Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20180651

Original Research Article

Comparative study of efficacy and safety of garenoxacin and moxifloxacin in acute exacerbation of chronic bronchitis in COPD patients

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Received: 09 June 2017
Revised: 27 January 2018
Accepted: 31 January 2018

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ABSTRACT

Background: Acute exacerbation of chronic bronchitis in COPD (AECB) is the major cause of morbidity, mortality and marked reduction in quality of life and imposes significant burden on both patients and healthcare systems. Bacterial infections causing AECB frequently require antibacterial treatment, so more evidences are needed to guide better antibiotic choice. Objective of the study was planned to compare efficacy and safety of Garenoxacin, a new fluoroquinolone versus moxifloxacin for treatment of Acute exacerbation of Chronic bronchitis in COPD patient.

Methods: This was a prospective open label comparative study done in department of pharmacology and T.B & Chest of Government Medical College attached Dr Shusila Tiwari Hospital, Haldwani. 60 subjects with clinical symptoms suggestive of Anthonisen type II AECOPD (any two of following criteria: Increased dyspnea, cough, sputum purulence) were enrolled and randomized to receive either Moxifloxacin 400 mg once daily for 7 days or Garenoxacin 400mg once daily for 7 days. The primary outcome measure was clinical success rate at day 7 visit. Secondary outcome measures were changes in clinical global impression (CGI) scales and incidence of adverse events.

Results: The mean age of patient was 60.98±9.9 years and 57.9±9.3 years in the Moxifloxacin and Garenoxacin groups. The clinical success rates were comparable with 86.2% in moxifloxacin group 84.6% and in garenoxacin group. Adverse effects were mild and self limiting. We observed two adverse effects in garenoxacin and three in moxifloxacin group.

Conclusions: The result of study showed that garenoxacin is comparable to moxifloxacin in terms of efficacy and safety.

Keywords: COPD, Exacerbation, Garenoxacin, Moxifloxacin

INTRODUCTION

Acute exacerbation of chronic bronchitis (AECB) is very common problem in COPD patients. Exacerbation is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations that need changes in medication.[1] COPD exacerbations are important because they are associated with significant morbidity, health care cost and mortality.[2]

The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults funded by the Indian Council of Medical Research had shown that the overall prevalence of chronic bronchitis in adults > 35 years is 3.49% and this study shows that COPD is an important public health problem in India.[3]

Acute exacerbation of chronic bronchitis (AECB) are most commonly precipitated by bacterial or viral infection and environmental factors such as air pollution or cold

temperatures.[4] Out of which bacterial infections are most important cause of AECB and patient suspected to be due to bacterial infections require antibiotic therapy and supportive measure to ensure quicker recovery.

The microorganisms commonly implicated in AECB are Haemophilus influenzae, Moraxella catarrhalis and streptococcus pneumoniae, and less common ones include, nonenteric, gram-negative organisms such as *Pseudomonas aureginosa*.

A number of antimicrobial agents are currently used in the treatment of AECB, which is typically initiated on an empiric basis with an agent whose spectrum of activity encompasses the most likely causative pathogens. It has become increasingly difficult to treat respiratory tract infections owing to the increase in resistant gram-positive bacteria.[1,5,6] Nowadays main problem of emerging resistance to antimicrobial requires arduous deal.

Fluoroquinolones are very effective in the treatment of AECB resistant to other antibiotics because of their potent antimicrobial activity against the major pathogens in COPD, excellent penetration into respiratory tissues, high oral bioavailability and proven efficacy in the treatment of exacerbations free interval.[7-9]

Garenoxacin mesylate hydrate (GRN) is a novel oral des-fluoro (6) quinolone with potent antimicrobial activity against common respiratory pathogens, including resistant strains. It has favourable pharmacokinetic profiles with good penetration into sputum and otorhinolaryngological tissues.[10]

Therefore, the aim of the present study was to compare the efficacy and safety of Garenoxacin with that of Moxifloxacin for the treatment of COPD patient with AECB.

METHODS

This was a prospective open label, comparative study done in Department of Pharmacology and TB and Chest Department of Dr Shusila Tiwari government Hospital and College, Haldwani. The study was planned and approved by Institute Ethical Committee and procedures followed in this study are in accordance with the ethical standard laid down by ICMR's ethical guidelines for biomedical research on human subjects and the Helsinki Declaration of 1975, as revised in 2008.

