diponegoro Semarang, Indonesia.
[2]University of Airlangga, Surabaya, Indonesia.
[3]University of Indonesia, Jakarta, Indonesia.
[4]University of Padjadjaran, Bandung, Indonesia.
[5]University of Brawidjaya, Malang, Indonesia.
[6]University of Hasanudin, Makasar, Indonesia.

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In this study, 137 patients treated for complicated typhoid fever were randomized to either intravenous levofloxacin 500 mg once daily (OD), which then switched to sequential oral 500 mg levofloxacin, or intravenous ciprofloxacin 400 mg twice daily (BID), which then switched to oral ciprofloxacin 500 mg BID in the same course of 10 days. Resolution of fever occurred on the average after 3.47 days of treatment in the levofloxacin group and 4.08 days of treatment in the ciprofloxacin group. A significant difference was obtained between the two groups. In both groups, there were cases of clinical relapse after typhoid fever treatment; one case (2%) in the levofloxacin group and three cases (4%) in the ciprofloxacin group. During treatment, one or more adverse events were reported in 8 out of 69 (11.6%) patients in the levofloxacin group as compared to 21 out of 68 (30.1%) patients in the ciprofloxacin group. Post treatment stool examination detected no carrier state in both groups of study. Compared to ciprofloxacin, levofloxacin 500 mg daily, administered intravenously which then switched orally, for complicated typhoid fever, showed better clinical as well as laboratory outcomes and less occurrence of adverse reactions.

Key words: Ciprofloxacin, levofloxacin, complicated typhoid fever.

INTRODUCTION

Typhoid fever is a potential life-threatening disease and may produce severe complications if not treated in its early stages. In the developing world, typhoid fever is still common; where it affects about 27 million people which suffer from enteric fever each year, with about 200,000 deaths (Crump et al., 2004). Ciprofloxacin is accepted as a drug of choice for typhoid fever and has been used for almost two decades (Manson-Hahr, 2009; World Health Organization, 2010; Braunwald et al., 2004) but reduced susceptibility to ciprofloxacin has been reported widely since 1994 (Chitnis et al., 2006).

More important is the fact that laboratory reports of resistance to ciprofloxacin are on the increase, especially in the South Asian subcontinent (Renuka et al., 2005; Mushtaq, 2006; Parry et al., 2006). At the present time, serious thought is being given about the wisdom of treating future typhoid fever cases with ciprofloxacin (Chitnis et al., 2006). Another fluoroquinolone, levofloxacin, is also very effective against the whole spectrum of Gram-negative microorganisms and it

*Corresponding author. E-mail: ali.alatas@yahoo.com

Table 1. Clinical score for typhoid fever.

S/N	Signs and symptoms	Score
1	Fever < 1 week	1
2	Headache	1
3	Weakness	1
4	Nausea	1
5	Abdominal pain	1
6	Anorexia	1
7	Vomiting	1
8	Disturbed GI motility	1
9	Insomnia	1
10	Hepatomegaly	1
11	Splenomegaly	1
12	Fever > 1 week	2
13	Relative bradycardia	2
14	Typhoid tounge	2
15	Melena tools	2
16	Impaired consciousness	2
Total score		20

exhibits excellent pharmacokinetic and pharmacodynamic properties (Davis and Bryson, 1994; Croom and Goa, 2003). The aim of this study is to compare the efficacy, safety and tolerability of levofloxacin versus ciprofloxacin in the treatment of complicated typhoid fever.

METHODS

This single-blind comparative open label study was conducted at the Division of Tropical and Infectious Diseases of 6 Faculties of Medicine in Indonesia, from April 2007 until April 2009. One hundred and thirty seven patients aged 18-65 years were recruited from teaching hospital of each faculty of medicine, but only 108 cases were actually studied.

The objectives of this study were to compare the efficacy, safety and tolerability of levofloxacin compared to ciprofloxacin in the treatment of complicated typhoid fever. All efficacy analyses excluded patients who did not fulfill final inclusion criteria. Primary end points used to summarize clinical outcome at post therapy and follow up study included: clinical cure rate at the end of treatment schedule, time to defervescence (resolution of fever), and microbiological clearance at end of treatment course. Secondary end points included clinical relapse rate after treatment and occurrence of carrier status. For safety end points, we evaluated adverse reactions in clinical observation and laboratory values.

