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Original Article

Retrospective Cohort Study Analyzing Clinical Utility of Cefpodoxime-ofloxacin Combination in Patients with Community-acquired Infection at Different Outpatient Setting across India

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Abstract

Background: In India, the infectious disease burden is among the highest in the world, and recent World Health Organization report showed the inappropriate and irrational use of antimicrobial agents against many diseases, which led to increase in the development of antimicrobial resistance. Third generation cephalosporins offer increased stability to β-lactamases and an extended spectrum of antibacterial activities, including Gram-positive and Gram-negative pathogen with low minimum inhibitory concentration against sensitive and resistance strain. Fluoroquinolones, a broad spectrum antibiotic, are widely regarded as the most effective drug for the treatment of community-acquired infection. Similarly, the need of broad spectrum antibiotics alone or in combination has been well highlighted in real-world setting due to overlapping symptom and limitation of available diagnostic technique.

Objective: The objective of this study is to evaluate the prescription of patients who were prescribed cefpodoxime-ofloxacin combination.

Materials and Methods: Retrospective cohort study conducted among 155 outpatient centers across India that analyzed prescriptions where the fixed-dose combination (FDC) of cefpodoxime and ofloxacin in the month of June-August 2015 was prescribed.

Results: Totally, 6274 study participants were included in the study, of which 58% were male, and 35% were female, the average age was 36.6 years (range 10-80 years). Typhoid (90%) was the most common indication for which the FDC was prescribed followed by urinary tract infection (UTI) (9%) and acute gastroenteritis (1%). Follow-up data of 85.6% participants were recorded, of which 46.6% has defervescence within 5 days. Cefpodoxime (200 mg)-clavulanic acid (200 mg) was prescribed for 7-14 days in typhoid fever, for 3 days in UTI and for 7 days in acute gastroenteritis. Diarrhea (0.1%) was the most common adverse effect noted which was mild in intensity and was managed symptomatically. There were no serious adverse events recorded.

Conclusion: Cefpodoxime-clavulanic acid combination is clinically feasible option for uncomplicated enteric fever, UTI, and AGE.

Key words: Cefpodoxime, Community, Ofloxacin, Typhoid, Urinary tract infection

INTRODUCTION

Tropical infections, which are prevalent in tropical and subtropical regions, are always considered whenever a pyrexial episode occurs. Fever, which occurs as a response to infection, is generally considered as a host defense response which helps in decreasing mortality and morbidity.[1] It is the most common and worrisome symptom that the health-care provider assess.[2] It may herald the onset of a serious and life-threatening disease such as meningitis or it may be the sole manifestation of a mild self-limited viral infection. Several clinical studies have shown that the magnitude of fever is associated with severity of infection, as a result patient with the highest fever tends to have high-mortality rate.[1] Among patients

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with febrile illness requiring admission, case fatality ratios are high, sometimes exceeding 20%.[3]

Antimicrobial therapy is the mainstay for the treatment of fever such as enteric fever or any other fever of bacterial origin, but there is emergence of multidrug resistant (MDR) typhoid fever in the late 1980s, in many parts of the world, including the Indian subcontinent.[2] Efficacy, availability, and cost are important criteria for the selection of first-line antibiotics to be used in developing countries. In a vast country like India, knowledge of areas, seasonality with recent outbreaks can be very helpful in recognizing the clinical entity.

Cephalosporins are commonly used to treat broad spectrum of bacterial infections. Over the past 40 years, many cephalosporins have been developed; of these, several orally absorbable molecules have been used mainly in community-acquired infections. Third-generation cephalosporins offer increased stability to β-lactamases and an extended spectrum of antibacterial activities, including Gram-positive and Gram-negative pathogen with low minimum inhibitory concentration against sensitive and resistance strain of *Streptococcus pneumonia*, *Haemophilus influenza,* and *Moraxella catarrhalis*. One of these is cefpodoxime proxetil, an esterified compound that exhibits an improved intestinal absorption and increased bioavailability compared with previously developed oral cephalosporins. The cost and emergence of resistance to the other oral cephalosporin, cefixime, has made cefpodoxime to be used widely.[4] The pharmacokinetic characteristics of cefpodoxime enable enterohepatic recycling while ensuring adequate cover against Gram-negative strain of *Salmonella typhi*.

