

Efficacy and safety of levofloxacin in the outpatient treatment of exacerbation of chronic obstructive pulmonary disease: levofloxacin 750 mg vs. levofloxacin 500 mg

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Abstract

Introduction: Bacterial pathogens occur in 40-60% of COPD exacerbations requiring appropriate and timely antimicrobial therapy.

Aim of the study: To compare efficacy and safety of oral levofloxacin 750 mg and levofloxacin 500 mg in the outpatient treatment of moderate bacterial exacerbations of COPD.

Methods: We performed an observational, non-randomized, open-label study (a real life-study) including 63 COPD patients with moderate bacterial exacerbation after treatment failure with some first-line antibiotic. They were divided in two groups: Group 1, treated 7 days with levofloxacin 750 mg once a day, and Group 2, treated 10 days with levofloxacin 500 mg once a day. All study subjects had intermediate visits at 3, 5, and 7 days (Group 1) and at 3, 5, 7, and 10 days (Group 2) at which they were evaluated about the duration of symptoms and the side-effects of the drug. Relapse rates were registered during a 20 days follow-up period in the patients with remission of the symptoms.

Results: We found high clinical success rate in both Group 1 and Group 2 (84.3% and 83.9%, respectively). The mean time for clinical remission in days was significantly shorter in the study subjects treated with levofloxacin 750 mg than in the study subjects treated with levofloxacin 500 mg (5.1 ± 1.6 vs. 6.9 ± 1.8 ; $P = 0.0001$). In both Group 1 and Group 2 during the treatment was registered similar incidence of mild side effects (12.5% vs. 12.9%; $P = 0.961$). Incidence of relapses over a 20-day following-up period was also similar in both examined groups (7.4% vs. 7.7%; $P = 0.968$).

Conclusion: Our findings supported the use of levofloxacin 750 mg as an alternative antibiotic in the treatment of COPD exacerbations due to its high efficacy and good tolerability.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD), defined as acute worsening of respiratory symptoms that results in additional therapy, are important events in the COPD course as they negatively impact health status, rates of hospitalization and readmission, and disease progression [1].

Although a number of factors may trigger COPD exacerbations, i.e. environmental factors (respiratory irritants and allergens, air pollutants, temperature changes, etc.), lack of compliance with therapy, and aggravating of comorbid conditions, infections are the most common trigger, with bacterial or viral pathogens accounting for 80% of these episodes in the course of the disease. Bacterial pathogens occur in 40-60% of COPD exacerbations requiring appropriate and timely antimicrobial therapy. The predominant bacteria recovered from the lower airways in patients with COPD exacerbations are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Atypical bacteria, e. g. *Mycoplasma pneumoniae* and *Chlamidia pneumoniae*, are implicated in up to 10% of exacerbations [2-4].

The criteria of Anthonisen, i.e. increased dyspnea, sputum volume and purulence, are still the most important classification system to identify patients likely to be infected with bacterial pathogens based on

presentation of clinical symptoms [5,6]. Current treatment guidelines recommend antibiotic therapy in patients with Anthonisen criteria of type I (all cardinal symptoms) or II (two cardinal symptoms) if increased purulence of sputum is one of the two symptoms and in patients who require mechanical ventilation (invasive or non-invasive).

According to their severity and management, COPD exacerbations are classified as mild, moderate and severe, and bacterial exacerbations commonly are moderate and severe. Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in outpatient or inpatient setting. More than 80% of COPD exacerbations are managed in outpatient

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setting with pharmacological treatment including short acting bronchodilators, antibiotics and/or corticosteroids [1]. The choice of the antibiotic is based on the local bacterial resistance pattern. Usually initial empirical treatment is an aminopenicillin with clavulonic acid, macrolide, or doxycycline. Resolution of exacerbation is considered as a complete resolution of cardinal symptoms or their return to the baseline severity [1,7,8].

Levofloxacin is a fluoroquinolone antibacterial that is the L-isomer of ofloxacin. Like other fluoroquinolones, levofloxacin is a potent antibiotic, due to high levels of susceptibility among Gram-negative, Gram-positive (including penicillin-resistant strains of *Streptococcus pneumoniae*) and atypical pathogens. Antibacterial spectrum of levofloxacin also includes anaerobes, as well as *Mycobacterium tuberculosis*, including *Mycobacterium avium* complex. Levofloxacin acts as a bactericide due to inhibition of bacterial DNA replication inhibiting the DNA gyrase and topoisomerase IV. It is used in the treatment of a number of bacterial infections, including upper and lower respiratory tract infections, urinary tract infections, abdominal infections, tuberculosis, meningitis, and pelvic infections. Levofloxacin is available by mouth, intravenously, and in eye drop form.

