“Evaluation of efficacy and safety of fixed dose combination of Cefixime and Ofloxacin (CO2 Tablet) in the management of typhoid fever.”

1 Dr. Arif A. Faruqui, 2 Wasim Siddique

Abstract:

Study Background: To evaluate the efficacy and tolerability of fixed dose combination of Cefixime and Ofloxacin (CO2 Tablet) in the management of typhoid fever a post marketing surveillance study was carried out among 30 patients of age group 18-72 years suffering from Typhoid fever.

Materials & Method: Study drug CO2 (Medley Pharmaceuticals Ltd. Mumbai) containing Cefixime 200 mg + Ofloxacin 200 mg was administered to patients suffering from typhoid fever.

Result: 100% patients reported fever on the first day of treatment. Body temperature was significantly reduced from baseline (mean± SD) value 101.5± 0.84 °F to 98.34± 1.42°F, 97.26 ± 2.04°F and 97.06 ± 2.03°F on 3rd, 7th and 14th day respectively. There was frequent nocturnal awakening at the time of diagnosis; (mean ± SD) value was 3.06 ± 0.88; nocturnal awakening was due to high fever interfering with sound sleep. On 3rd day and onward there were no or few cases of nocturnal awakening. As per investigators assessment, 66.60% (20/30) of patient reported excellent, 30% (9/30) remarked as good and only 3.3% (1/30) of patient reported poor efficacy. As per investigators assessment about tolerability 56.6% (17/30) of patient reported excellent, 36.6% (11/30) of patient marked good and only 6.6% of patient reported poor tolerability. Rare incidences of headache and nausea were reported. No serious adverse events were reported which led to withdrawal of patients from the study.

Conclusion: Result of this study shows that combination of cefixime and ofloxacin is effective in the management of typhoid fever with excellent tolerability and safety.

Introduction:

Typhoid fever is a systemic infection caused by Salmonella typhi (S. typhi). The disease remains an important public health problem in developing countries. Transmission of the disease occurs through faecal-oral route, upon ingestion of contaminated water and food and inadequate sanitation, consuming raw milk products, flavored drinks and ice-creams. This disease can also spread through consumption of raw fruits and vegetables grown in fields irrigated with sewage water and fertilizer. Occurrence of the disease has to be confirmed by the presence of the pathogen either S. typhi or S. paratyphi in patient, which requires isolation of the bacteria from blood, stool or bone marrow.

In addition to the disease burden and mortality, over the last few decades, emergence of drug resistance among S.typhi and Salmonella paratyphi, which causes a clinically indistinguishable infection, poses major challenges. The emergence of multi drug resistance to S. typhi (MDRST) has been of major concern in recent years. MDRST is defined as strains of S. typhi resistant to all three first line antibiotics (chloramphenicol, ampicillin, and co-trimoxazole) for typhoid fever. The number of reported multi resistant typhoid fever increased rapidly throughout the world from 1989 onwards.
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Combination of cefixime & ofloxacin has been recently approved by DCGI and not many studies have been published about the efficacy and safety of cefixime with ofloxacin in management of typhoid fever in Indian patients. This study was conducted to find out the clinical experience of doctors with use of CO2 in typhoid fever.

**Materials and Method:**
The post marketing surveillance study was a non-randomized, open, non-comparative, multi centric and the drug CO2 tablet (Fixed dose combination of Cefixime 200 mg and Ofloxacin 200 mg, Medley Pharmaceuticals Ltd. Mumbai) was administered to 30 patients suffering from typhoid fever.

**Inclusion Criteria**
Patients of either gender 18 years or more willing to give informed consent were eligible to be included in the study if they had clinically suspected or culture confirmed or Widal test confirmed uncomplicated typhoid fever.

**Exclusion Criteria**
Patients were excluded from entry into the study if they had a known/suspected history of hypersensitivity to any of the antibiotic, hepatic encephalopathy, gastrointestinal bleeding, and known cases of hepatic or renal insufficiency, cardiac disease, pregnant or lactating women.

**Assessment of outcome**
Patients were prescribed to receive CO2 (cefixime 200 mg and Ofloxacin 200 mg) every 12 hrs for 10-14 days. At the time of entry into the study, base-line data were recorded. Patients were observed on 3rd, 7th and 14th day after enrolment into the study for assessment of symptoms.

Following parameters were observed:

**Assessment of primary outcome measure:** a) The reduction in body temperature on 3rd, 7th, and 14th day from baseline b) The time to defervescence (normalization of fever, i.e. achievement of body temperature of ≤ 98.4 degree Fahrenheit) during the study period c) Evaluation of respiratory rate d) Interference in sleep.