Fluoroquinolones, a broad spectrum antibiotic, are widely regarded as the most effective drug for the treatment of typhoid fever.[5] They are relatively inexpensive, well tolerated and more rapidly and reliably effective than the former first-line drugs, namely, chloramphenicol, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole. They produce a rapid therapeutic response, i.e. clearance of fever and symptoms in three to 5 days, and very low rates of post-treatment carriage.[6] Ciprofloxacin, ofloxacin, perfloxacin and fleroxacin are common fluoroquinolones proved to be effective and used in adults.[7] Fluoroquinolones also have the advantage of lower rates of stool carriage than the first-line drugs.[8]

The combination of cefpodoxime and ofloxacin when used as a fixed-drug combination (FDC) acts on different target sites providing a synergistic effect against most of the pathogens. Cefpodoxime kills bacteria by inhibiting bacterial cell wall synthesis, and ofloxacin kills by affecting bacterial DNA gyrase. And also, both cefpodoxime and ofloxacin have been recommended by the World Health Organization for the treatment of community-acquired infection.[6]

In this regards, a retrospective study was conducted to evaluate the prescription of cefpodoxime-ofloxacin combination in the treatment of fever.

MATERIALS AND METHODS

This was a retrospective cohort study conducted among 155 outpatient centers across India that analyzed prescription prescribed the FDC of cefpodoxime and ofloxacin in the month of June-August 2015. Confidentiality of the patient data was ensured by the doctors who record the relevant details and identifiers on the case sheet distributed to the center in September 2015. The data collected was compiled, analyzed and was expressed in terms of arithmetic mean and percentage.

RESULTS

Base line data were collected from 155 different outpatient center across India, in which prescriptions of patients who were prescribed cefpodoxime-ofloxacin combination as FDC were analyzed. Totally,739 prescriptions were reported and were subjected for analysis, among which, the clinical data for 1465 patients in terms of patient's identifier and diagnosis were incomplete and therefore omitted from the final analysis. The remaining 6274 prescriptions with definitive diagnosis such as enteric fever, urinary tract infection (UTI), and gastroenteritis were analyzed in the study. Among the study participants, 62% (3889) were male, and 38% (2385) were female, the average age was 36.6 years (range 10-80 years). Enteric fever (90%) was the most common indication for which the FDC was prescribed followed by UTI (9%) and acute gastroenteritis (1%) (Figure 1). Cefpodoxime 200 mg and ofloxacin 200 mg were prescribed for 7-14 days for enteric fever, 3 day in UTI, and 7 days in patients diagnosed with acute gastroenteritis (Table 1). Among 5667 patients of enteric fever, 5144 (90.77%) were diagnosed with typhoid. Follow-up data of 4402 (85.6%) patients diagnosed with

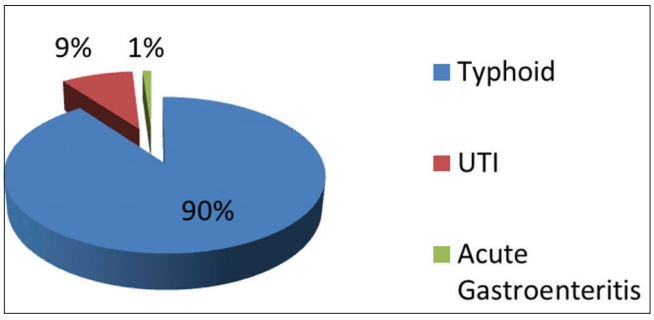

Figure 1: Baseline demographic details for the cefpodoxime-proxetil combination prescription analyses

typhoid fever was available and analyzed. Totally, 43 (0.8%) patients were given concomitant parenteral therapy. Among the typhoid patients, 2053 (47%) had defervescence within 5 days, of which, 233 (11%) had therapy duration for ≤5 days. Remaining 53% had defervescence within 14 days of therapy. History of prior antibiotic therapy for current condition was available in 708 patients diagnosed with typhoid, among whom, 357 patients had no prior antibiotic intake whereas 351 patients revealed prior antibiotic therapy. Amoxicillin, cephalosporin, and ciprofloxacin were the common antibiotics taken. Diarrhea (0.1%) was the most common adverse effect noted (Table 2). Other adverse effects noted were nausea, vomiting, decreased appetite, abdominal pain, and giddiness. There were no serious adverse events (SAEs) recorded.

DISCUSSION

Enteric fever is considered as an important cause of illness with estimated global burden of >27 million cases per annum with a clinical relapse rate of 5-20%. Antimicrobial resistance is a major public health problem in both *S. typhi* and *Salmonella paratyphi* and timely treatment with appropriate antimicrobial agents is important for reducing the mortality of enteric fever. Antimicrobial resistance has rendered many drugs, particularly older fluoroquinolones useless as therapy for typhoid.[9] Despite many efforts, including the implementation of faster and more accurate diagnostic tools, such as biomarkers, polymerase chain reactions, and radiological tests, the tests lack sufficient speed and reliability to justify clinical decision-making based on test results alone. Hence, both identification of bacterial infection and risk stratification remains very difficult and time-consuming in these patients in the emergency setting.[10-12] As a result, empirical therapy is mostly initiated by the practicing physician which is leading to the worldwide problem of antibiotic resistance.

