Efficacy of levofloxacin versus cefuroxime in treating acute exacerbations of chronic obstructive pulmonary disease

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Background: Antibiotic treatment is one of the major pharmacologic treatments for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, the choice of antibiotic depends on the local resistance pattern. A multicenter, randomized, controlled trial was done in patients with AECOPD to compare the efficacy of levofloxacin with that of cefuroxime axetil.

Methods: Patients with AECOPD and without radiographic evidence of pneumonia were enrolled and randomized to either levofloxacin 500 mg daily or cefuroxime 250 mg twice daily in the mild-moderate exacerbation group, or 500 mg twice daily in the severe exacerbation group, for seven days. Clinical efficacy and microbiologic response were evaluated 5–7 days after the last dose.

Results: Treatment was clinically successful in 90.4% of patients in the levofloxacin group, and in 90.6% of patients in the cefuroxime group (95% confidence interval −9.40 to 10.91), within a noninferiority margin of 10%. The microbiologic response appeared to be higher in the levofloxacin group, but the difference was not statistically significant. The safety profile was similar in both groups.

Conclusion: Levofloxacin is not inferior to cefuroxime with regard to clinical efficacy in treating AECOPD.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, levofloxacin, cefuroxime

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a serious event. It is related to decreased health status, increased medical and social costs, and increased mortality.1–3 The mainstay of pharmacologic treatment for AECOPD includes antibiotics and systemic steroids.4 Antibiotics have been shown to be beneficial in patients with increased or purulent sputum and in those with severe exacerbations requiring ventilatory support.5–9 A recent report showed that antibiotics in addition to systemic steroids in AECOPD have a short-term effect on clinical outcome and microbiologic success.10

However, the choice of antibiotic is a more complicated issue. Organisms frequently isolated from patient with AECOPD are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, so-called atypical pathogens, and respiratory viruses11–16. In more severe exacerbations and in patients with risk factors, it is known that *Pseudomonas aeruginosa* and *Enterobacteriaceae* can be pathogenic organisms.17–21 Moreover, the prevalence of each pathogen can be different according to the regional microbiologic environment, so it is crucial to consider individual characteristics and
randomization was performed at the study coordinating center by a single person who was not otherwise involved in the study. A central computer was used to randomize patients stratified by site.

Patients in the levofloxacin group were treated with a once-daily dose of 500 mg for seven days, and those in the cefuroxime group were treated for seven days with 250 mg twice daily (mild to moderate exacerbations) or 500 mg twice daily (severe exacerbations). All patients provided their informed consent, and the study protocol was approved by the local institutional review board for all hospitals.

Outcomes and follow-up
On the first return visit (3–5 days after the initial visit) and the second return visit 2 (5–7 days after final dose), all patients were evaluated for clinical response, side effects, and compliance with medication. Plain chest radiography was obtained at the initial visit, sputum for Gram stain and microbiologic culture was obtained at all visits, and laboratory tests for blood cell counts, serum chemistry, and urinalysis were also performed at the initial and second visits. Two sets of blood cultures were obtained at the initial visit for patients in whom bacteremia was suspected, and at subsequent visits in cases of proven bacteremia.

The primary outcome was clinical success of antibiotic therapy. Clinical response was graded as cure, improved, or failure, and a clinical response of cure and improved at the second visit were defined as clinical success. The secondary outcome was microbiologic efficacy. Microbiologic response was graded as eradication (disappearance of pathogenic bacteria on the second visit), presumed eradication (inability to produce sputum due to improvement), persistence (persistence of initial pathogenic bacteria), presumed persistence (detection of pathogenic bacteria only on the second visit with clinical evidence of persistence), or superinfection (appearance of pathogenic bacteria other than initial ones) at the second visit. A microbiologic response of eradication, presumed eradication, or superinfection was defined as effective.

Statistical analysis
Based on a previously reported clinical success rate of 75% for levofloxacin and 76% for cefuroxime, we estimated that 62 patients would be needed in each group to demonstrate that clinical success in the levofloxacin group was not lower than 10% compared with the cefuroxime group, with a statistical power of 80%. Therefore, we enrolled 70 patients in each treatment group, assuming a 12% dropout rate.