Inclusion criteria

A total of 61 clinically diagnosed COPD patients of either sex in age group of 25-70 years with clinical symptoms suggestive of Anthonisen type II criteria of Acute exacerbations of COPD (AECOPD), i.e. with any two of following symptom: Increased dyspnea, cough, sputum volume and purulence with baseline respiratory score (Table 1) ≥6 and ≤12 were enrolled.[11]

Exclusion criteria

Female patients who were pregnant or lactating or cases of AECB who had severe disease requiring hospitalization or parenteral antibiotic treatment, or suspected or proven cases of pneumonia, bronchial asthma, pulmonary tuberculosis or tubercular pleural effusion, lung cancer or lung metastasis, bronchiectasis, interstitial lung disease or patients who had a course (3 days or more) of antibiotic for respiratory ailments in the preceding 4 weeks of screening or chronic respiratory insufficiency associated with resting hypoxemia or baseline respiratory symptom score <6 and >12 or presence of comorbidities, Patient with History of seizure and anti-seizure medication, Patient with history of corrected QT prolongation or hypersensitivity to penicillin or any of the study medications were excluded.

A written informed consent was obtained from all the patients who participated in the study after explaining the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of the proposed treatment, alternative treatment and the risks and benefits of the alternative treatment. Randomization was done by using computer generated random list. After randomization, the patients were divided into two treatment groups. Group A Moxifloxacin 400mg once daily for 7 days while Group B received Garenoxacin 400mg once daily for 7 days.

Table 1: Anthonisen respiratory symptom Score.

Signs/ Symptoms	Score 0	Score 1	Score 2	Score 3
Fever (day time axillary temperature)	<98.6ºF	>98.6ºF<100ºF	>100ºF but<102ºF	>102ºF
Increase in cough severity	NIL	Slight	Moderate	Severe
Dysonea severity	NIL	Slight	Moderate	Severe
Wheeze severity	NIL	Slight	Moderate	Severe
Sputum volume (early morning)	<2 ml	Scanty (3-4ml)	Moderately copious (6-14ml)	Copious (>15ml)
Nature of sputum	Watery	Mucoid	Muco-Purulent	Frankly Purulent

Clinical assessment

Primary efficacy parameter

It is the percentage of subject achieving treatment success in each treatment arm. Treatment success at day 7 visit and was subdivided as either.

- Clinical cure if respiratory symptom score was <5 at day 7 visit.
- Clinical improvement score was at least one score less than the baseline score or between 6 and 10.
- Treatment Failure if score remain same or even worsen.

Secondary global parameters

Changes in clinical global impression scales on a 5 point scale with 1 as worsened state and 5 as the very much improved state were the secondary efficacy parameters. CGI denoted overall clinical assessment of patients condition by the physician and were noted during follow-up visit and at the end of the study.

CGI was categorized on a 5-point scale with 1 as the worsened state, 2 as no improvement, 3 as mild improvement, 4 as moderate improvement and 5 as very good improvement states.

A subject was categorized as 'treatment failure if there was no change or increase in the baseline respiratory symptom score at day 7 visit and failure to respond to the trial medication and thereby requiring modification of the antibiotic therapy or parenteral antibiotics.

Main outcome measures

Primary efficacy measure was to assess treatment success percentage in each treatment limb.

Safety assessment

Observation of side effects of treatment in both groups during the study period was done by subject as well as investigator and recorded as adverse event. Causality analysis was done using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria.[12]

Statistical analysis

Statistical analysis of the data was performed by using Microsoft excel sheet 2007. Categorical data parameters were presented in the form of percentage. Comparison was performed by chi-square test for categorical data.

Probability level (P-level) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.01and very highly significant if P-value was less than 0.001P-value was considered and non-significant if greater than or equal to 0.05.

The total duration of the study was 3 months from September 2014 to November 2014. Patients were followed for a week. At day zero baseline evaluation was done for inclusion of subjects and then follow up at day 3rd, 7th day was observed. At each visit all outcome measure were computed.

During the study period, subjects had concomitant medication like Bronchodilators, E.g. Beta 2 agonists by inhalational route, anticholinergics, theophylline derivatives and anti-inflammatory agents like inhalational corticosteroids but they were instructed and allowed not to take any other antibiotic or Herbal medicine for any medical or surgical cause. All recruited subjects were advised to stop smoking and instructed for breathing exercise during study period.

RESULTS

A total of 63 patients screened and 60 patients fulfilled the selection criteria and randomized to Group A (Moxifloxacin) and Group B (Garenoxacin) with 30 subjects in each. However, one subject in group A and four subjects in group B were lost to follow-up and did not attend the hospital after the first visit. The mean age of patients was 60.98±9.9 years and 57.9±9.3 years in the Moxifloxacin and Garenoxacin groups, respectively. Twenty patients (86.9%) in the Garenoxacin group and 18 patients (81.8%) in the other group were males. The duration of chronic bronchitis at screening was 7.92±5.02 and 8.15±4.74 years in the Moxifloxacin and Garenoxacin groups, respectively. There was no statistically significant difference in the baseline demographic profile, smoking status and disease related profile (baseline symptom score and duration of chronic bronchitis at screening).

