Open Study on Efficacy and Tolerability of Ciprofloxacin XR Compared with Ciprofloxacin BID in The Treatment of Typhoid Fever

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ABSTRACT

Aim: to compare the efficacy and tolerability of ciprofloxacin extended-release and ciprofloxacin intermediate release in the treatment of typhoid fever.

Methods: a prospective, open labelled, clinical trial, comparing the safety and efficacy of extended-release ciprofloxacin 1000 mg once daily (Ciprofloxacin XR) and ciprofloxacin intermediate release 500 mg two times daily (Ciprofloxacin bid) was performed in adult with typhoid fever. Diagnosis for typhoid fever was based on Widal serology test, blood culture and Polymerase Chain Reaction (PCR) for Salmonella typhi. A two-sided student t-test and chi-square or Fisher’s exact test were used for the analysis of clinical responses.

Results: good clinical responses were obtained in 32 subjects (14 with Intermediate release ciprofloxacin and 18 with Extended-release ciprofloxacin) and there were no failure case (0%). Day to reach defervescence in Ciprofloxacin BID (mean 3.28 days) was similar to Ciprofloxacin XR group (mean 3.72 days) with p=0.43. Mild side effects were noted in 7.1% of subjects who received Ciprofloxacin BID compared by 22.2% in subjects who received Ciprofloxacin XR, with p=0.29. There were no moderate or severe side effects on both drugs.

Conclusion: clinical outcomes were similar for the two treatments and both treatments were well tolerated. Once daily ciprofloxacin XR was safe, effective, and non-inferior to twice-daily ciprofloxacin IR in the treatment of typhoid fever.

Key words: ciprofloxacin XR, ciprofloxacin BID, typhoid fever.

INTRODUCTION

Typhoid fever is an acute systemic infection caused by Salmonella enterica serotype typhi or paratyphi. This disease is endemic in developing countries such as India, Southeast Asia (including Indonesia), Central America and other countries with high population, which have high urbanization and lack of proper hygiene and sanitation.1-7

The fluoroquinolones are widely regarded as optimal for the treatment of typhoid fever in adults. They are relatively inexpensive, well tolerated and more rapidly and reliably effective than the former first-line drugs, such as: chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole. The majority of isolates are still sensitive. The fluoroquinolones attain excellent tissue penetration, kill S. typhi in its intracellular stationary stage in monocytes/macrophages and achieve higher active drug levels in the gall bladder than other drugs. They produce a rapid therapeutic response, i.e. clearance of fever and symptoms in three to five days, and very low rates of post-treatment carriage.1-8

Ciprofloxacin is a fluoroquinolone derivative which is well absorbed in GI tract and achieves high concentrations in the plasma and tissue/cell and thus has potential advantages over other antimicrobials in the treatment of typhoid fever (gram negative bacteria). Ciprofloxacin extended-release tablets contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration, ciprofloxacin extended-release tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The advanced bi-layer matrix formulation of ciprofloxacin extended-release provides rapid and sustained in vitro activity 35% of ciprofloxacin extended-release is delivered immediately, providing high levels in the bloodstream within the first 1-2 hours. Ciprofloxacin extended-release is well tolerated. In a
clinical trial, no significant differences in adverse events between ciprofloxacin extended-release and ciprofloxacin were observed in patients with urinary tract infections (UTI). There was no report about usage of ciprofloxacin extended release in typhoid fever.8-11

This is the first open study aimed at comparing the efficacy and tolerability of ciprofloxacin XR and ciprofloxacin BID treatment in patients with typhoid fever.

METHODS

The open label study was conducted at the Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, University of Indonesia, Persahabatan Hospital from July 2005 to June 2006.

The inclusion criteria were: male or female aged between 18 to 65 years old with clinically typhoid fever without any complication; agree to join this study after being properly informed and to sign of the informed consent. The study protocol had been approved by the Ethic Committee Medical Faculty University of Indonesia.