The main inclusion criteria were patients with definite case of complicated typhoid fever. Definite case of complicated typhoid fever was diagnosed based on fever (> 37.8°C) for 3-20 days, having a clinical score for typhoid fever ≥ 10 (Table 1) with either one or more of the following criteria: positive result of *Salmonella typhi* culture, positive result of PCR for *S. typhi*, positive result of Tubex-TF (Anti *S. typhi* IgM), more than four-fold increase of Widal titer (1 week), titer Widal O 1/640 or H 1/640 at repeated examination; and patient with one or more complication, namely: chronic carrier, convalescent carrier, intestinal bleeding, perforation, perforation-peritonitis, reactive hepatitis, typhoid hepatitis, gastritis, paralytic ileus, bronchopneumonia, myocarditis, encephalopathy, toxic typhoid, febrile convulsion, acute renal failure, typhoid nephropathy, sepsis, septic shock, selapse, psychosis, and death. Probable case was defined as titer Widal O 1/160 or H 1/320 at single examination, whereas possible case was defined as clinical typhoid fever that does not meet the criteria as mentioned above. The analysis was performed for definite cases only. Following the explanation of the nature of the study, the patient was required to sign the informed consent. A female of childbearing potential may be enrolled in this study if she has a negative pregnancy test before starting the study, is routinely using adequate contraception prior to and during the study, and agreed not to attempt to become pregnant during the study.

As shown in Table 1, the total score has a maximum of 20. If the total score is >13, the patient is most likely to suffer from typhoid fever. If the total score is 8 - 12, the patient has 50% chance of suffering from typhoid fever. If the total score is <7, the patient has very limited chance of suffering from typhoid fever (Nelwan, 1991).

We excluded patients who have fever more than 21 days; patients with serum creatinine > 1,4 g/dL, D-dimer > 500 mg/mL, a history of adverse reaction or known allergy to quinolone, a suspected infection at another site that requires systemic antibacterial therapy, a life threatening infection or terminal illness with fatal outcome within 48 h, a serious underlying illness, including immunocompromised conditions and/or neutropenic patients, a history of convulsive disorders, a history of photosensitive reaction, has previously been enrolled in this study, theophylline or warfarin medication; patients who need specific treatment and care such as required for disseminated intravascular coagulation [DIC], in need of instant blood transfusion or has to be admitted to the intensive care unit; patients transferred to ICU due to deteriorating conditions within 48 h will be considered as dropped out cases; and history of having parental antibiotics within the last 72 h. The study was reviewed and approved by the Ethics Committee of the University of Indonesia.

We randomized 137 treated patients to receive either levofloxacin or ciprofloxacin. From these 137 patients, 121 fulfilled the criteria of typhoid fever diagnosis. Among the 121 patients with confirmed diagnosis of typhoid, 3 patients were categorized as clinical (probable/possible) cases, and 10 patients dropped out (excluded from the study) so that finally we only have 108 evaluable patients

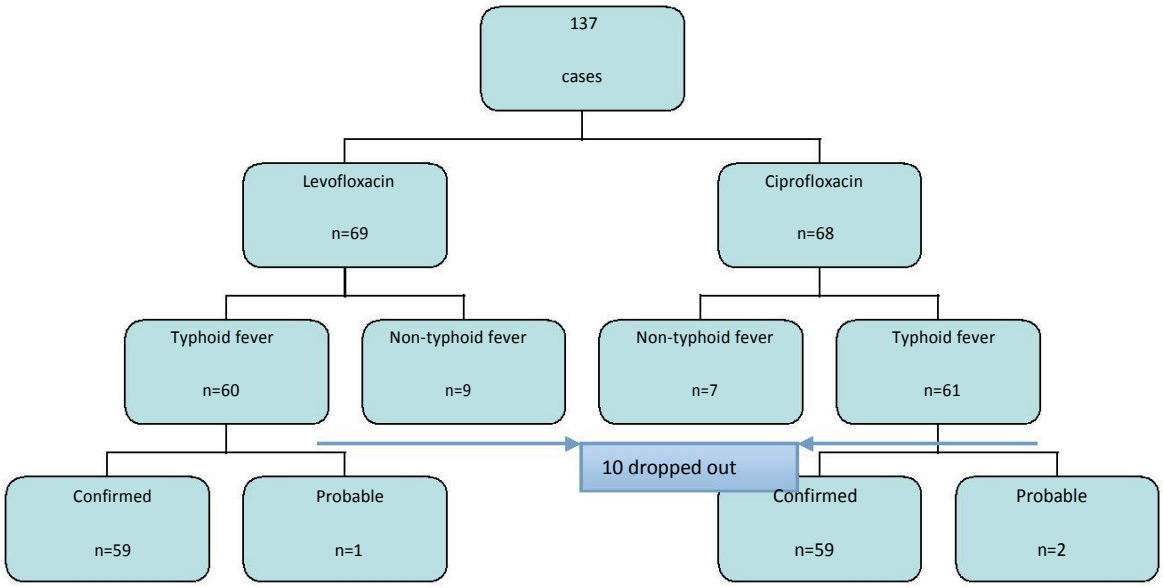

Figure 1. Flow chart of patients' randomization.

