

Efficacy and safety of levofloxacin and cefuroxime axetil in acute exacerbation of chronic bronchitis: A comparative study

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ABSTRACT

Background: Acute exacerbation of chronic bronchitis (AECB) is a commonly encountered clinical problem and those suspected to be due to bacterial infections require antibiotic therapy.

Objective: The study was designed to evaluate the effectiveness and safety of two commonly used antibiotics levofloxacin, a second generation fluoroquinolone, versus cefuroxime axetil, an oral second-generation cephalosporin, for the treatment of mild to moderately severe cases of AECB.

Materials and Methods: This is a prospective, open labeled randomized study involving a total of 60 adult subjects diagnosed with chronic bronchitis with clinical symptoms suggestive of an Anthonisen type II acute exacerbation (any two of the following criteria - increased dyspnea, cough, sputum purulence). Forty eight patients who fulfilled the selection criteria were randomized to receive either levofloxacin 500 mg once daily or cefuroxime axetil 250 mg twice daily orally for 7 days. The primary outcome measure was clinical success rate at day 14 visit and the secondary outcome measures were changes in Clinical Global impression (CGI) scales and incidence of adverse events (AEs).

Results: The clinical success rates were comparable (82.6% in levofloxacin group versus 77.3% in cefuroxime group) and no statistically significant difference was observed between the groups. AEs were mild, self-limiting and few (two in levofloxacin and three in cefuroxime arm) and tolerability was also good.

Conclusion: A 7-day course of levofloxacin was convenient with once daily dose, was found to be economical and therapeutically comparable to cefuroxime in terms of both clinical effectiveness and safety for the treatment of AECB patients

Key words: Levofloxacin, cefuroxime, spirometry, dyspnoea

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INTRODUCTION

Acute exacerbation of chronic bronchitis (AECB) is a common but serious respiratory tract ailment associated with significant morbidity and impact on healthcare costs. Bacterial infections are an important cause of AECB.^[1] Where bacterial infections are suspected, early institution of antimicrobial therapy and supportive measures ensure quicker recovery.^[2,3] The organisms commonly implicated in AECB are *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*, and the less common ones include nonenteric, gram-negative organisms such as *Pseudomonas aeruginosa*.^[1]

The commonly used antibiotics were amoxicillin, trimethoprim, doxycycline which

were later on superseded by fluroquinolones, macrolides, second- or third-generation cephalosporins, amoxicillin-clauvulanic acid, due to the emergence of antimicrobial resistance.^[4,5] Mild to moderately severe cases of AECB comprise a significant number of patients who attend the outpatient clinics, and institution of oral antibiotic therapy that is effective and tolerable is indicated for those who are of suspected bacterial etiology.^[6]

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Levofloxacin is a second generation fluoroquinolone which is a commonly used drug in ACEB because of its spectrum which includes most of the bacteria which cause ACEB^[7-9] and also due to its more penetration in to the bronchial and respiratory tissues for which it is called as one of the member of respiratory fluroquinolones. Cefuroxime axetil is a second generation oral cephalosporin which is again a commonly used drug for treating ACEB.^[10-12]

Even though there are some studies which have compared levofloxacin and cefuroxime,^[13,14] all the studies were from the developed countries and surprisingly, there was no study which compared the above commonly used agents in AECB in Indian population. The objective of this study was to evaluate the comparative efficacy, safety and cost effectiveness of two commonly used antibiotics levofloxacin and cefuroxime axetil in patients with AECB.

MATERIALS AND METHODS

Study design

This was a prospective, randomized, open, parallel group comparative study between levofloxacin and cefuroxime axetil in patients with acute exacerbation of chronic bronchitis. The duration of the study was two weeks in the later half of March, 2013 (from 15/03/2013 to 29/03/2013). The study was conducted at outpatient department of Pulmonology, Rajiv Gandhi Institute of Medical Sciences, Kadapa, India. The trial was not registered in any of the clinical trial registry. A total of 60 patients with acute exacerbation of chronic bronchitis were screened from the outpatient department of Pulmonology of our institute for nearly one week prior to the start of the study and out of which 48 patients fulfilling the required criteria and those who accepted to participate in the study were asked to come on next Monday (18-03-13), the first

day of the study period. The study was 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 (2006) and the Helsinki Declaration of 1975, as revised in 2008. 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 received levofloxacin tablet 500 mg once daily, while group B received cefuroxime axetil tablet 250 mg twice daily.

Inclusion criteria

Adult subjects of either sex, in the age group 25 to 70 years and clinically documented cases of chronic bronchitis, presenting with clinical symptoms and signs suggestive of acute exacerbation of the disease (type II Anthonisen) due to bacterial pathogen, as evidenced by the presence of at least two of the following three Anthonisen criteria:^[15] exacerbation of cough, dyspnea, and increase in the expectoration volume. A baseline respiratory symptom score of > 6 but ≤12 were recruited (Table 1).