**Assessment of secondary outcome measure:** Global assessment of efficacy and safety; efficacy was evaluated at the end of the study by investigator. The incidences of adverse events were recorded. Tolerability and efficacy was evaluated based on the global assessment by the investigator on a 3 point scale marked as excellent/good/poor.

**Statistical analysis :**
Data analysis on patient demographics and various outcome measures were performed using graph pad prism 5. Comparison between the baseline values with the value on the 3rd, 7th and 14th day of treatment were made, as well as comparison in between these days by applying one way analysis of variance & the post hoc Turkeys multiple comparison test. Value of P<0.05 were considered significant.
Table 1.

Changing resistance pattern of *S.* enterica serotype typhi strains isolated at Kolkata, India

<table>
<thead>
<tr>
<th>Year</th>
<th>Ampicilin</th>
<th>Chloramphenicol</th>
<th>Cotrimoxazole</th>
<th>Tetracycline</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1992</td>
<td>All strain 100% resistant</td>
<td>All strain 100% resistant</td>
<td>All strain 100% resistant</td>
<td>All strain 100% resistant</td>
<td>All strain 100% resistant</td>
</tr>
<tr>
<td>1993-1997</td>
<td>30-35% strain regained susceptibility</td>
<td>30-35% strain regained susceptibility</td>
<td>30-35% strain regained susceptibility</td>
<td>30-35% strain regained susceptibility</td>
<td>30-35% strain regained susceptibility</td>
</tr>
<tr>
<td>1990-1999</td>
<td>All strains isolated during 1990-1999 were uniformly (100%) resistant to ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>40% strain susceptible to Ampicillin</td>
<td>50% susceptible to Chloramphenicol</td>
<td>40% strain susceptible</td>
<td>50% susceptible</td>
<td>Nine strains of typhi showed resistant to ciprofloxacin</td>
</tr>
</tbody>
</table>

**Observations:**

**Patient distribution**

A total of 30 patients were monitored in the study. All the patients completed the study and finally they were included for the final analysis. The patients were in the age range of 18-72 years old with 16 Male and 14 female. Study was conducted in 5 centres across India. Patients had a variety of complaint (Table 2.) including fever, sleep interference and increased respiratory rate.
Demographic and clinical characteristics (Baseline):

### Table 2.

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics (Baseline)</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>30/30 (100%)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>27/30 (90%)</td>
</tr>
<tr>
<td>Elevated Respiratory rate</td>
<td>14/30 (46.6%)</td>
</tr>
</tbody>
</table>

**Evaluation of Fever**:

Oral temperature was recorded at the baseline and on subsequent 3\(^{rd}\), 7\(^{th}\) and 14\(^{th}\) days of treatment. 100% patient reported fever on the first day of treatment. Body temperature was significantly reduced from baseline (mean ± SD) value 101.5± 0.84 °F to 98.34± 1.42°F, 97.26 ± 2.03°F and 97.06 ± 2.03°F on 3\(^{rd}\), 7\(^{th}\) and 14\(^{th}\) days of treatment respectively (Table 3). The reduction in body temperature was significantly (p< 0.0001) lower from baseline to 3\(^{rd}\) day and onwards. Also the time taken to achieve the normal body temperature was 2.93 ± 0.23 days.

### Table 3.

<table>
<thead>
<tr>
<th>Body surface temperature (°F)</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>101.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Day 3(^{rd})</td>
<td>98.34*</td>
<td>1.42</td>
</tr>
<tr>
<td>Day 7(^{th})</td>
<td>97.26*</td>
<td>2.04</td>
</tr>
<tr>
<td>Day 14(^{th})</td>
<td>97.06*</td>
<td>2.03</td>
</tr>
</tbody>
</table>

* (p< 0.0001)

![Figure 1. Effect of Cefixime-Ofloxacin combination on fever](image)
**Evaluation of Sleep Interference**

There was frequent nocturnal awakening at the time of diagnosis; (mean±SD) value was 3.06 ± 0.88; this nocturnal awakening was due to high fever interfering with sound sleep. On 3\(^{rd}\) day nocturnal awakening was reduced to 2.27± 0.70 and on 7\(^{th}\) day it was further reduced to 1.41± 0.73 and on 14\(^{th}\) day there was no or few cases of nocturnal awakening mean value was 0.44 ± 0.57. There was significant reduction in the nocturnal awakening from the baseline on 3\(^{rd}\) day of treatment and onward 7\(^{th}\) and 14\(^{th}\) day of treatment (P<0.001).