We used SAS version 9.1.2 (SAS Corporation, Cary, NC, USA) for data management and statistical analysis. The
lower limit of the 95% confidence interval for a difference in clinical success (success rate of levofloxacin group – success rate of cefuroxime group) of −10% was defined as the criterion for noninferiority. The intention-to-treat population was used for all analyses. The clinical success rate in the two groups was compared by Chi-square test.

**Results**

**Baseline characteristics**

Of 142 patients screened, 141 were eligible for the study. Four patients refused to give their consent, and 137 were randomized to receive levofloxacin (n = 65) or cefuroxime (n = 72). Eighty-eight percent of patients in the levofloxacin group and 86% of those in the cefuroxime group completed therapy. There was no statistically significant difference in dropout rates between the groups (Figure 1). Table 1 shows the baseline characteristics of the subjects. There was no notable difference between the two groups in terms of gender, age, smoking status, and severity of exacerbation.

**Clinical success rates**

Clinical response as evaluated by respiratory specialists at the second visit was comparable in both groups. Clinical success was achieved in 90.4% of patients in the levofloxacin group and 90.6% of those in the cefuroxime group. The minimum and maximum value for the 95% confidence interval of the difference between the groups was −9.40 and 10.91, respectively, confirming that the clinical success rate of levofloxacin was not inferior to that of cefuroxime.

**Figure 1** Scheme of study enrollment, randomization, and follow-up.
Microbiologic efficacy rates

Microbiologic efficacy rates were 85.7% in the levofloxacin group and 68.8% in the cefuroxime group (Table 3). However, because of the small number of patients who were available for evaluation, the difference was not statistically significant.

Micro-organisms identified

Table 4 shows the organisms identified in each group. Thirty-seven pathogens from 12 species were isolated. Of those, *S. pneumoniae* accounted for 40.5% (15 isolates), *M. catarrhalis* for 13.5% (five isolates), and *Klebsiella pneumoniae* for 10.8% (four isolates).

Safety

The safety evaluation was performed in all patients who were randomized and took the test medication. Side effects related to medication were found in three cases from each group. There were four cases of mild dyspepsia, one of headache, and one of insomnia. None were serious, and no death was reported because of side effects.

Discussion

We found that levofloxacin was not inferior to cefuroxime in terms of clinical response rate and safety in the treatment of AECOPD. The findings of this study suggest that levofloxacin 500 mg daily for seven days is at least as effective as cefuroxime 500 mg daily for mild to moderate AECOPD and 1000 mg daily for severe AECOPD. The microbiologic response seemed higher in the levofloxacin group, but because of the small number of patients in whom analysis was possible, this result was not statistically significant. The safety profiles of both groups were also comparable.

To our knowledge, this is the first study comparing the efficacy of levofloxacin and cefuroxime in the treatment of AECOPD. Previous studies comparing levofloxacin versus cefuroxime in treating exacerbations of chronic bronchitis have reported similar results. Shar et al have reported the results of their randomized double-blind study of levofloxacin versus cefuroxime in acute exacerbations of chronic bronchitis. In their study, three groups of patients (receiving levofloxacin 250 mg or 500 mg daily or cefuroxime 250 mg twice daily) showed similar clinical success rates and tolerability. Petitpretz et al reported the results of another randomized clinical trial of levofloxacin 500 mg daily versus...
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The efficacy of an antimicrobial agent is determined by many factors, including regional antimicrobial resistance. South Korea, where this study was conducted, has a very high rate of antimicrobial-resistant respiratory pathogens. For instance, pneumococcal resistance to penicillin ranges from 60% to 75%. Considering the fact that *S. pneumoniae* is the most frequent pathogen implicated in AECOPD, levofloxacin could be a more appropriate choice than macrolides or beta-lactams in treating AECOPD in Korea. In conclusion, levofloxacin is not inferior to cefuroxime in regard to clinical efficacy when treating AECOPD.

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Disclosure

The authors report no conflicts of interest in this work.

References