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 or hypersensitivity to penicillin or any of the study medications were excluded.

Primary efficacy parameter

Percentage of subjects achieving "treatment success" in each treatment arm was the primary efficacy parameter. Treatment success was defined on the basis of changes in the respiratory scores at day 14 visit and was subdivided as either (a) clinical cure if the respiratory symptom score was <5 at day 14 visit or (b) clinical improvement if the respiratory symptom score was at least one score less than the baseline score or between 6 and 10.

Secondary efficacy parameters

Changes in clinical global impression (CGI) scales on a 5-point scale with 1 as the worsened state and 5 as the very much improved state were the secondary efficacy parameters. CGI denoted overall clinical assessment of patient's condition by the physician and was noted during follow-up visits 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 state.

Treatment failure was defined as failure to respond to the trial medication and thereby requiring modification of the antibiotic therapy or parenteral antibiotics. A subject was categorized as "treatment failure" if there was no change or increase in the baseline respiratory symptom score at day 14 visit.

Study visits and activities

The total duration of the study was 2 weeks; the first 7 days were active treatment

period, followed by 7 days of "treatment-free follow-up". All subjects were evaluated at baseline and at all subsequent follow-up visits (day 3, 7, 14) clinically and the respiratory symptom score (which included symptoms of fever, increase in cough, dyspnea and wheeze severity, sputum volume and nature) was computed. Spirometry, serum creatinine, urea, plasma sugar, hemoglobin, total leukocyte count differential leukocyte count, erythrocyte sedimentation rate (ESR), platelet count and chest X-ray were performed at screening and at the end of study period.

Study medications were dispensed once at baseline visit for 3 days and subsequently at the first follow-up visit for the next 4 days. Patients were instructed to take one tablet of their respective study medication (either levofloxacin 500 mg once daily orally or cefuroxime 250 mg orally twice daily) after food for the first 7 days. Compliance was assessed by traditional "pill-count" method at each follow-up visit and at the end of the study.

During the study period, subjects were not allowed to take any other systemic antibiotic or indigenous medicines for any medical or surgical cause. However, in cases of treatment failure or worsening of clinical condition, the subject was withdrawn from the trial prematurely. Bronchodilators like beta 2 agonists (salbutamol, levosalbutamol) by inhalational route, anticholinergics, theophylline derivatives and anti-inflammatory agents like inhalational corticosteroids were allowed. All the subjects participating in the trial were advised to stop smoking, and breathing exercises were advised for all subjects during the study period.

Safety monitoring was done continuously throughout the study. All adverse events (AEs) spontaneously reported by the subjects or elicited by the investigators were recorded and causality analysis was done.

Any significantly abnormal deviation of baseline investigation report values was considered as an AE and recorded as such.

We also made an attempt to assess the cost effectiveness of a 7-day course both the test drugs by comparing the market prices of the test brand versus the control brand.

Statistical analysis

Parametric tests were used for comparison of normally distributed numerical variables. Categorical data were compared between groups by Chi-squared test or Fisher's exact test, as appropriate. Repeated measure non-parametric data within group analysis was done by Friedman's analysis of variance (ANOVA) and between group analysis was done by Mann Whitney U test. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Out of 60 subjects screened, 48 fulfilled the selection criteria and were randomized to group A (levofloxacin) and group B (cefuroxime) with 24 subjects in each. However, one subject in group A and two 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 57.6 ± 6.9 years and 56.9 ± 7.3 years in the levofloxacin and cefuroxime groups, respectively. Twenty patients (86.9%) in the levofloxacin 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 levofloxacin and cefuroxime 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. Within group analysis of changes in baseline versus first, second follow-up and the study end scores showed a highly significant ($p < 0.05$) 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 levofloxacin and cefuroxime 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 differences in treatment success rates between the groups (Table 3). It can be concluded that both levofloxacin and cefuroxime are equally effective antibiotics for the management of AECB.

Table 1 : Anthonisen Respiratory Symptom Score^[15]

Signs/ Symptoms	Score 0	Score 1	Score 2	Score 3
Fever (day time axillary temperature)	< 98.6°F	> 98.6°F, < 100°F	> 100°F but < 102°F	>102°F
Increase in cough severity	NIL	Slight	Moderate	Severe
Dyspnea 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

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 83.6% of the subjects in levofloxacin group and 81.2% in cefuroxime 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.

