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## EVALUATION OF EFFICACY AND SAFETY OF FIXED DOSE COMBINATION OF CEFIXIME AND OFLOXACIN (CO2 TABLET) IN THE MANAGEMENT OF RESPIRATORY TRACT INFECTION

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### ABSTRACT

Acute lower respiratory tract infections (LRTI) range from acute bronchitis and acute exacerbations of chronic bronchitis to pneumonia. Among these, pneumonia represents the most frequent cause of mortality, hospitalisation and medical consultation. **Objective:** To evaluate the safety and tolerability of fixed dose combination of Cefixime and Ofloxacin (CO2 Tablet) in the management of Respiratory tract infection a post marketing surveillance study was carried out among 215 patients of age group 18-72 years suffering from respiratory tract infection. **Materials & Method:** Study drug CO2 (Medley Pharmaceuticals Ltd. Mumbai) containing Cefixime 200 mg + Ofloxacin 200 mg was prescribed to be taken twice daily for a duration of 7-14 days depending upon the severity. Cough intensity, frequency of cough, fever and respiratory rate were recorded during three visit on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day of treatment. Safety and efficacy was evaluated based on the global assessment by the investigator based on a three point scale marked as excellent /good/poor. **Result:** 93.95% patients reported fever on the first day of treatment. Body temperature was significantly reduced from baseline mean value  $101 \pm 0.49$  °F to  $99.72 \pm 0.09$ °F,  $98.18 \pm 0.142$  and  $97.95 \pm 0.161$  on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day respectively. Similarly the cough intensity was significantly reduced on: 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day from baseline. On day 3<sup>rd</sup> cough intensity was reduced by 29.4% ( $p < 0.0001$ ), on the day 7<sup>th</sup> cough intensity was reduced by 58.90% ( $p < 0.0001$ ) and on 14<sup>th</sup> day it was further reduced by 79.63% ( $p < 0.001$ ) from the base line. There were repeated bouts of cough at the time of diagnosis; mean  $\pm$  SD value was  $15.59 \pm 11.65$  at base line. On day 3<sup>rd</sup>, number of bouts of cough was reduced to ( $10.6 \pm 8.7$  vs.  $15.5 \pm 11.6$ ) ( $p < 0.05$ ), on 7<sup>th</sup> day it was reduced to ( $5.804 \pm 5.707$  vs.  $15.59 \pm 11.65$ ) ( $p < 0.05$ ) from the base line and on the 14<sup>th</sup> day of treatment it was reduced to ( $2.024 \pm 3.751$  vs.  $15.59 \pm 11.65$ ) ( $p < 0.05$ ). On 14<sup>th</sup> day almost all the patients were devoid of bouts of cough. As per investigators assessment, 98 % of patients reported good to excellent and 2 % reported poor efficacy. As per investigators assessment about safety of CO2 97.9% of patient reported good to excellent and 2.1% 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:** In conclusion this postmarketing surveillance study of fixed dose combination of cefixime and ofloxacin (CO2 Tablet) antibiotic therapy achieves a better outcome for the empirical management of respiratory tract infection with excellent efficacy, tolerability & safety in the treatment of respiratory tract infection

**Keywords:** LRTI, Pneumonia, Bronchitis, Cefixime, Ofloxacin and CO2

## INTRODUCTION

Acute lower respiratory tract infections (LRTI) range from acute bronchitis and acute exacerbations of chronic bronchitis to pneumonia. Approximately five million people die from acute respiratory tract infections annually. Among these, pneumonia represents the most frequent cause of mortality, hospitalisation and medical consultation<sup>1</sup>. Antimicrobial treatment in LRTI has to be effective, partly because of the need to reduce the cost and also the problem of increasing resistance to the commonly used antibiotics<sup>2</sup>. It has also been suggested that the start of therapy should not be delayed for longer than six hours for diagnostic studies<sup>3</sup>. Compliance is also important, particularly in outpatient patients. A study related to medical compliance for the outpatient management of infectious diseases indicated that there was an inverse relationship between frequency of dose and compliance.

The most common symptom is cough, which is new or changed in character. Other symptoms include sputum production, breathlessness, wheezing, chest pain, fever, sore throat and coryza.