Table 2. Baseline demographic and clinical data.

Characteristic	Levofloxacin group (n=59)	Ciprofloxacin group (n=59)
Male:female ratio	1.16	0.9
Mean age (years)	32.1	32.2
Mean clicical [clinical] score (points)	12.22	12.45
Mean duration of fever (days)	9.05	9.58

(Figure 1).

In this comparative open label clinical study, one group receiving levofloxacin intravenously 500 mg once daily which may be switched to sequential oral 500 mg levofloxacin as a condition improved with total length for 10 days. The other group will receive ciprofloxacin intravenously 400 g bid for comparison and as a condition improved the IV-oral switch may be carried out using oral ciprofloxacin 500 mg bid, the whole course also lasting for 10 days.

One month later in the post treatment period, a final check-up will be done in all positive cases by having stool sample and clinical evaluation of complications previously present in these typhoid fever cases and to note the possible emergence of relapse and carrier cases of *S. typhi*. Any case that before one month suffered again from a fever should be reported immediately to the clinician for further examination of possible clinical relapse of typhoid fever. Demographic and clinical baseline data as well as clinical and micobiological responses to either levofloxacin 500 mg OD or ciprofloxacin 400 mg BID were analysed statistically. For baseline characteristic, gender was compared between each of the two treatment groups using X^2 Chi square. For ages, days of fever before hospital admission, clinical score and efficacy were compared between each of the two groups using Mann Whitney U Test.

RESULTS

A total number of 137 cases were recruited for this study on alpha and beta basis, which were then randomized into levofloxacin (69 patients) and ciprofloxacin group (68 patients). Typhoid fever was diagnosed in 59 patients for both groups. No statistically significant difference ($p > 0.05$) was observed for gender, age, race, infection status, and clinical condition for the final 59 confirmed patients in the levofloxacin and ciprofloxacin group (Table 2).

During the study, 2 patients in the levofloxacin group and 8 patients in the ciprofloxacin group dropped out for various reasons, so that we only have 57 and 51 evaluable cases in levofloxacin and ciprofloxacin groups, respectively. The most complication found in both groups was shown in Table 3. Clinical efficacy of both arms is shown in Table 4. Resolution of fever in the levofloxacin

Table 3. Complication of typhoid fever in evaluable cases.

Type of complication	Levofloxacin group (n=57)	Ciprofloxacin group (n=51)
Encephalopathy (disturbed consciousness), n (%)	5 (9)	8 (16)
Gastrointestinal bleeding, n (%)	9 (16)	9 (18)
Upper respiratory tract infection, n (%)	7 (12)	4 (8)
Lower respiratory tract infection, n (%)	5 (9)	4 (8)
Reactive hepatitis, n (%)	12 (21)	12 (24)
Cholecystitis, n (%)	0	1 (2)
Pancreatitis, n (%)	2 (4)	0
Pericarditis, n (%)	1 (2)	0
Abdominal colic, n (%)	3 (5)	1 (2)
Hypokalemia, n (%)	0	1 (2)

Table 4. Clinical efficacy of levofloxacin versus ciprofloxacin in complicated typhoid fever.

Clinical efficacy	Levofloxacin (n=57)	Ciprofloxacin (n=51)	p value
Mean defervescence, days	3.47	4.08	<0.05
Clinical relapse, n (%)	1 (2)	3 (4)	>0.05

Table 5. Treatment-related clinical and laboratory adverse events of levofloxacin and ciprofloxacin.

Adverse events	Levofloxacin (n=8)	Ciprofloxacin (n=20)
↑ Liver function test, n (%)	1 (1.4)*	2 (3.4)*
Allergy unspecified, n (%)	1 (1.4)	0
Pruritus, n (%)	3 (4.3)	5 (7.4)
Facial urticaria, n (%)	1 (1.4)	0
Rash, n (%)	0	4 (5.9)
Hot rash, n (%)	1 (1.4)	0
Urine:erythrocyte ↑, n (%)	1 (1.4)**	0
Chest depression, n (%)	0	1 (1.5)
D-dimmer ↑, n (%)	0	1 (1.5)***
Laryngospasm, n (%)	0	1 (1.5)
Sneezing, n (%)	0	1 (1.5)
Nausea, n (%)	0	3 (4.4)
Insomnia, n (%)	0	1 (1.5)
Pain injection site, n (%)	0	1 (1.5)

*During treatment increase of SGOT/SGPT >3 times; **Slight increase of erythrocytes in urine (case with abdominal colic); ***Prolonged increase of D dimer (case with gastrointestinal bleeding).

and ciprofloxacin group occurred on the average after 3.47 and 4.08 days of treatment, respectively. A significant difference (P=0.03) of mean defervescence was obtained between the two groups. In both groups, there were cases of clinical relapse after typhoid fever treatment, one case in the levofloxacin group and three cases in the ciprofloxacin group of patient.