Safety analysis was done and only five AEs were noted during the entire study period - three AEs in cefuroxime group, which were

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

Visit	Group A (n = 23)	Group B (n=22)
	Levofloxacin	Cefuroxime
Base line score	9.1 ± 1.38	9.7 ± 1.18
First follow – up	7.9 ± 1.16	8.4 ± 1.56
2nd follow – up	6.8 ± 2.18	7.1 ± 1.97
End of study	6.4 ± 2.10	6.8 ± 2.42
P value*	0.001	0.001

* p value with respect to baseline scores of respective group

Table 3 : Between group comparison of treatment success rates

Scores	Group A (n = 23)	Group B (n=22)	p Value
	Levofloxacin	Cefuroxime	
Treatment success	22	20	0.80*
Clinical cure	6	3	
Clinical improvement	16	17	
Treatment failure	4	4	0.65*

* $p > 0.05$, Group A vs Group B

mild diarrhea, and two AEs in levofloxacin group, one case each of rash and dizziness.

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-Uppsala Monitoring Centre (WHO-UMC) criteria^[16] showed that they were in the "possible" category. 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 doxophylline or theophylline.

DISCUSSION

The results of this study have proved that levofloxacin is therapeutically comparable to cefuroxime in clinically suspected cases of AECB, both in terms of efficacy and safety. 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: 82.6% in the levofloxacin group and 77.3% in the cefuroxime group.

In relation to the secondary outcome measures, the change in CGI assessed by the physician at the study end visit showed that 83.6% of the subjects in levofloxacin group and 81.2% in cefuroxime group had a mild or moderate improvement of their clinical condition which was comparable in both the treatment groups.

The other secondary outcome measure was about the adverse effects in both the groups

which were very less, i.e., two in the levofloxacin group and three in the cefuroxime group. These adverse events were all mild and non-serious in nature and did not require dose modification or withdrawal of drug therapy. Patient compliance in both the groups was also good.

Several published studies have evaluated the effectiveness of different flouroquinolones (ciprofloxacin, moxifloxacin, levofloxacin, gemifloxacin, prulifloxacin) with macrolides (clarithromycin, azithromycin, roxithromycin) or with amoxicillin/clavulanate acid for the treatment of AECB,^[17-22] but there are no published comparative controlled trials which evaluated a fluoroquinolone with an oral cephalosporin in India.

The results of this study were comparable to that of other published studies which evaluated levofloxacin or cefuroxime for the treatment of AECB using clinical improvement treatment outcomes. The clinical success rate with the quinolones was about 83-84%, which is comparable to our study results. Regarding cost effectiveness of a 7-day course of levofloxacin versus cefuroxime, we computed the current costs of both therapies by comparing the market prices of the test brand versus the control brand. Results revealed that levofloxacin therapy was significantly less expensive (about 5-fold less; Rupees 50 versus 250) compared to cefuroxime therapy.

The results obtained in our study are in accordance with those of other studies performed like Weiss et al., who did a study on a total of 262 patients with acute exacerbation of chronic bronchitis and compared clarithromycin, levofloxacin and cefuroxime axetil, found clinical cure or improvement in 87.9% of those treated with clarithromycin, 87.4% of those treated with levofloxacin, and 79.8% of those treated with cefuroxime axetil.^[14] Shah et al., compared levofloxacin with cefuroxime

axetil trough a randomized, double blind comparative trial where the efficacy of levofloxacin was found to be 79% while that of cefuroxime was 66%.^[23] Petitpretz et al., in a 6-month, randomised, open-label study, the efficacy of 10 days of oral levofloxacin 500 mg once daily and cefuroxime 250 mg twice daily was evaluated in 689 well-defined patients experiencing AECB episodes. In the clinically evaluable per-protocol (PPc) population, the clinical cure rates were 94.6% for levofloxacin versus 93.8% for cefuroxime.^[13]

In a randomized, open-label, controlled, multicentre study, Wilson et al., compared oral levofloxacin once daily for 5 days compared with sequential therapy with i.v. ceftriaxone/oral cefuroxime (maximum of 10 days) in the treatment of hospitalized patients with acute exacerbations of chronic bronchitis and found that the clinical success rates at follow-up (21-28 days post-therapy) were 86.8% for levofloxacin vs. 81.3% for ceftriaxone/cefuroxime.^[24]

Some limitations of this study were as follows. As this was an investigator initiated academic project a double-blind study could not be conducted due to financial constraints and logistic problems. The dosing schedule of cefuroxime was twice daily while that of levofloxacin was once daily. Hence, for conducting a double-blind study, supply of dummy medications was essential but it could not be arranged. Secondly, we did not perform microbial efficacy 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.

Therefore, we conducted this study 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. 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.

The results of this study demonstrated that a 7-day course of levofloxacin is comparable to cefuroxime axetil in terms of both clinical effectiveness and safety for the

treatment of AECB in an outpatient setting. Levofloxacin has the additional advantage of a once daily dosing compared to a twice daily dosing for cefuroxime and a lesser cost of therapy.

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