Post-Approval, Observational Study with Garenoxacin a Newer des-fluoroquinolone in Uncomplicated Urinary Tract Infections in Vadodara, India

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Abstract

Background: Urinary tract infection (UTI) is one of the most important global health issues, which has raised the morbidity and mortality rates in both the genders. Strategies that are proposed in the management of UTIs include use of empirical antibiotics with a broad spectrum of coverage. Urine specimen culture plays a pivotal role to evaluate the organism responsible for the pathogenesis.

Methods: This observational study was conducted at Vadodara comprised of 50 patients suffering from UTI. All the patients that included in the study were examined for side-effects during the entire period of the drug therapy. Clinical response was judged by subjective assessment for control of presenting symptoms.

Results: Data were obtained from 50 patients. Garenoxacin was prescribed as a first-line therapy to the patients with UTI. Four patients received the drug for 5 days and 44 patients received the drug for 7 days. Escherichia coli was the most common organism obtained from the urine culture, followed by Staphylococcus saprophyticus and Enterobacter species. Clinical cure/improved was established in 98% of cases. One case of therapy failure was reported. Negligible side-effects such as nausea, vomiting, and abdominal pain were reported.

Conclusions: Garenoxacin with its superior yet differentiated pharmacodynamic and pharmacokinetic profile involving low minimum inhibitory concentrations with high target site tissue concentrations definitely finds a merit for further evaluation. With superior safety profile, excellent antimicrobial coverage and a convenient once a day dosing garenoxacin appears to improve the patient compliance.

Keywords: Garenoxacin, Infection, Urinary tract infections

INTRODUCTION

Urinary tract infection (UTI) appears to be the second most common entity in current clinical practice.1 UTI is usually defined as infiltration of the otherwise sterile urinary tract by microbes. UTIs includes infections of urethra (urethritis), bladder (cystitis), ureter (urethritis) and kidney (pyelonephritis).2 Currently, UTIs are the most frequently occurring infection in outpatient setting. UTIs are more commonly seen in women than men more likely due to the result of anatomic differences. Other factors that increase the likelihood of female preponderance of cystitis include. Colonization of vaginal introitus by gastrointestinal pathogens, urinary tract obstruction, incomplete voiding, aberrant structural anatomy, past history of UTIs, vaginal intercourse within 2 weeks, use of contraceptives with spermicides, lower levels of estrogens and genetic background.3-6

Escherichia coli appears to be the primary pathogen accounting for 75-90% of the cases, followed by Staphylococcus saprophyticus, Klebsiella spp., Proteus spp., Enterococcus spp. and Enterobacter spp.7-9

METHODS

This was a retrospective observational study done to explore the potential benefits of garenoxacin a newer fluoroquinolone as an alternate antibacterial agent in uncomplicated UTIs. The study was conducted at Dhiraj Hospital, Sumandeep Vidyapeeth, Vadodara. A study was
conducted to assess the efficacy of garenoxacin on the outcome and safety profile in cases of UTI, between 25th March 2014 and 25th May 2014. A case record form (CRF) was prepared to include the observations from each patient involved in the study. Garenoxacin at a dose of 400 mg (200 mg × 2 tablets OD) was prescribed for 5-7 days on the basis of condition of the patient. Adverse events if any arising during the therapy were entered in the CRF. The patients were observed for the entire period of the therapy for the health outcome and safety profile. Fifty patients with the symptoms suggestive of UTI are included in the study with the symptoms for inclusion criteria being burning micturition and increased urinary frequency. Pregnant females and children were excluded from the study. Urine samples of all the subjects were sent to the microbiology laboratory for culture and sensitivity testing.

RESULTS

Baseline Demographics
About 70.5% of the patients were males and 29.5% patients were females with mean age being 45.9 years and mean weight 59.5 kg. Patients were initiated on garenoxacin therapy based on clinical suspicion of bacterial etiology, especially in terms of presenting symptoms. The demographic parameters are shown in Table 1.

All the patients included in the study presented with the complaint of burning micturition. 50% of the patients also had associated increased frequency of micturition. 16% patients had complained of lower abdominal pain associated with burning micturition. Of the 66 patients, only 50 patients returned for the follow-up. Garenoxacin was administered for 5 days in 4 patients and for 7 days in 46 patients. In 24 (48%) patients UTI was associated with cystitis and in 9 (18%) patients it was associated with benign hyperplasia of prostate (Figure 1).

Of the 50 patients the urine culture was positive for 44 patients. The culture report did not suggest any organism in 6 patients. The organism profile of the 44 patients is given in Table 2.