The changes in the respiratory symptom score from baseline values are enlisted in Table 2 and shown in Figure 1 and 2. Within group analysis of changes in baseline versus first and second follow-up scores showed a very highly significant ($p < 0.001$) reduction in both the groups, denoting that there was a clinically significant improvement in the signs and symptoms of the acute exacerbation episode of the disease. Therefore, it can be concluded that both Garenoxacin and Moxifloxacin are effective antibiotics for the management of AECB. A between group analysis of the symptom scores showed that there was no statistically significant difference in the baseline, follow-up and end of study scores in the respiratory symptom score. There was no significant difference in treatment success rates between the groups (Table 3). It can be concluded that both Garenoxacin and Moxifloxacin are equally effective antibiotics for the management of AECB.

Changes in CGI assessed by the physician were noted in a 5-point Likert scale at each visit and the results at the end

of study visit showed that 82.4% in Moxifloxacin group and 79.2% of the subjects in Garenoxacin group achieved a score of either 3 or 4 (mild or moderate improvement of the clinical condition). There was no statistically significant difference between groups (p = 0.90) in the end of the study CGI scores. The subject compliance of both the groups was comparable and majority of the subjects showed excellent compliance. There were no subjects who were categorized in the "poor" compliance group.

Table 2: Within group comparison of respiratory symptom scores (Mean±SD).

Visit	Group A (n = 29) Moxifloxacin	Group B (n=26) Garenoxacin
Base line score	9.28±2.89	9.42±2.56
First follow- up	7.79±2.57	7.65±2.30
End of study	5.62±2.61	4.96±2.39
P value*	<0.001	<0.001

*p value with respect to baseline scores of respective groups

Table 3: Between group comparison of treatment success rates.

Scores	Group A (n=29) Moxifloxacin	Group B (n=26) Garenoxacin	p Value
Treatment success	25(86.2%)	22(84.6%)	0.86*
Clinical cure	6	2	
Clinical improvement	19	20	
Treatment failure	4	4	

Safety analysis was done and only five Adverse Event (AEs) were noted during the entire study period - three AEs in Moxifloxacin group, which were of mild diarrhea, and two AEs in Garenoxacin, one case of diarrhea and one of dizziness.

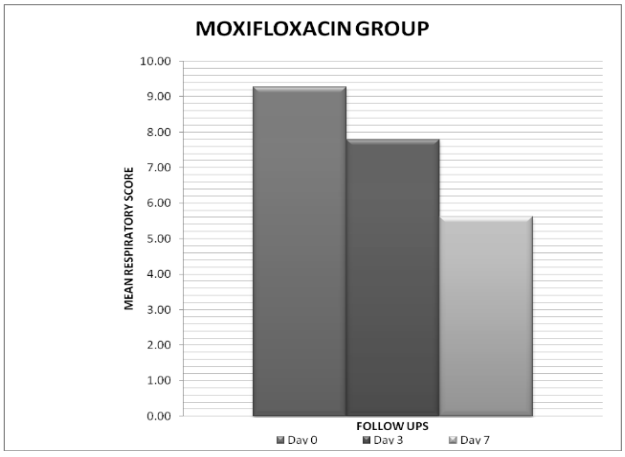

Figure 1: Changes in respiratory score in Moxifloxacin Group.

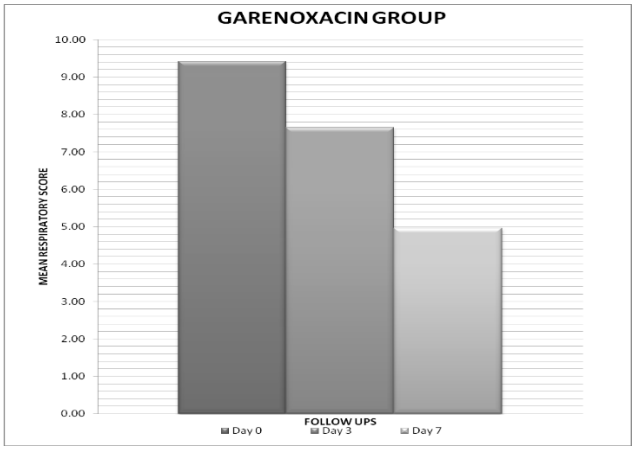

Figure 2: Changes in respiratory score in Garenoxacin Group.