Distinguishing pneumonia from non-pneumonic lower respiratory tract infection in the community is also difficult, particularly without diagnostic radiology. So the empirical therapy is required with the combination of antibiotics with wider range of spectrum.

There is currently no general agreement on the definition of an exacerbation in COPD. A commonly used definition is based on an increase in symptoms of dyspnoea, sputum volume and sputum purulence with or without symptoms of upper respiratory infection. Bacteria are isolated from between 40-60% of acute exacerbations of COPD.

Since RTI involves more than one pathogen, so combination of antibiotic with wider spectrum of activity is suitable option for empirical therapy. As shown in Table 1. Following are the microorganisms that are frequently found in respiratory tract infection<sup>4</sup>.

**Table 1: Common organisms involved in respiratory tract infection & MIC<sub>90</sub> of cefixime and ofloxacin**

ORGANISM	CEFIXIME	OFLOXACIN
	[MIC <sub>90</sub> ( µg per ml)]	[MIC <sub>90</sub> ( µg per ml)]
<b>Organisms involved in respiratory tract infection</b>		
<i>Streptococcus pneumoniae</i>	0.12	2
<i>Staphylococcus aureus</i>	> 128.0	0.5-2 (MSSA)
<i>Staphylococcus epidermidis</i> (MSSE)	—	0.25-1 (MSSA)
<i>Staphylococcus epidermidis</i> (MRSE)	—	0.5 ≥16 (MRSA)
<i>Streptococcus pyogenes</i>	—	2
<i>Clostridium perfringens</i>	—	0.5-2
<i>Haemophilus influenzae</i>	0.04	0.03-0.06
Ampicillin-sensitive		
<i>Klebsiella</i> spp.	0.12	—
<i>Moraxella catarrhalis</i>	—	0.06-0.125
<i>Legionella pneumophila</i>	—	0.03-0.25
<i>Chlamydia pneumoniae</i>	—	1
<i>Mycoplasma pneumoniae</i>	—	1-2

A wide array of organisms may cause acute pneumonia and published reports vary in the organisms isolated due to differences in patient groups, presence of epidemic organisms and diligence of the investigation.

*Streptococcus pneumoniae* is the most frequently identified pathogen in CAP. Other organisms commonly reported include *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and influenza viruses. Common pathogens such as *Streptococcus pneumoniae* may exhibit more resistance to common antibiotics<sup>5</sup>.

## 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 patients suffering from respiratory tract infection for duration of 7-14 days. Informed consent was obtained from the patients & the post marketing surveillance was in accordance with the clinical principles laid down in declaration of Helsinki. 279 subjects were monitored across India.

### Inclusion Criteria

Patients of either gender 18 years or more willing to give informed consent were included. Clinical criteria included cough, sputum volume, and dyspnea. 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.

After informed consent was obtained, patients were prescribed to receive CO2 (cefixime 200 mg and Ofloxacin 200 mg) every 12 hrs for 7-14 days. At the time of entry into the study, base-line data

were recorded. Patients were observed on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day after enrollment into the study for assessment of symptoms.

Following parameters were observed:

### Assessment of primary outcome measure:

Following parameters were evaluated at baseline and at the end of the study: a) Body temperature on 3<sup>rd</sup>, 7<sup>th</sup>, and 14<sup>th</sup> day as well as time taken to achieve the normal body temperature b) Evaluation of cough frequency c) Evaluation of cough intensity 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.