Therapy with garenoxacin was advice for 5 days in 4 patients and 7 days in 46 patients (Table 3).

In 49 (98%) patients a complete clinical cure was established. Lack of clinical efficacy was seen in one patient that was attributed to the poor compliance from the patient.

Safety Profile
Very few side-effects were reported with garenoxacin. Gastrointestinal disturbances in the form of nausea, vomiting, and diarrhea were reported in the study. None of the patients reported any serious adverse event, which required discontinuation of therapy or hospitalization of the patient. The safety profile of garenoxacin is shown in Figure 2.

DISCUSSION

Uncomplicated UTIs are infections of the urinary tract in healthy premenopausal, non-pregnant women with no history of an abnormal urinary tract. They tend to typically include cases of cystitis and pyelonephritis. In 3 women will develop prompt UTI that would require antibiotics by the age of 24 and 50% women experience at least one UTI during their entire lifetime. Among young and healthy female with established cystitis, the incidence of recurrence of infection is 25% within 6 months after the first UTI and the recurrence rate increases with more than one prior UTI. In comparison to cystitis, the incidence of acute pyelonephritis much less with a peak annual incidence of 25 cases per 10,000 females, belonging to the 15-34 years of age.

Two predominant aims in the treatment of both uncomplicated as well as complicated UTIs. Rapid response to the therapy and preventing recurrence in the patient treated and
preventing resistance to the chemotherapy in the microbial environment or prevention of further increase in the resistance.

Current management protocol of UTI in adults includes β-lactams (like amoxicillin/clavulanate, ampicillin/sulbactam, cefixime etc.), fluoroquinolones (like norfloxacin, levofloxacin, ciprofloxacin etc.), oxazolidinones (like nitrofurantoin, linezolid) and pyrimethamines (like trimethoprim/sulfamethoxazole).

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.13 It has been shown to have activity against a broad range of clinical isolates. The efficacy of garenoxacin has also been assessed against resistant strains of Staphylococcus aureus with specific topoisomerase mutations, and it has been documented that garenoxacin has similar potency against both topoisomerase IV and DNA gyrase.14 Although, a major reason for increased ciprofloxacin-resistant strains, is the horizontal transfer, where the role of antimicrobial selection have an important role.15

Garenoxacin is found to have lower minimum inhibitory concentration (MIC) values (Fung Tomc) to the common UTI pathogens. As garenoxacin is excreted in the unchanged form in urine, it is believed to exert its antibacterial properties against the UTI pathogens.16 For antibacterial such as fluoroquinolone which are known to exhibit killing depending on its concentration, an increase in the area under curve (AUC)/MIC ratio, increase the bactericidal property. Now-a-days, AUC/MIC ratio of 125-150 h and 30-40 h for Gram-negative and positive organisms respectively are recommended.17

Table 4 shows the in vitro profile of garenoxacin against UTI pathogens. It was also found to be superior in the area of safety profile. Garenoxacin was well-tolerated by healthy subjects at oral doses up to 1200 mg/day for up to 14 days.16 A post-marketing surveillance study done at Japan by Hori et al. in 6412 patients confirmed the high tolerability with garenoxacin.18

**CONCLUSION**

UTIs are often considered to be easily managed, but they are still a huge burden for millions of individuals and our health care system. The increasing prevalence of antibiotic resistance among the uropathogenic organisms acts as a major obstacle in the clinical management of UTIs. The need of the hour is to start therapy right away with an empirical antibiotic that has a broad spectrum of coverage. Due to the high efficacy and safety profile, Garenoxacin is an ideal option for management of uncomplicated UTIs. The pharmacokinetic/pharmacodynamic profile of Garenoxacin also adds up to the selection of resistant mutants. Convenient once a day dosing has improved the compliance.

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**REFERENCES**


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**Table 4: In-vitro profile of garenoxacin against common UTI pathogens**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC$_{90}$ (μg/ml)</th>
<th>AUC/MIC</th>
<th>Cmax/MIC</th>
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<tbody>
<tr>
<td>E. coli</td>
<td>0.06</td>
<td>1678.3</td>
<td>123.8</td>
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<tr>
<td>K. pneumonia</td>
<td>0.5</td>
<td>201.4</td>
<td>14.9</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>1</td>
<td>100.7</td>
<td>7.4</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>0.5</td>
<td>201.4</td>
<td>14.9</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>0.12</td>
<td>839.2</td>
<td>62</td>
</tr>
</tbody>
</table>

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**Figure 2:** Safety profile of garenoxacin


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