These AEs were non-serious and mild in nature and did not require any dose reduction or withdrawal of the study medications. Causality analysis using the World Health Organization-Uppasala Monitoring Centre (WHO-UMC) criteria showed that they were in the "possible" category.[12] Laboratory parameters were within normal ranges in both the study groups and no significant changes were detected between baseline and study end. Therefore, the safety and tolerability profile of both the study drugs were good without any reported cases of serious AE. The use of concomitant medications in both the groups was comparable and no statistically significant difference was noted between groups. Most of the subjects had taken inhalational salbutamol or levo-salbutamol, ipratropium bromide, and few had also taken oral doxofylline or theophylline.

DISCUSSION

The present study compared the efficacy and safety of Moxifloxacin and Garenoxacin for the treatment of acute exacerbation of COPD patients. Both drugs showed comparable efficacy and good safety profile.

After treatment with a 7-day course, the clinical success rate, which was the primary outcome measure of this study, was comparable in both the treatment groups: 86.2% in the Moxifloxacin group and 84.6% in the Garenoxacin. Patient compliance in both the groups was also good. Adverse events related to study drugs in both groups were all mild and non-serious in nature and did not require dose modification or withdrawal of drug therapy. In this study the most common adverse events for both Moxifloxacin and Garenoxacin were gastrointestinal disturbance.

Recent studies indeed show differences in clinical outcomes among antibiotics used in exacerbations. A recent meta-analysis of antibiotic comparison trials, which were quite homogenous, demonstrated that amoxicillin results in suboptimal outcomes with increased risk of

clinical failures in COPD.[13] This has been seen particularly since the early 1990s, when resistance emerged to this agent. Interestingly, two trials included in the analysis by Puhan et al, both not showing a significant benefit of antibiotics, used amoxicillin and were conducted in the 1990s.[14,15] Two trials comparing fluoroquinolones with non-fluoroquinolone antibiotics, the GLOBE and MOSAIC trials, showed more complete clinical resolution of exacerbations and a prolonged time to the next exacerbation.[16,17]

But there are very few study which evaluated an older fluroquinolone Moxfjloxacin with a newer fluroquinolone garenoxacin. So Innovative approaches to the use of fluoroquinolones are worth testing in further in vitro experiments as well as in clinical trials.

According to study showed that garenoxacin and moxifloxacin, which always showed larger intracellular activity in comparison with levofloxacin and ciprofloxacin.[18]

In one experimental study, compared the antibacterial effectiveness of two new quinolones, garenoxacin (BMS; BMS-284756) and moxifloxacin (MOX) in experimental meningitis caused by a vancomycin (VAN)-tolerant S. pneumoniae strain found comparable result.[19]

Moxifloxacin and Garenoxacin showed similar adverse event profiles in the present study. Gastrointestinal problems like diarrhea were the most common drug-related adverse events. There were no serious adverse events that were related to both drugs. Both drugs were generally well tolerated. This result is compatible with that of a previous study comparing moxifloxacin with levofloxacin.[20]

Our study has some limitations. As this was an investigator initiated academic project a double-blind study could not be conducted due to financial constraints and logistic problems. Secondly, we did not perform microbial assessment of the cases since there are several reports which have stated that mere identification of organisms from the expectorated sputum is not representative of the organism causing AECB as the specimen gets contaminated by the upper airway and laryngeal commensals. Another reason is that very often clinicians start antimicrobial therapy at outpatient setting before the microbial culture report arrives which takes about 72 hours. Third, a prolonged follow-up of subjects to compute the relapse rates also was not done formally as part of the study but we have requested all subjects to come for monthly follow-ups for 6 months after study end visit.

Based on the MOSAIC and GLOBE studies results it would be tempting to prescribe fluoroquinolones for all moderate to severe exacerbations.[17,18] Therefore, this study was conducted mainly to provide information to clinicians on the comparative effectiveness of these two antibiotics as initial antibiotics for AECB patients based on clinical assessment scores.

CONCLUSION

The results of this study demonstrated that a 7-day course of Garenoxacin is comparable to Moxifloxacin in terms of both clinical effectiveness and safety. However, study would have provided better insight into treatment if microbial assessment and relapse rate had been done.

ACKNOWLEDGEMENTS

Authors would like to thank Pulnomary and Chest Department of institution for their cooperation and special thanks to Dr. Punera and Dr. Bhawana for their everlasting guidance.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sinha AK, Srivastava B, Punera DC, Khanchandani R. Comparative study of efficacy and safety of garenoxacin and moxifloxacin in acute exacerbation of chronic bronchitis in COPD patients. Int J Basic Clin Pharmacol 2018;7:410-5.