In both groups, post treatment stool examination at day 30-40 did not show any isolate of *S. typhii*, which means that no carrier status was detected. During treatment, one or more adverse events were reported in 8 out of 57 patients (14.3%) in the levofloxacin 500 mg OD group, while in the ciprofloxacin group, one or more adverse events were reported in 21 out of 51 patients (41.1%). The most common treatment related adverse event found was pruritus occurring in both groups with more or less in the same frequency.

There was a significant higher proportion of skin adverse reactions in the ciprofloxacin group patients (P<0.05) (Table 5).

DISCUSSION

The average duration of fever was 9.05 days in levofloxacin group and 9.58 days in ciprofloxacin group. A clinical severity score used for bed side diagnosis of typhoid fever scored 12.2 points for levofloxacin group and 12.45 for ciprofloxacin group. In the final typhoid cases, the clinical diagnosis was endorsed by microbiology culture, PCR, Tubex F, IgM/Elisa, or serology.

The most prominent complication in both groups was reactive hepatitis. Multiple complications were recorded in 17 patients of each group, such as gastrointestinal bleeding, disturbed consciousness, reactive hepatitis, bronchopneumonia, etc. We also recorded cases with comorbid conditions namely urinary tract infection, asthma bronchiale, type 2 diabetes, severe constipation, etc., in 13 (22.8%) and 11 (21.5%) patients from levofloxacin and ciprofloxacin group, respectively.

Defervescence of fever was averagely seen within 3 and 4 days after starting levofloxacin and ciprofloxacin treatment, respectively. One relapse occurred in the levofloxacin group while 3 relapses occurred in the ciprofloxacin group. Relapse finding in this study similar with the former reports about fluoroquinolones used in Indonesia for uncomplicated typhoid fever which definitely showed clinical relapse (Davis and Bryson, 1994). Further investigation is needed to find out whether this is a sign of increasing resistance against fluoroquinolones. No carrier of *S. typhi* was found in both groups at day 30-40. We detected 2 cases with positive Salmonella spp isolate in levofloxacin group but were not further analyzed because the sample is very limited.

Adverse reactions were more pronounced in the ciprofloxacin group (2.5 fold higher) compared to the levofloxacin group. In this study, we also observed reactions to the parenteral formulation of levofloxacin and ciprofloxacin. In the levofloxacin group, one patient complained of pruritic rash and in the ciprofloxacin group, 2 patients complained of pain and pruritic rash. In all those cases, treatment was discontinued. The one who complained of pain at intravenous injection site was switched to levofloxacin that was surprisingly well tolerated.

Besides local immediate reaction at injection site, we also found systemic adverse reactions especially in ciprofloxacin group, in which patients with pruritus, rash, pruritic rash, chest depression, laryngospasm, and convulsion, were discontinued for the medication. Two patients in levofloxacin group also discontinued the medication due to urticaria and unspecified cause.

Another point of intent in the study was the adverse reactions after IV-oral switch. One patient in the levofloxacin group had pruritic reaction but was able to continue the medication. In the ciprofloxacin group, we recorded 1 patient with pruritic and 1 patient with abdominal pain which made them to discontinue the medication. This study found fewer incidences of adverse reactions with levofloxacin as compared with ciprofloxacin. It can be said that levofloxacin is one of the safest and well tolerable fluoroquinolone. The finding of this study matches with the findings of previous similar studies (Nelwan et al., 2013; Lipsky and Baker, 1999; Rodvald, 2006; Hadisaputro, 2012).

Conclusion

In conclusion, complicated typhoid fever marked by either gastrointestinal or extra-gastrointestinal complication, could be treated by both treatment regimens consisting of initial parenteral 500 mg levofloxacin once daily or 400 mg ciprofloxacin BID which then switched to oral 500 mg levofloxacin OD or 500 mg ciprofloxacin BID, with excellent result of clinical and bacterial efficacy. Adverse reactions in the levofloxacin group were less severe, indicating greater tolerability compared to ciprofloxacin group. Besides giving a better result, this trial also shows that levofloxacin provided a more simple drug administration hence the drug can become a better option for drug of choice in complicated typhoid fever management.

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