Original Article

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A Case Cohort Study on Clinical Utility of Garenoxacin Mesylate in Typhoid: Retrospective Analyses

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Abstract

Purpose: Typhoid is an important public health problem globally with the highest crude incidence in the Indian subcontinent. Rising incidence of multidrug-resistant *Salmonella typhi* strains in Asian countries including India is a therapeutic challenge.

Aim: The aim was to assess the clinical efficacy and safety profile of the drug garenoxacin in typhoid patients.

Methods: This retrospective case series cohort study was conducted at Chavi Medical Centre, Delhi comprised of patients suffering from typhoid who received fluoroquinolones including garenoxacin. Clinical response was evaluated by subjective assessment for control of presenting symptoms. All the patients were examined for side effects.

Results: Retrospective analyses among fluoroquinolone cases revealed 25 patients receiving garenoxacin as first line therapy after being diagnosed with uncomplicated typhoid. Therapy with garenoxacin was advised for 7-14 days in 95.4% cases. Clinical success was established in 100% patients. There is no case of therapy failure was reported. None of the cases reported any serious adverse event.

Conclusion: Fluoroquinolones remain the therapeutic choice of drugs in uncomplicated cases of typhoid. Garenoxacin is a structurally modified new generation quinolone offering clinical utility against *S. typhi* related infections with the better safety profile.

Key words: Fluoroquinolones, Garenoxacin, *Salmonella typhi*, Typhoid

INTRODUCTION

Typhoid (enteric) and paratyphoid fever remain important public health problems globally and major causes of morbidity in the developing world.[1] Typhoid and paratyphoid fever are acute, invasive, and often life-threatening febrile illnesses caused by systemic infection with the bacterium Salmonella enterica serotype typhi and paratyphi, respectively. Ratio of incidence of disease caused by *S. typhi* to *Salmonella paratyphi* is about 10:1.[2] The World Health Organization (WHO) estimates annual global incidence of typhoid fever about 21.6 million cases and results in at least 215,000 deaths annually.[1] The Indian subcontinent has the highest incidence of typhoid worldwide. The crude incidence of typhoid in south central Asia is 622/1,00,00 cases/year.[1] A review article by Kothari *et al.* (2008) found the incidence of typhoid 9.8/1000 cases/year in Delhi and incidence of 2.14/1000 cases/year in Kolkata.[3]

Humans are the only natural host and reservoir. The infection is transmitted by ingestion of fecally contaminated food or water. Hallmark features of typhoid are prolonged fever (38.8°C - 40.5°C) in >75% cases and abdominal pain in 30-40% cases at presentation.[4] In absence of appropriate treatment, typhoid fever has a case-fatality rate of 10-30%,

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however this number may be reduced to 1-4% with suitable therapy.[5] In last two decades multidrug resistant (MDR) strains of *Salmonella typhi* have emerged, resistant to chloramphenicol, ampicillin, and trimethoprim - antibiotics long used to treat typhoid fever.[4] Recent WHO Guidelines for management of typhoid fever recommends fluoroquinolones (ciprofloxacin or ofloxacin) as optimal therapy, in mild to severe illness caused by fully sensitive or MDR strains.[2] Increased the use of fluoroquinolones to treat MDR typhoid lead to emergence of *S. typhi* strains with reduced susceptibility and rising minimum inhibitory concentration (MIC) (0.125-1 ug/ml) to ciprofloxacin in the Indian subcontinent, southern Asia, and sub-Saharan Africa; and have been associated with clinical treatment failures.[4]

Garenoxacin a novel des fluoroquinolone offers long-lasting inhibition against both DNA gyrase and DNA topoisomerase IV due to modification structure activity relationship and also exhibits broad-spectrum coverage against both Gram-positive, Gram-negative, and also atypical pathogens including *S. typhi* with the MIC_{90} value of 0.12 ug/ml while achieving high tissue concentrations and high tissue/fluid: Plasma concentration ratio in hepato-biliary tissues.[6-9]