As the two pharmacologically distinct categories of drugs, i.e. cephalosporins and fluoroquinolones act through a different mechanism, they provide rapid bacteriological eradication, thus it is empirical to combine them for management of enteric fever. Improved efficacy of the combination compared with a fluoroquinolones alone is considered because of its synergistic effect; cefpodoxime inhibits bacterial cell wall synthesis and ofloxacin affects bacterial DNA gyrase. As both acts on different target sites, combination provides synergistic effect against most of the pathogens. Current, the incidence of MDR *S. typhi* (MDRST) varies from 25% to 55% in India.[13] Resistance has developed against most of the important therapies which were previously used as a 1st line of therapy.[14] Studies indicate that emergence of resistance is less common when combination therapy is used.[15]

In the present study, we analyzed the prescriptions of 6274 patients, who were prescribed cefpodoxime-ofloxacin combination as FDC, among them 62% were male and 38% were females, which can be due to treatment-seeking behavior, occupational activities- and sociocultural barriers promote male to reach the higher health centers,[16] similar results were also seen in studies conducted by Jain *et al*.[17] and Pathak *et al*.[18] Typhoid was the most common indications for which the combination was prescribed followed by UTI and acute gastroenteritis. Cefpodoxime being a third-generation cephalosporin is active against most of Gram-positive and Gram-negative bacteria and has also shown to have excellent activity against *Salmonella* species.[19] It is considered as an effective and cheap oral option for treatment of uncomplicated typhoid fever.[20]

S. typhi and *S. paratyphoid* A, B, and C are usually, extremely sensitive to the newer fluoroquinolones antibiotics. In time-kill studies, the fluoroquinolones are significantly more rapidly bactericidal than other antibiotics used for treatment. The fluoroquinolones should now be regarded as the treatment of first choice for typhoid fever. They sterilize the blood more rapidly than other drugs, and in general, fever clearance times have ranged between 3 and 5 days. They give the most rapid response rates, the highest cure rates, and the lowest rates of residual stool excretion without significant adverse effects in treatment courses as short as 2 days.[21]

The combination achieves high biliary concentration which enhances the killing of organisms persisting in the biliary passage and thus reduces the rates of relapse and chronic carriage of typhoid pathogen. Favorable pharmacokinetic profile of the combination allows twice daily administration of the drug.

Diarrhea (0.1%) was the most common adverse effect reported in the study. It was mild to moderate in severity and so was managed symptomatically with antidiarrheal medication. No SAE was reported in our study.

Table 1: Posology details for the cefpodoxime proxetil/ofloxacin combination

Indication	Number of patients (%)	Duration of therapy (days)	Dose
Enteric fever	5667 (90)	7-14	Cefpodoxime 200 mg+ofloxacin 200 mg
UTI	563 (9)	3	
Acute gastroenteritis	67 (1)	7	

UTI: Urinary tract infection

Table 2: Adverse events reported for cefpodoxime proxetil/ofloxacin combination

Adverse event (total)	Number of patients (%)
Diarrhea	6 (0.1)
Decreased appetite	2 (0.0)
Vomiting	5 (0.1)
Nausea	3 (0.0)
Rash	2 (0.0)
Gastritis	6 (0.1)
Metal taste	1 (0.0)
giddiness	1 (0.0)
Abdominal pain	3 (0.0)
Fatigue	1 (0.0)
Total	30 (0.5)

In tropical country like India with contrasting availabilities of diagnostic tests or labs, a clinical case of fever especially during monsoon presenting with overlapping symptoms is often managed by cephalosporin combinations including cefpodoxime proxetil/ofloxacin as empirical therapy especially in real world outpatients settings.

With the recent increase in the prevalence of resistance to β-lactam and fluoroquinolones monotherapy for *S. typhi*, combination therapy has shown quick defervescence and less side effect, so, should be considered as front line in the treatment of enteric fever.

CONCLUSION

Infection caused by *S. typhi* remains an important public health problem, particularly in developing countries like India. Considering the cost, availability, and efficacy of the treatment, FDC of cefpodoxime and ofloxacin offers "therapeutic compliance" for empirical management of Gram-positive and Gram-negative pathogen with excellent tolerability and safety.

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