The exclusion criteria were: age below 18 years old, fever > 21 days, pregnant or lactation, severe cases, severe underlying disease including immune system disturbance, renal insufficiency (serum creatinine > 2.0 g/dl or creatinine clearance < 20 ml/min/1.73 m²), history of allergy to fluoroquinolone, convulsion, photosensitive reaction, had participated in this study before, and using drugs potentially interact with Ciprofloxacin such as theophyllin or warfarin.

In subjects who formerly took antibiotics, a wash-out period of about 2-3 days was implicated. Patient with fever persist after wash out period would be treated with ciprofloxacin extended release (Ciproxin® XR, Bayer) 1000 mg od (oral) or ciprofloxacin 500mg BID (Ciproxin®, Bayer) for 7 days which was given with random allocation. Other concomitant treatments were recorded. Antipyretic was given if body temperature reached 40°C or above.

Diagnosis for typhoid fever was performed by Widal serology test, Gall culture (from blood) and PCR for Salmonella typhii. Hematology, biochemical, serological and urine examination (Leucocytes, differentiatated count, CRP, Bilirubin, ALT, AST, Creatinin) were performed to asses the clinical response and adverse reaction.

Diagnostic criteria were classified into definite and probable cases. Definite cases defined if positive gall culture or PCR Salmonella typhi or Widal serology agglutinin O titer ³ 1/640 or H liter >1/1280 or increased of O titer twice or more. Probable cases defined if Widal serology agglutinin O titer 1/320 or H titer 1/640. Clinical efficacy was defined as success, fail or indefinite.

Day to reach decreased fever (defervescence) was also recorded. Adverse reactions were classified into mild, moderate or severe.

Student t-test, chi square or Fischer exact test were used for statistical analysis. A p value of < 0.05 was taken as the limit of significance.

RESULTS

Fifty subjects were enrolled in this study. From 21 patients who received Ciprofloxacin bid: 1 patient was excluded because of other diagnosis (pancreatits and peritonitis) and 6 patients excluded because of unfulfilled microbiological and serological criteria (clinical diagnosis). From 29 patients who received Ciprofloxacin XR: 1 patient was excluded because of allergic reaction and clinical diagnosis, 1 patient excluded because of adverse reactions of the drug (nasea and vomits), 2 patients excluded because of other diagnosis (malaria falciparum and pneumonia) and 7 patient excluded because of clinical diagnosis.

Thirty two subjects were analyzed, consisting of 24 males and 8 females. Fourteen subjects (the first group) were given ciprofloxacin bid: age between 18 to 35 years old (mean 23.5 years), duration of fever before treatment between 5 to 14 days (mean 7.57 days). Eighteen subjects (the second group) were given ciprofloxacin XR: age between 18 to 47 years old (mean 26.4 years), duration of fever before treatment between 5 to 20 days (mean 8.67 days). Generally, from their socio-demographic characteristics, these 2 groups were equal and there were no significant differences between them. (Table 1)

Definite diagnosis of typhoid fever was obtained in 29 subjects (90.6%) and probable cases in 3 subjects (9.4%). Distribution of subjects according to diagnostic criteria can be seen in Table 2.

Good clinical response was obtained in 32 subjects (14 with Ciprofloxacin bid and 18 with Ciprofloxacin XR/ 100 %) and there were no failure case (0 %). Day to reach fever decreased (defervescence) in Ciprofloxacin bid group was between 2 to 6 days (mean 3.28 days) and in Ciprofloxacin XR group was between 2 to 6 days (mean 3.72 days), but there were no significant differences between 2 goups. (Table 3 and 4)

Mild adverse reactions were experienced by 1 of 14 patients who received Ciprofloxacin bid (7.1 %). Meanwhile, from 18 subjects who received Ciprofloxacin XR, 4 subjects experienced mild adverse reaction (22.2 %). There were no significant differences between groups. There were no moderate or severe adverse reactions. (Table 5)
Evidence from various settings in Asia indicates that the fluoroquinolones are equally effective in the treatment of typhoid fever in children. However, the emergence of multidrug resistance (MDR) strains has reduced the choice of antibiotics in many areas. There are two categories of drug resistance: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (MDR strains) and resistance to fluoroquinolone drugs. Resistance to fluoroquinolones may be total or partial. The so-called nalidixic-acid-resistant *S. typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones compared with nalidixic-acid-sensitive strains. Nalidixic acid itself is never used for the treatment of typhoid. These isolates are susceptible to fluoroquinolones in disc sensitivity testing according to current guidelines. However, the clinical response to treatment with fluoroquinolones of nalidixic-acid-resistant strains is significantly worse than with nalidixic-acid-sensitive strains.\(^1,12,13\)