METHODS

A retrospective case series cohort was analyzed to evaluate the role of fluoroquinolones including garenoxacin as empirical therapy for adults with suspected typhoid infection. The case of typhoid was defined as patient with prolonged persistent fever (>38°C) with significant baseline widal test titers and with or without the negative peripheral smear for malarial parasite. Cases were identified from a database of all adult patients who were treated with fluoroquinolones for fever attending to Chavi Medical Centre, Delhi during July 2014 - September 2014, where the provisional diagnosis was made by treating physician. Patients were under observation for the entire therapy period. Epidemiological, demographic, microbiological, medical history, prior history of antibiotic or fluoroquinolone use, treatment, clinical outcome, and adverse event data were gathered from analyses. Therapeutic response was assessed as a clinical success or complete resolution signifying significant improvement or complete resolution at the end of suggested therapy of 5-14 days. Serious adverse event (SAE) defined as death, disability, hospitalization or prolonged hospitalization, congenital anomaly, or medical abnormality of significance was confirmed to be reported to central or regional pharmacovigilance center by the doctor.

Statistical Analysis

Descriptive statistics were used to tabulate the data with percentage rate calculated for all categorical nominal and ordinal data variables.

RESULTS

Between July 2014 and September 2014, 25 cases of typhoid treated with garenoxacin mesylate were analyzed among 114 cases of fever treated with fluoroquinolones at Chavi Medical Centre, Delhi.

Baseline Demographics

Of 25 cases analyzed 52% were male, and 48% were female (Table 1). Totally, 28% of cases had significant comorbidities, included dyslipidemia, diabetes, and hypertension. There was no history of asthma, chronic obstructive pulmonary disease, tuberculosis. Totally, 24% cases had concomitant risk factors, included history of smoking and history of hypertension. Concomitant medication included antidiabetics, statins, antihypertensives, laxative, none of the cases were prescribed antibiotics or fluoroquinolones other than garenoxacin.

Clinical Features

The cases included in the study presented with the complaint of prolonged fever (>38°C) (100%), loose motions (4%), burning micturition (16%), swelling (4%). All of these cases had Widal test titers for "O" and "H" agglutinin that were significantly higher than the suggested normal values for the geographic population ("O" agglutinin ≥1:40 and "H" agglutinin ≥1:40 or ≥1:80).[10] Peripheral smear for malarial parasite was negative in all cases. Garenoxacin was administered to these cases at a dose of 400 mg (200 mg × 2 tablets OD) for 5-14 days (Figure 1).

Therapy with garenoxacin was adviced for ≥7-14 days in 95.4% cases, and for <7 days in 4.6% cases. Clinical success was established in 32% cases at the end of 5 days of therapy, and 100% cases at the end of 7-14 days therapy. There is no case of therapy failure was reported (Figure 1).

Table 1: Baseline demographic parameters of the study (*n*=25)

Total number of patients	25
Average age	38.2 years
Average weight	67.1 kg
Study details	**Number of patients *n* (%)**
Gender	
Males	13 (52)
Females	12 (48)
Medical history	
Dyslipidemia	6 (24)
Diabetes	5 (20)
Hypertension	3 (12)

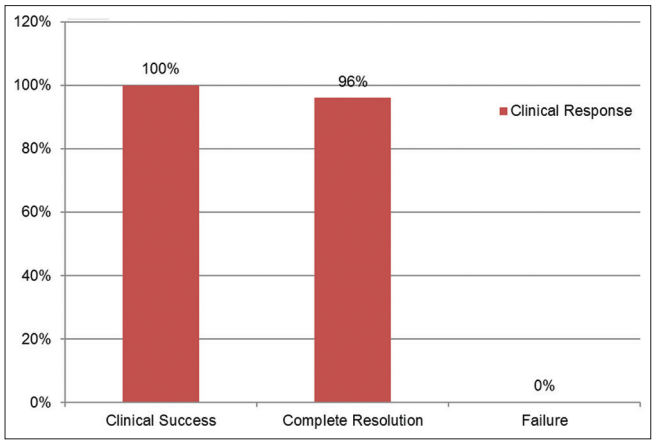

Figure 1: Clinical response at end of 7-14 days therapy

Safety Profile

None of the cases reported any adverse event or SAE, which required discontinuation of therapy or hospitalization.