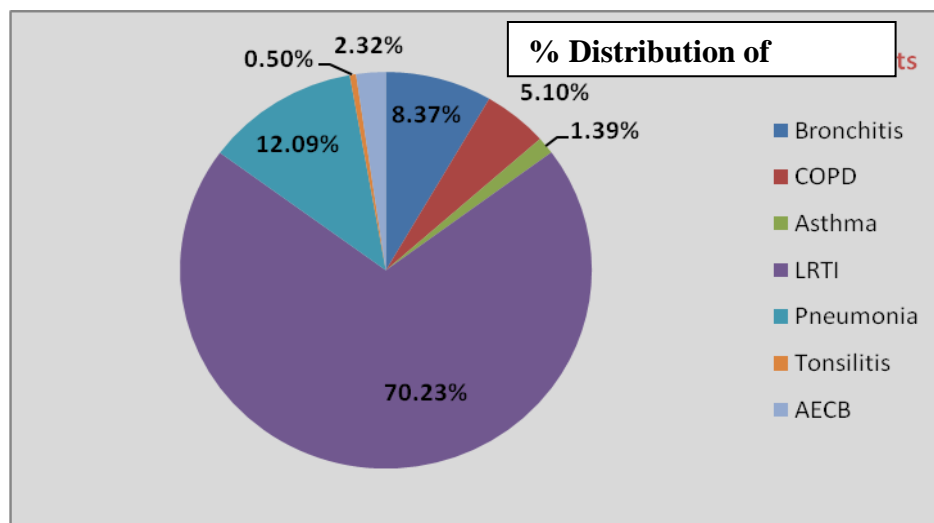
### Statistical analysis

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 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> 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.

## OBSERVATIONS

### Patient distribution

A total of 279 patients were monitored in the study. Two hundred and fifteen patients were included for the final analysis. The patients were in the age range of 18-72 years old with 137 Male and 78 female. Study was conducted in 28 centres across India. Patients had a variety of complaint (Table 2.) including cough, fever and sleep interference.



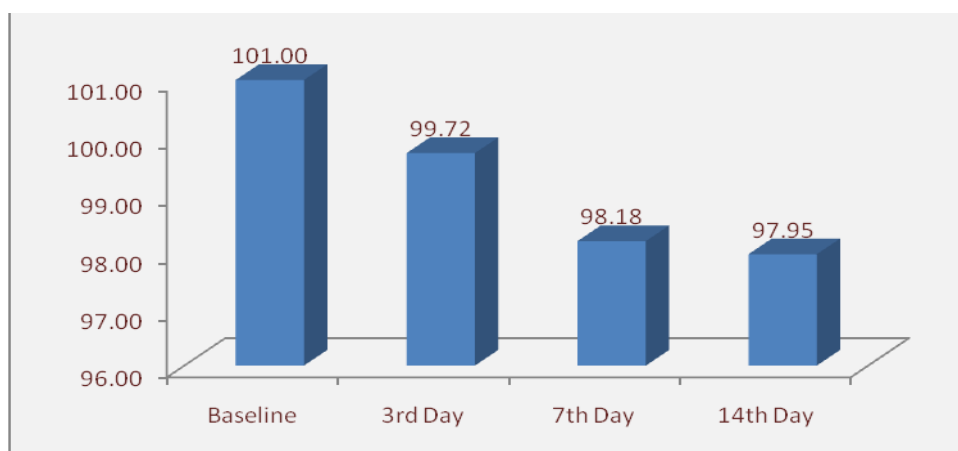
**Table 2: Demographic and clinical characteristics (Baseline)**

Demographic and clinical characteristics (Baseline)	Number of cases
<b>Sex</b>	
Male	137
Female	78
<b>Clinical Characteristics</b>	
Fever	202 (93.95%)
Cough	196 (91.16%)
Sleep disturbances	195 (90.69%)

### Evaluation of Fever

Oral temperature was recorded at the baseline and on subsequent 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> days of treatment. 93.95% patient reported fever on the first day of treatment. Body temperature was significantly reduced from baseline mean value  $101 \pm 0.49$  °F to

$99.72 \pm 0.09$ °F,  $98.18 \pm 0.142$  and  $97.95 \pm 0.161$  on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> days of treatment respectively. The reduction in body temperature was significantly ( $p < 0.05$ ) lower from baseline to 3<sup>rd</sup> day and onwards (Figure 1)



**Figure 1: Effect of Cefixime-Ofloxacin combination on fever**

Also the time taken to achieve the normal body temperature was  $2.45 \pm 1.68$  days

### Evaluation of Cough Intensity

With regards to cough intensity, there was significant reduction in cough intensity at days: 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day from baseline. On day 3<sup>rd</sup> cough intensity was reduced by 29.4% ( $1.94 \pm 0.08$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.0001$ ), on the day 7<sup>th</sup> cough intensity was reduced by 58.90% ( $1.13 \pm 0.06$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.0001$ ) and on 14<sup>th</sup> day it was reduced by 79.63% ( $.56 \pm 0.06$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.001$ ) from the base line (Figure 2). On the

basis of turkeys multiple comparison test there was significant lowering ( $p < 0.05$ ) in the cough intensity not only from the baseline but also there was significant lowering in cough intensity in subsequent days of observation i.e. 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day. Cough intensity was recorded as mild, moderate and severe with numbering as 1, 2 and 3 respectively while no cough or slight cough numbered as 0 or less than 1.

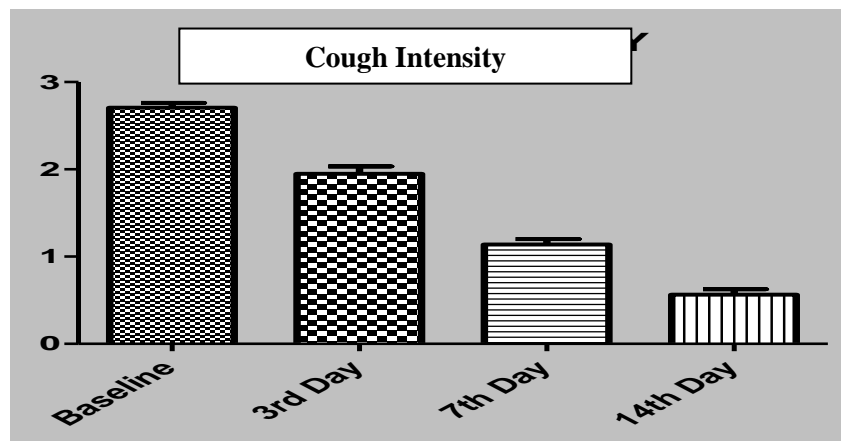


Figure 2. Effect of Cefixime-Ofloxacin combination on cough intensity

### Evaluation of cough frequency

With regards to cough frequency, there were repeated bouts of cough at the time of diagnosis; mean  $\pm$  SD value was  $15.59 \pm 11.65$  at base line. On day 3<sup>rd</sup> and onward the number of bouts of cough was significantly reduced from baseline. On the day 3<sup>rd</sup> number of bouts of cough was reduced by 31.61% ( $10.6 \pm 8.7$  vs.  $15.5 \pm 11.6$ ) ( $p < 0.05$ ), on

7<sup>th</sup> day it was reduced by 62.58% ( $5.804 \pm 5.707$  vs.  $15.59 \pm 11.65$ ) ( $p < 0.05$ ) from the base line and on the 14<sup>th</sup> day of treatment it was reduced by 86.96% ( $2.024 \pm 3.751$  vs.  $15.59 \pm 11.65$ ) ( $p < 0.05$ ). Also the number of bouts of cough was significantly reduced in the subsequent days on 3<sup>rd</sup> vs. 7<sup>th</sup> and 7<sup>th</sup> vs. 14<sup>th</sup> day of the treatment (Figure 3).

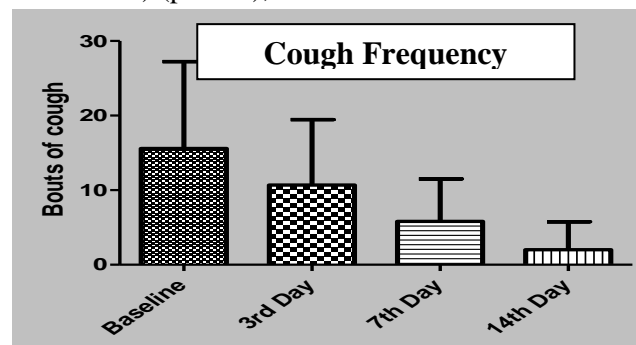


Figure 3: Effect of Cefixime-Ofloxacin combination on cough intensity

### Evaluation of sleep Interference

There was frequent nocturnal awakening at the time of diagnosis; mean $\pm$ SD value was 4.12 $\pm$  3.13; this nocturnal awakening was due to coughing interfering with sound sleep. On 3<sup>rd</sup> day nocturnal awakening was reduced to 2.62 $\pm$ 2.27 and on 7<sup>th</sup> day it was further reduced to 1.31 $\pm$  1.7

and on 14<sup>th</sup> day there was no or few cases of nocturnal awakening mean value was 0.581  $\pm$  1.1. There was significant reduction in the nocturnal awakening from the baseline on 3<sup>rd</sup> day of treatment and onward 7<sup>th</sup> and 14<sup>th</sup> day of treatment (P<0.05).

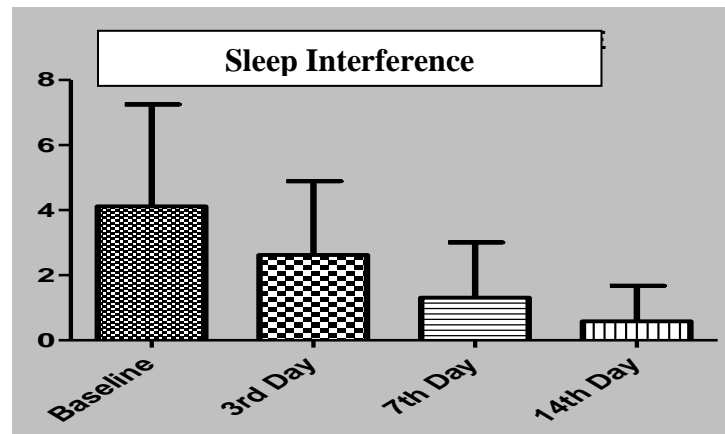


Figure 4: Effect of Cefixime-Ofloxacin combination on sleep interference

### Evaluation of Respiratory rate

There was increased respiratory rate at the baseline; mean value $\pm$ SD was 27.78 $\pm$  12.8; there was significant lowering in respiratory rate at days: 7<sup>th</sup> and 14<sup>th</sup> day from baseline. On day 3<sup>rd</sup>

respiratory rate was 25.37 $\pm$  13.7 (non significant from base line), on the day 7<sup>th</sup> it was reduced to 21.4 $\pm$ 4.89 (p<0.05) and on 14<sup>th</sup> day it was further reduced to 19.9 $\pm$ 4.31) (p<0.05) from the base line (Figure 5).

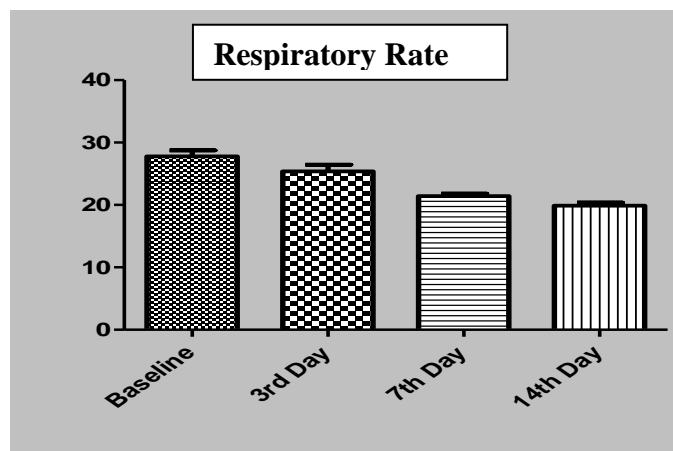


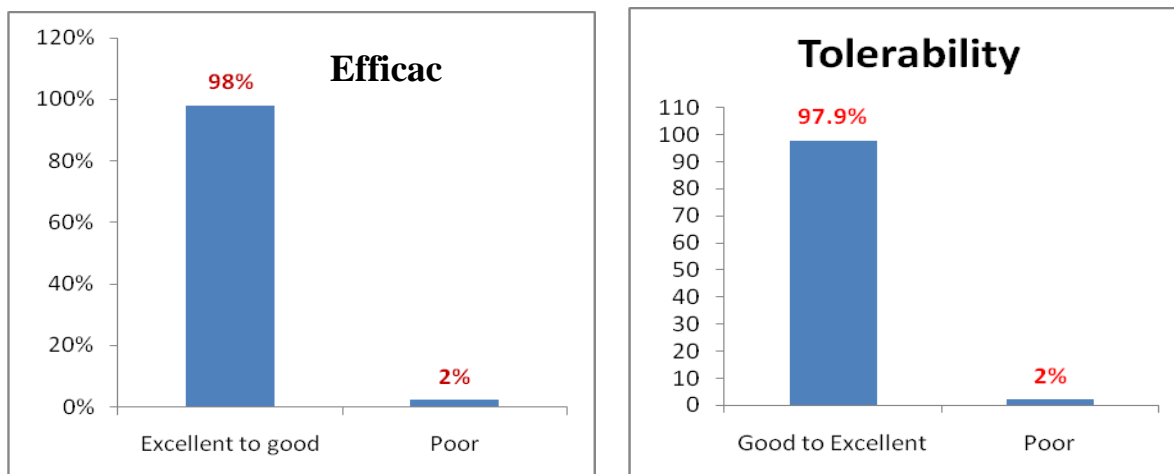
Figure 5: Effect of Cefixime-Ofloxacin combination on sleep interference

### Adverse Event

Concerning the adverse effect; rare cases of nausea (1%), headache (1%) and epigastric pain (2%) 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), 98% of patient reported good to excellent and only 2 % of patient reported poor efficacy. As per investigators assessment about tolerability 97.90% of patient reported good to excellent and 2.1 % of patient reported poor tolerability.



**Figure 6: Global assessment on efficacy and safety of the combination of cefixime-ofloxacin**

### DISCUSSION

Respiratory tract infections are associated with significant morbidity and mortality. In World Health Report 2004, the World Health Organization estimated that respiratory tract infections were the fourth major cause of mortality, responsible for 4.0 million deaths or 6.9% of the global number of deaths in 2002<sup>6</sup>.

Community-acquired pneumonia (CAP) is a common and potentially serious illness that is associated with morbidity and mortality. Although medical care has improved during the past decades, it is still potentially lethal. *Streptococcus pneumoniae* is the most frequent microorganism isolated. Treatment includes mandatory antibiotic therapy and organ support as needed<sup>7</sup>.

Nearly 80% of the treatment for this condition is provided in the outpatient setting. Treatment of

CAP for the most part is empirical; therefore, any antibiotic treatment should cover both typical and atypical pathogens. The beta-lactams have historically been considered standard therapy for the treatment of CAP. However, the impact of rising resistance rates is now a primary concern facing physicians<sup>8</sup>.

In one study it has been found that in the management of community acquired pneumonia, mono-therapy was effective in 70% of cases; the combination of two or more antibiotics (cephalosporin + quinolones) was required in 91.2% of patients<sup>9</sup>.

The combination of a fluoroquinolone and a  $\beta$ -lactam, which are directed against different targets (one for DNA gyrase and other cell wall) improve efficacy compared with a fluoroquinolone alone and may reduce the chance of fluoroquinolone-resistant bacteria.<sup>10</sup>

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.

In the present study we evaluated the efficacy and safety of fixed dose combination of cefixime and ofloxacin (CO2 tablet) in respiratory tract infection on various objective & subjective parameters like evaluation of fever, cough frequency, cough intensity and interference in sleep.

Fever which is commonly associated in respiratory tract infection (93.95%) was significantly reduced from the baseline on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day of the treatment. The mean defervescence time (no fever) was  $2.45 \pm 1.68$  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<sup>11</sup>.

With regard to cough intensity, there was significant reduction in cough intensity at days: 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day from baseline. On day 3<sup>rd</sup> cough intensity was reduced by 29.4% ( $1.94 \pm 0.08$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.0001$ ), and reduced by 58.90% ( $1.13 \pm 0.06$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.0001$ ) and 79.63% ( $0.56 \pm 0.06$  vs.  $2.75 \pm 0.05$ ) ( $p < 0.001$ ) respectively on 7<sup>th</sup> and 14<sup>th</sup> day of treatment from the base line. Regarding the cough frequency, there were repeated bouts of cough at the time of diagnosis; mean  $\pm$  SD value was  $15.59 \pm 11.65$  at base line. On day 3<sup>rd</sup> and onward the number of bouts of cough was significantly reduced from baseline. Similarly there was increased respiratory rate which was lowered down to normal on 7<sup>th</sup> and 14<sup>th</sup> day of treatment. Regarding the evaluation of global efficacy and tolerability by the investigator, the combination showed very good efficacy and excellent tolerability & safety. Concerning the

adverse effect; rare cases of nausea (1%), headache (1%) and epigastric pain (2%) has been found which was of mild to moderate intensity & did not require discontinuation of therapy.

## CONCLUSION

In conclusion this fixed dose combination of cefixime and ofloxacin (CO2 Tablet) antibiotic therapy achieves a better outcome for the empirical management of respiratory tract infection with excellent efficacy, tolerability & safety in the treatment of respiratory tract infection.

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