There is a significant number of MDR strains from the Indian subcontinent and some other Asian countries (not Indonesia). *S. typhi* has recently emerged as a problem in Kenya. Nalidixic-acid-resistant strains are now endemic in many areas of Viet Nam and have also been reported from the Indian subcontinent and Tajikistan. There are disturbing recent reports of the emergence of fluoroquinolone-resistant isolates in various parts of Asia and there have been a few reports of resistance to third-generation cephalosporins in the same region. Reassuringly, however, many of these reports are coupled with evidence of the re-emergence of sensitive isolates in the same regions.\(^1,12,13\)
Our experience in treatment of typhoid fever with Ciprofloxacin bid and Ciprofloxacin XR showed that these drugs were effective with 100% clinical response. This result corresponds to previous result of trial of patient with UTI using ciprofloxacin XR (Clinical cure in 95.5%). This result also corresponds to previous typhoid fever trial using ciprofloxacin bid (clinical cure in 97.9%).

Day of defervescence of Ciprofloxacin bid (mean 3.28 days) was similar to Ciprofloxacin XR (mean 3.72 days) with p= 0.305. This result corresponds to previous typhoid fever trial using ciprofloxacin bid which showed mean defervescence on 3.9 days.\(^1\)\(^{10}\)

Mild adverse reactions were noted in 7.1% of subjects who received Ciprofloxacin bid compared by 22.2 % in subjects who received Ciprofloxacin XR, with p= 0.6. The adverse reaction of Ciprofloxacin bid was nausea (2 %), and the adverse reaction of Ciprofloxacin XR were nausea (2%), vomit (2%) and rash (4%). There were no moderate or severe adverse reactions on both drugs. Adverse reactions encountered in our study (GI discomfort) were difficult to differentiate with the main GI symptoms of typhoid fever itself. Others may be contributed to known quinolone adverse reactions. The result of mild adverse reactions (nausea and vomits) corresponds to the result of previous trial of patients with UTI (0.6 and 2.2 %).\(^8\)

**CONCLUSION**

This open study on efficacy and tolerability of ciprofloxacin XR compared with ciprofloxacin BID in treatment of uncomplicated typhoid fever showed that both of the drugs have relatively equal efficacy and safety/tolerability (there are no significant differences between adverse reaction and day of defervescence). So, ciproxin XR can be used as an alternative drug of choice instead of ciprofloxacin BID in order to increase the compliance of the patient.

**REFERENCES**


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**Table 4. Day of Defervescence**

<table>
<thead>
<tr>
<th>Treatment results</th>
<th>Ciproxin bid (n=14) %</th>
<th>Ciproxin XR (n=18) %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(^{nd}) day of treatment</td>
<td>4 28.6</td>
<td>4 22.2</td>
<td>0.305(^\dagger)</td>
</tr>
<tr>
<td>3(^{rd}) day of treatment</td>
<td>4 28.6</td>
<td>3 16.7</td>
<td></td>
</tr>
<tr>
<td>4(^{th}) day of treatment</td>
<td>5 35.7</td>
<td>6 3.3</td>
<td></td>
</tr>
<tr>
<td>5(^{th}) day of treatment</td>
<td>0 0</td>
<td>4 22.2</td>
<td></td>
</tr>
<tr>
<td>6(^{th}) day of treatment</td>
<td>1 7.1</td>
<td>1 5.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^\dagger\) Fischer exact test

**Table 5. Distribution of Adverse Reaction of Ciprofloxacin bid and Ciprofloxacin XR (n=32)**

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Ciprofloxacin bid</th>
<th>Ciprofloxacin XR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>7.1</td>
<td>1</td>
</tr>
<tr>
<td>Vomit</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

\(^\dagger\) Fisher’s exact test