DISCUSSION

Typhoid fever is a public health problem globally. Typhoid is endemic in India, south central Asia especially Indian subcontinent documents the highest crude incidence of typhoid worldwide.[1] The emergence of MDR strains (resistant to chloramphenicol, ampicillin, and co-trimoxazole) resulted in widespread use of ciprofloxacin as first-line therapy against both the susceptible and MDR strains of *S. typhi*, especially in Indian subcontinent over past two decades.[4] Recent WHO guidelines also recommend use of fluoroquinolones (ciprofloxacin or ofloxacin) as optimal therapy against both fully sensitive or MDR strains of *S. typhi*.[2]

Frontline use of ciprofloxacin has documented definite treatment failures. Studies have documented that increase in nalidixic acid resistant *S. typhi* strains associated with a consistent increase in ciprofloxacin MIC levels. Decreased susceptibility to ciprofloxacin is defined as ciprofloxacin MIC of 0.12-1 ug/ml. Current MIC_{90} levels for ciprofloxacin have graduated from 0.12 ug/ml to 0.5 ug/ml against *S. typhi* based on updated Clinical and Laboratory Standards Institute (CLSI) evidence-based guidelines, 2012.[11] According to epidemiological surveillance data on reanalysis of 488 clinical isolates with interpretation based on 2012 CLSI evidence-based guidelines only 3% remained susceptible and majority (88%) fell in intermediate susceptible range,[11] where the role of novel therapies or quinolones can be considered.

Garenoxacin is a new generation fluoroquinolone launched in India by Glenmark Pharmaceuticals Ltd., Mumbai. Garenoxacin is desfluoroquinolone that is devoid of a fluorine molecule at the C-6 position and have fluorine incorporated through a C-8 difluoromethyl ether linkage.[8] The clinical efficacy of garenoxacin has been complimented by its dual action against both DNA gyrase and topoisomerase IV in both Gram-positive and Gram-negative pathogens,[6,7] thus requiring mutations in both enzymes for resistance to occur. The MIC_{90} of garenoxacin against salmonella is 0.12 µg/ml.[8] Garenoxacin achieves high tissue concentrations (gall bladder 11.59 mcg/g, liver 1.84 mcg/g) and high tissue/fluid: Plasma concentration ratio (gall bladder 1.70, liver 1.92) in typhoid related tissues.[9] Tissue concentration achieved by garenoxacin in hepato-biliary tissues almost twice and sufficient to exceed MIC_{90} requirements for *S. typhi*. The area under the curve (AUC)/MIC ratio is one of the most important predictors for clinical efficacy of fluoroquinolones.[7] Higher AUC/MIC values have been associated with reducing the emergence of resistance, while still higher values have been found to hasten bacterial eradication and clinical response.[12] At 400 mg daily dose garenoxacin demonstrates AUC/MIC ratio of that is clearly above 125 as stated by FDA guidelines,[7,13] on the other hand AUC/MIC ratio demonstrated by ciprofloxacin (500 mg) and ofloxacin (200 mg) are 23.2 and 117.5 respectively,[8,11,14,15] that is often considered inadequate to offer treatment while "stoking" resistance.

Garenoxacin was also found to be superior in terms of safety profile. A post-marketing surveillance study was done at Japan by Hori *et al*. in 6,412 patients confirmed the superior tolerability profile of garenoxacin with minimal or negligible incidence of gastrointestinal, cardiovascular or central side effects.[16]

The findings of these retrospective analyses are exploratory and need to be further confirmed in larger multicenter, randomized, double-blind clinical trial settings.

CONCLUSION

Typhoid is currently a global burden to the community. The increase in the incidence of resistant strains appears to be a challenge to the treating physicians. Garenoxacin is a newer generation structurally modified des(f)-quinolone offering dual and persistent action against relevant target site enzymes involved in Gram-negative pathogens including *S. typhi*. With once a day dosing regimen along with better safety profile garenoxacin appears to have added to the armamentarium of the treating physicians.

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