Indian Journal of Basic & Applied Medical Research; September 2012: Vol.-1, Issue-4, P. 296-303

"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[1].

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[2]. 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

[1] Associate Vice President-Medical Services
Medley Pharmaceuticals Ltd.D-2,MIDC,
Andheri East,Mumbai-400093
Email: drfaruqui@medleylab.com
[2] Officer-Medical Services
Medley Pharmaceuticals Ltd.D-2, MIDC,
Andheri East,Mumbai-400093

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[1].

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[2]. 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 with most of the cases from the Middle East and Asia especially in the Indian subcontinent[3].

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 $\leq$ 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					
Year	**Ampicilin**	**Chloramphenicol**	**Cotrimoxazole**	**Tetracycline**	**Ciprofloxacin**
1990-1992	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant
1993-1997	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility
1990-1999					All strains isolated during 1990-1999 were uniformly (100%) resistant to ciprofloxacin
2000	40% strain susceptible to Ampicilin	50% susceptible to Chloramphenicol	40% strain susceptible	50% susceptible	Nine strains of typhi showed resistant to ciprofloxacin

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.

Demographic and clinical characteristics (Baseline)	Number of cases
Sex	
Male	16
Female	14
Clinical Characteristics	
Fever	30/30 (100%)
Sleep disturbances	27/30 (90%)
Elevated Respiratory rate	14/30 (46.6%)

Evaluation of Fever :

Oral temperature was recorded at the baseline and on subsequent 3rd, 7th and 14th 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 3rd, 7th and 14th days of treatment respectively (Table 3). The reduction in body temperature was significantly ($p < 0.0001$) lower from baseline to 3rd day and onwards. Also the time taken to achieve the normal body temperature was 2.93 ± 0.23 days.

Table 3.

Body surface temperature (°F)		
	Mean	**S.D.**
Baseline	101.5	0.84
Day 3rd	98.34*	1.42
Day 7th	97.26*	2.04
Day 14th	97.06*	2.03

* ($p < 0.0001$)

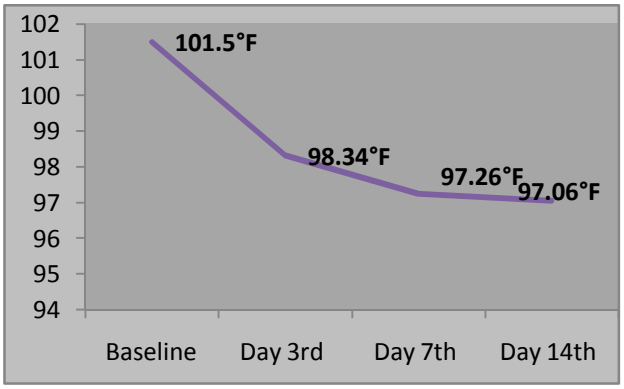

Figure1. Effect of Cefixime-Ofloxacin combination on fever

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 3rd day nocturnal awakening was reduced to 2.27± 0.70 and on 7th day it was further reduced to 1.41± 0.73 and on 14th 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 3rd day of treatment and onward 7th and 14th day of treatment (P<0.001).

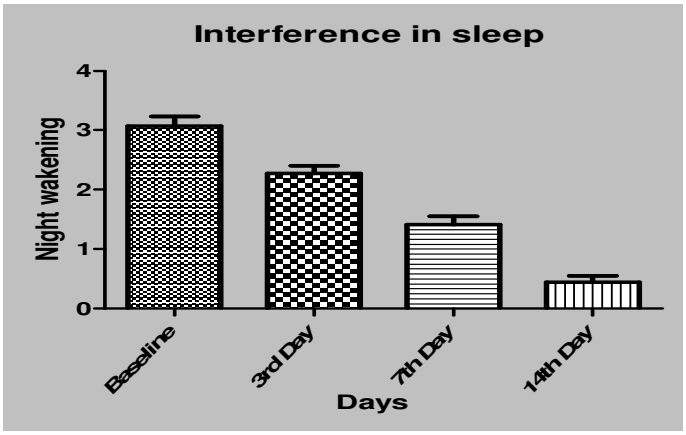

Figure 2. Effect of Cefixime-Ofloxacin combination on sleep Interference

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 3rd respiratory rate was 16.83± 4.6 (non significant from base line), and on subsequent 7th and 14th day of treatment respiratory rate became normal (15.3± 4.5 and 13.03 ± 4.32 respiration/min respectively)

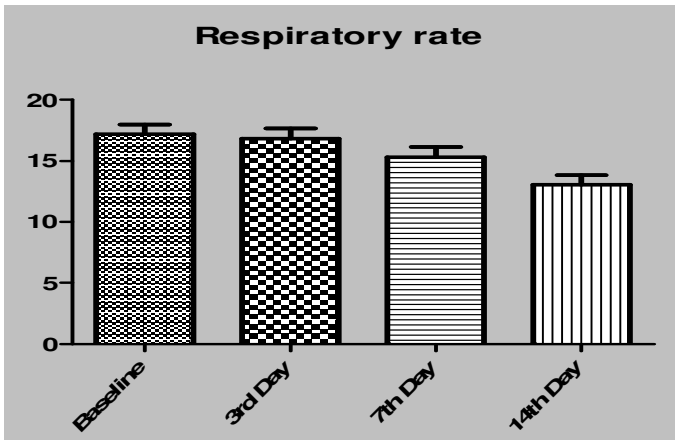

Figure 3. Effect of Cefixime-Ofloxacin combination on Respiratory Rate

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.