![Interference in sleep](image)

**Figure 2. Effect of Cefixime-Ofloxacin combination on Sleep Interference**

**Evaluation of Respiratory Rate**

There was slight increased respiratory rate at the baseline; (mean ± SD) value was 17.2± 4.2 respiration/min, on day 3\(^{rd}\) respiratory rate was 16.83± 4.6 (non significant from baseline), and on subsequent 7\(^{th}\) and 14\(^{th}\) day of treatment respiratory rate became normal (15.3± 4.5 and 13.03 ± 4.32 respiration/min respectively).

![Respiratory rate](image)

**Figure 3. Effect of Cefixime-Ofloxacin combination on Respiratory Rate**
Adverse Event
Concerning the adverse effect; rare cases of nausea (1/30), headache (2/30) and in one patient epigastric pain were reported which was of mild to moderate intensity & did not require discontinuation of therapy.

Global efficacy and safety evaluation
As per investigators assessment about efficacy of CO2 tablet (Cefixime 200 + Ofloxacin 200 mg), 66.60% (20/30) of patient reported excellent, 30% (9/30) remarked as good and only 3.3% (1/30) of patient reported poor efficacy. As per investigators assessment about tolerability 56.6% (17/30) of patient reported excellent, 36.6% (11/30) of patient marked good and only 6.6% of patient reported poor tolerability.

Discussion:
Today typhoid fever is a treatable disease. Improvement in personal hygiene, sanitation, early diagnosis, systemic screening to detect chronic typhoid careers, treatment of the careers, better treatment options have all improved the outcome of typhoid fever. But there are certain limitations in the management of typhoid fever like; difficulty in diagnosis and to overcome the development of resistance.
In the first week diagnosis is difficult because in this invasive stage the symptoms are those of a generalised infection without localizing features. Organisms are more frequently found during the second and third week in feces. So the diagnosis takes some time to find out the underlying cause of fever⁴.
Since diagnosis of typhoid fever is a time consuming activity in general practice so empirical therapy is mostly initiated by the practising physician. As the two pharmacologically distinct categories of drugs i.e. cephalosporins and fluoroquinolones act through different mechanism, they provide rapid bacteriological eradication, thus it is empirical to combine them for management of enteric fever.

Figure 4. Global assessment on efficacy and safety of the combination of Cefixime-Ofloxacin
Also WHO has recommended Cefixime & Ofloxacin as first line Therapy in Typhoid Fever. Moreover, DCGI (Drug controller General of India) approved (26/04/2010) this combination of Cefixime with Ofloxacin in the management of typhoid fever.

Studies indicate that emergence of resistance is less common when combination therapy is used. Improved efficacy of the combination compared with a fluoroquinolone alone is considered because of its synergistic effect; Cefixime inhibits bacterial cell wall synthesis & ofloxacin affects bacterial DNA gyrase. As both acts on different target sites, combination provides synergistic effect against most of the pathogens.

For the management of typhoid fever rapid cure is desirable to prevent the acute and chronic complications of salmonella infection. Drug resistance among S Typhi and Salmonella Paratyphi poses major challenge in management of typhoid fever.

Currently, the incidence of MDRST (multi drug resistance to S. typhi) varies from 25- 55% in India. Resistance has developed against most of the important therapies which were previously used as a 1st line of therapy.

In the present study we evaluated the efficacy and safety of fixed dose combination of cefixime and ofloxacin (CO2 tablet) in typhoid fever on various parameters like evaluation of fever, respiratory rate, interference in sleep during typhoid.

At baseline 100% of the patients reported with fever. There was significant reduction in fever from the baseline on 3rd, 7th and 14th day of the treatment. The mean defervescence time (no fever) was 2.93 ± 0.23 days with combined therapy of cefixime plus ofloxacin. This result was comparable to the previous study on the use of combination of cefixime and ofloxacin in the treatment of typhoid fever, where the mean defervesce time was 3.2 days.

Regarding respiratory rate 46.6% of patient had increased respiratory rate. Respiratory rate was lowered down to normal on the subsequent 3rd, 7th and 14th day of treatment. Sleep interference was observed in the study due to fever. Duration of sound sleep increased with fever subsiding from day 3rd onward and the nocturnal awakening was reduced from a baseline of 3.06 ± 0.88 to 2.27± 0.70, 1.41± 0.73 & 0.44 ± 0.57 on 3rd, 7th & 14th day respectively.

Regarding the evaluation of global efficacy and tolerability by the investigator, the combination showed very good efficacy (96.6% marked as good to excellent) and excellent tolerability (93.2%) & safety. Concerning the adverse effect; rare cases of nausea, headache and epigastric pain has been found which was of mild to moderate intensity & did not require discontinuation of therapy.

**Conclusion**:

In conclusion the fixed dose combination of cefixime and ofloxacin therapy achieves a better outcome (rapid clinical cure) for the empirical management of typhoid fever with excellent tolerability & safety.

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References: