Evaluation of efficacy and safety of fixed dose combination of Cefixime and Ofloxacin in the management of Urinary tract infection

Abstract
Urinary tract infections are one of the most common types of bacterial infection in humans occurring both in the community and health care settings. In the present work an attempt has been done to evaluate the safety and tolerability of fixed dose combination of Cefixime and Ofloxacin in the management of urinary tract infection. Present study was carried out among 34 patients of age group 19-65 years suffering from urinary tract infection by using the combination of Cefixime and Ofloxacin. Results from the present study indicates that, fixed dose combination of Cefixime and Ofloxacin achieved an excellent outcome in the empirical management of urinary tract infection with excellent efficacy and tolerability.

Keywords: Urinary tract infections, Cefixime, Ofloxacin
1.0 Introduction
Urinary tract infection (UTI) is an infection that can occur anywhere along the urinary tract. Urinary tract infections have different names, depending on which part of the tract is infected. Names given to urinary tract infection (UTI) include cystitis which is infection of the bladder, urethritis which affects the urethra. Infection of kidneys leads to a more serious condition called pyelonephritis. UTI describes a condition in which micro organisms are established and multiply within the urinary tract. It is most often due to bacteria (95%), but may also include fungal and viral infection [1]. Uncomplicated UTIs typically occur in the healthy adult non-pregnant woman, while complicated UTIs (cUTIs) may occur in both genders and all age groups and are frequently associated with either structural or functional urinary tract abnormalities. The largest group of patients with UTI are adult women [2, 3]. Women are more susceptible to UTI because a woman’s urethra is short, allowing quick access of bacteria to the bladder. Also a woman’s urethral opening is near sources of bacteria from the anus and vagina. The incidence increases with age and sexual activity [4]. Rates of infection are high in postmenopausal women, because of bladder or uterine prolapse causing incomplete bladder emptying; loss of estrogen with attendant changes in vaginal flora, loss of Lactobacilli, which allows periurethral colonization with gram negative aerobes, such as E. coli [5, 6]. Catheterization is also associated with a very high incidence of UTI [7]. Gram negative enteric bacilli, especially Escherichia coli and Klebsiella spp. are the leading pathogens though Enterococcus spp., yeasts and Staphylococcus aureus have emerged as prominent agents in recent years, many of them resistant to multiple antibiotics [8]. Combinations of antibiotics are being used in the community as an empirical therapy for the treatment of UTI. Thus there is an urgent need to find out the effectiveness of combinations of oral antibiotics in the treatment of UTI. The objective of this study was to find the efficacy and tolerability of a combination of Cefixime and Ofloxacin in the treatment of UTI.

2.0 Materials and methods
The study was a non-randomized, open, non-comparative, multi centric study. Fixed dose combination of Cefixime 200 mg and Ofloxacin 200 mg, was administered to patients suffering from urinary tract infection for duration of 7-10 days. Informed consent was obtained from the patients and the study was in accordance with the clinical principles laid down in declaration of Helsinki.

Inclusion criteria
Patients of either gender, 18 years or more willing to give informed consent were included. Basic history of the patient was taken and 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 fixed dose combination of Cefixime 200 mg and Ofloxacin 200 mg every 12 hrs for 7-10 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.

Assessment parameters
Assessment of primary outcome measure
Various parameters which were evaluated at baseline and at the end of the study were
a) Frequency of urination on 3rd, 7th, and 14th day as well as time taken to achieve the normal frequency of urination
b) Painful burning sensation at the baseline and at 3rd, 7th and 14th day of treatment
c) Evaluation of fever
d) Interference in sleep.
Moreover investigator analysed the report of urine examination of those patients to whom doctor advised for urine analysis.
Assessment of secondary outcome measure
Assessment of efficacy and safety of drugs used in the present study was also recorded. The incidence of adverse events was recorded. Tolerability and efficacy was evaluated based on the global assessment pattern on a 3 point scale marked as excellent/good/poor.

Statistical analysis
Data analysis on patient demographics and various outcome measures were performed using a 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 and the post hoc Turkeys multiple comparison test. Value of P<0.05 were considered significant.

3.0 Results and discussion
Patient distribution
Total of 34 patients suffering from urinary tract infection were monitored in the study and analysed. The patients were in the age range of 19-65 years old. Majority of the patients with urinary tract infection were female; as out of 34 patients 20 were female and only 14 were male. Study was conducted in 10 centres across the state of Maharashtra (India).

Evaluation of frequency of micturition
Frequency of micturition (number of times in 24 hrs) was recorded at the baseline and on subsequent 3rd, 7th and 14th days of treatment. Almost all the patients were reported with increased frequency of urination at baseline 11.82 ±2.27 (Mean ± SD). There was significant reduction in the frequency of urination from the baseline mean value 11.82 ±2.27 to 8.05 ± 2.20, 6.38±1.34 and 5.70 ± 1.60 on 3rd, 7th and 14th day of treatment respectively. Overall after 1 week of the treatment frequency of urination came down to normal (Figure1).

Figure-1: Frequency of urination
Evaluation of painful burning sensation during micturition
Painful burning sensation at the baseline and at 3rd, 7th and 14th day of treatment were recorded on the basis of three point scale (0-No, 1-mild, 2-moderate and 3 stands for severe pain/burning sensation during micturition). 88% of the patients complained about pain/burning sensation during micturition at baseline and was recorded as mean value score 2.424 ± 0.5607 (mean ±SD). There was significant reduction after 3rd day of treatment recorded as mean value score 1.45 ±0.81 (Mean±SD), further at 7th and 14th day from the start of therapy there was significant decrease (p< 0.0001) in these symptoms and recorded as mean value score 0.712 ±1.341 (Mean ±SD) and 0.514 ±2.6 (Mean±SD) respectively (Figure 2).
Evaluation of fever
Fever was recorded at baseline and on subsequent 3rd, 7th and 14th days of treatment. Fever was recorded as mean value 100.9 ± 0.3381 °F (Mean ± SEM) at baseline. There was significant reduction in fever recorded as mean value 98.71 ± 0.2673°F, 97.17 ± 0.2671°F and 96.65 ± 0.1373°F respectively on 3rd, 7th and 14th day of treatment (Figure 3).

Evaluation of sleep Interference
There was frequent nocturnal awakening (number of awaking during sleep) at the time of diagnosis; Mean±SEM value was 4.75±0.35; this nocturnal awakening was due to frequent urge for urination. On 3rd day nocturnal awakening was reduced to 2.57± 0.22 and on 7th day it was further reduced to 0.56±0.14 and on 14th day there was no or few cases of nocturnal awakening mean value comes down to 0.39 ± 0.12. There was significant reduction in the nocturnal awakening from the baseline just after 3rd day of treatment and onward 7th and 14th day of treatment (P<0.0001).

Evaluation of Urine Examination
With regards to urine examination, 53% (18/34) patients underwent twice urine examination like at the time of diagnosis (baseline) and after 14 days of the start of therapy. Before starting the therapy there was abundant pus cells, RBCs and Leukocytes was found in urine. After 14 days of the start of therapy in 2 patient traces of pus cells, RBCs and Leukocytes were found in urine. But all the patients were devoid of any symptoms of urinary tract infection.
Adverse Event
Concerning the adverse effect; rare cases of Gastritis and headache 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 fixed dose combination of Cefixime 200 + Ofloxacin 200 mg tablet, 76.5% of patients reported good and 23% reported excellent efficacy. 98% of patients reported good to excellent tolerability towards Cefixime and Ofloxacin and only 2% of the patient reported poor tolerability. Rare incidences of headache and nausea have also been reported. No serious adverse events were reported which led to withdrawal of patients from the study. (Figure 5,6).

Figure-4: Data of study of sleep interference

Figure-5: Diagrammatic representation of global efficacy of drugs used in the present study

Figure-6: Diagrammatic representation of tolerability of drugs used in the present study

UTI are one of the most common types of bacterial infections in humans occurring both in the community and health care settings ranks the highest among the most common reasons that compel an individual to seek medical attention [9]. Today it represents one of the most common diseases encountered in medical practices, affecting people of all ages, from the neonate to the geriatric age group[10]. UTI are often treated with different broad-spectrum antibiotics. Widely used agents in the treatment of UTI include fluoroquinolones, cephalosporins and other β-lactam antibiotics. Ciprofloxacin and ofloxacin are the most extensively used fluoroquinolones
for the treatment of UTI. But recently, several studies have revealed increasing trends of resistance to many antimicrobials including the fluoroquinolones. With the increasing trend of antibiotic resistance in E. coli, the management of urinary tract infections is likely to become complicated with limited therapeutic options [11]. It is important to note that delay in adequate therapy will lead to adverse outcomes and potentially increased mortality.

Combinations of antibiotics are being used as an empirical therapy for the treatment of UTI. The combination of a fluoroquinolone and a β-lactam, which is directed against different targets (one for DNA gyrase and other cell wall), has been shown to have improved efficacy compared with a fluoroquinolone alone and may reduce the chance of fluoroquinolone-resistant bacteria[12]. 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 an attempt has been done to evaluate the efficacy and safety of fixed dose combination of Cefixime and Ofloxacin in urinary tract infection on various objective and subjective parameters like evaluation of frequency of urination, painful/burning micturition, fever, and nocturnal awakening. Frequent urination which is commonly associated in urinary tract infection was significantly reduced from the baseline on 3\textsuperscript{rd}, 7\textsuperscript{th} and 14\textsuperscript{th} day of the treatment. Mean ± SD value was 11.82 ±2.27 (Mean ± SD) at base line. There was significant reduction in the frequency of urination from the baseline mean value 11.82 ±3.28 to 8.05 ± 2.20, 6.38± 1.34 and 5.70 ± 1.60 on 3\textsuperscript{rd}, 7\textsuperscript{th} and 14\textsuperscript{th} day of treatment respectively. Overall after 1 week of the treatment, frequency of urination came down to normal. With regards to painful burning sensation during micturition, Majority (88%) of the patient complained about pain/burning sensation during micturition at the start of therapy. There was significant reduction after 3\textsuperscript{rd} day of treatment recorded as mean value score 1.45 ±0.81 (Mean±SD), further at 7\textsuperscript{th} and 14\textsuperscript{th} day from the start of therapy there was significant decrease (p< 0.0001) in these symptoms and recorded as mean value score 0.712 ±1.341 (Mean ±SD) and 0.514 ±2.6 (Mean±SD) respectively. Fever which is one of the symptom of urinary tract infection, 80.0% of patients with urinary tract infection recorded high body temperature. Body temperature was recorded as mean value 100.9 ±0.3381 °F (Mean ± SEM) at baseline. There was significant reduction in fever just after 3\textsuperscript{rd} day of treatment, recorded as mean value 98.71± 0.2673°F, 97.17 ± 0.2671°F, and 96.65 ± 0.1373°F respectively on 3\textsuperscript{rd}, 7\textsuperscript{th} and 14\textsuperscript{th} day of treatment respectively. There were frequent nocturnal awakening due to urge of urination. On day 3\textsuperscript{rd} and onward there was significant reduction in the nocturnal awakening from the baseline. Regarding the evaluation of global efficacy and tolerability, the combination showed very good efficacy and excellent tolerability and safety. Rare cases of headache, gastritis and abdominal discomfort has been found which was of mild intensity and did not require discontinuation of therapy.

4.0 Conclusion

In conclusion, fixed dose combination of Cefixime and Ofloxacin therapy achieves a better outcome for the empirical management of urinary tract infection with excellent efficacy, tolerability and 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 literature for this article has been reviewed and discussed. We also acknowledge the support of doctors who provided the
observations on effect of Cefixime plus Ofloxacin fixed dose combination in patients suffering from urinary tract infection.

Reference