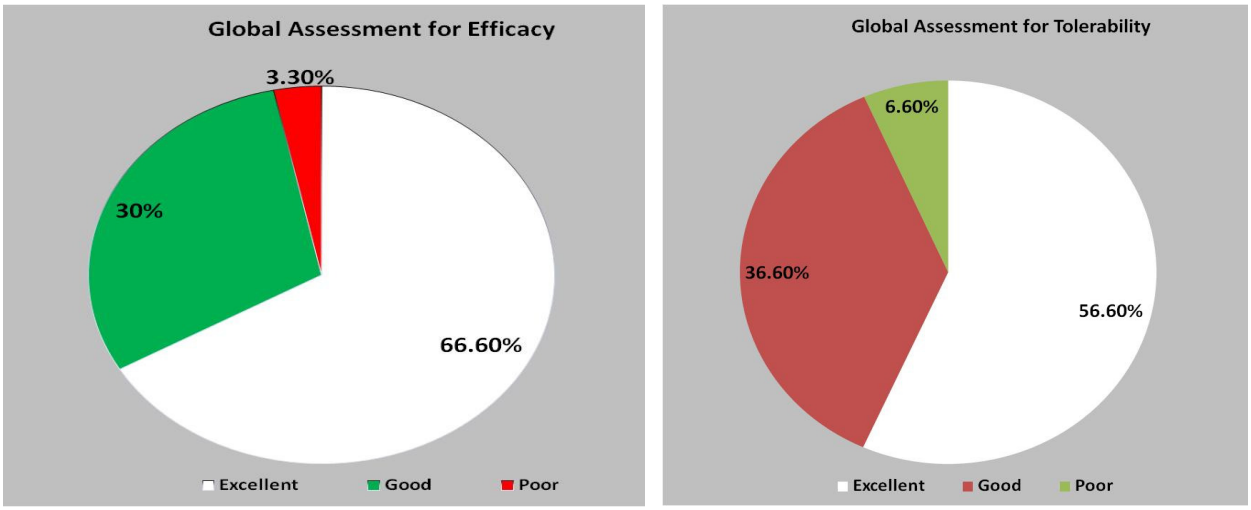

Figure 4. Global assessment on efficacy and safety of the combination of Cefixime-Ofloxacin

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 fever[4].

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.

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[5].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[6]. Resistance has developed against most of the important therapies which were previously used as a 1st line of therapy[4].

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 defervescence time was 3.2 days[7].

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.

Acknowledgement :

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/ publishers of all those articles, journals and books from where the literaturefor this article has been reviewed and discussed. We also acknowledge the support of following doctors for providing the observations on effect of CO2 in patients suffering from typhoid fever.

Dr. Deepak Saxena, Dr. Sanjay Dhar, Dr. Prawin Chandra, Dr. D. K. Arora, Dr. I. K. Shukla

References:

1. Sandhya A. Marathe, Amit Lahiri ,Vidya Devi Negi & Dipshikha Chakravortty. Typhoid fever & vaccine development. Indian J Med Res February 2012; 135: pp 161-169.
2. Gupta SK, Medalla F, Omondi MW et al. Laboratory-based surveillance of paratyphoid fever in the United States: travel and antimicrobial resistance. Clin Infect Dis. 2008 Jun 1; 46(11):1656-63.
3. K.H.Khan, Deepak Ganjewala and K.V. Bhaskara Rao. Recent advancement in Typhoid research - a review. Advanced Biotech; October 2008: 35-41.
4. Davidson's Principle and practice of Medicine 20th Edition: Page No: 324
5. Mouton JW. Combination therapy as a tool to prevent emergence of bacterial resistance Infection. 1999; 27 Suppl 2: S24-8.
6. Gautam V, Gupta NK, Chaudhary U, Arora DR. Sensitivity pattern of *Salmonella* serotypes in northern India. Braz J Infect Dis 2002; 6: 1-9.
7. Naik M, Braganza L, Nair S, Khandeparkar P. Open, Non-comparative evaluation of fixed dose combination of cefixime and ofloxacin in the treatment of uncomplicated typhoid fever. Indian Medical Gazette November 2010; Vol. CXLIV, No. 8, Page No. 415-421.

Date of manuscript submission: 30 July 2012 **Date of initial approval: 12 August 2012**
Date of Peer review approval: 20 August 2012 **Date of final draft preparation: 28 August 2012**
Date of Publication: 5 September 2012
Conflict of Interest: Nil, Source of Support: Nil.