Common side effects of levofloxacin (occurring in more than 1 in 100 people) include nausea, diarrhea, headache, and skin rash. Severe side effects (occurring in equal or less than 1 in 10,000 people) include tendon inflammation and tendon rupture, seizures, psychosis, peripheral nerve damage, and aortic aneurism. Due to aortic aneurism risk in certain patients, the Food and Drug Administration in December, 2018, recommended levofloxacin and other fluoroquinolones not to be used in patients at increased risk (those with a history of blockages or aneurisms of the aorta or other blood vessels, uncontrolled hypertension, certain genetic disorders that involve blood vessels change, and the elderly) unless there are no other treatment options available [9-11].

Aim of the study

Aim of the study is to compare efficacy and safety of oral levofloxacin in doses of 750 mg and 500 mg in the outpatient treatment of moderate bacterial exacerbations of COPD. The present study is a continuum of our investigations of efficacy and tolerability of various antimicrobial regimens in outpatient treatment of COPD exacerbations [12,13].

Methods

Study design and setting

An observational, non-randomized, open-label study (a real life-study) was carried out in the period August – December 2019 at the Institute for Occupational Health of R. North Macedonia, Skopje. The study of the effects of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and COPD carried out by Miravittles, *et al.* [14] was used as a model.

Study population

Study subjects included 63 COPD patients with moderate bacterial exacerbation after treatment failure (i.e. symptoms did not improve 3 days after initiation of the treatment) with other antibiotic (aminopenicillin with clavulonic acid, clarithromycin, or doxycycline), 37 males and 26 females, aged 44 to 74 years. The diagnosis of COPD in all patients was established according to the actual GOLD criteria [1]. All participants were informed about the study and their written consent was obtained.

Including criteria was the presence of a moderate exacerbation of bacterial origin after treatment failure with other antibiotic which can be managed on outpatient basis. The diagnosis of bacterial exacerbation was defined by the patient's symptoms, using the criteria described by Anthonisen *et al.* (5).

Excluding criteria were mild and severe exacerbations, patients with exacerbation type III or type II if increased purulence of sputum was not one of the two symptoms, patients on long-term oxygen therapy and arterial oxygen saturation less than 92%, patients with asthma, cystic fibrosis, malignancy, pneumonia and pulmonary embolism, patients with known hypersensitivity to levofloxacin, patients with a history of aneurisms of the aorta or other blood vessels or uncontrolled hypertension, and/or patients with certain genetic disorders that involved blood vessels change (Marfan syndrome and Ehlers-Danlos syndrome).

All study subjects underwent clinical examination, spirometry, blood gas measurements, ECG, and laboratory analysis. Chest X-ray was performed in a part of the patients by indications.

The study subjects were divided in two groups, Group 1 (32 subjects) and Group 2 (31 subjects). Study subjects from the Group 1 were treated 7 days with levofloxacin 750 mg once a day per os, while study subjects from the Group 2 were treated 10 days with levofloxacin 500 mg once a day per os. All study subjects were advised to continue the regular treatment of stable COPD, as well as to use short-acting bronchodilators when needed.

Study protocol

All study subjects had intermediate visits at 3, 5, and 7 days (Group 1) and at 3, 5, 7, and 10 days (Group 2) at which they were evaluated about the duration of symptoms and the side-effects of the drug. The course of exacerbation was evaluated as a function of the resolution of the symptoms and the treatment was considered to be successful if complete resolution of cardinal symptoms or their return to the baseline severity was achieved.

In addition, spirometric parameters, i.e. forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, mean expiratory flow at 50% of FVC (MEF_{50}), mean expiratory flow at 75% of FVC (MEF_{75}), and mean expiratory flow at 25-75% of FVC (MEF_{25-75}), at the first visit and at the end of the treatment were measured according to the actual recommendations [15]. Relapse rates were registered during a 20 days follow-up period in the patients with remission of the symptoms.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Chi-square test was used for testing difference in the prevalence. Comparison of the mean time to relief of the symptoms and of the mean FEV_1 values was performed by independent-samples *t*-test. A *P*-value less than 0.05 was considered as statistically significant.

Results

Demographic and other characteristics of the study subjects is shown Table 1.

Levofloxacin was not discontinued prematurely in any patient enrolled in the study. The percentage of clinical success (i.e. complete resolution of the cardinal symptoms or their return to the baseline

severity) in the Group 1 and 2 was similar (84.3% [27/32] and 83.9% [26/31]) ($P = 0.956$) (Figure 1).

The mean time in days to complete resolution of the symptoms or their return to the baseline severity in the Group 1 was significantly shorter as compared to the mean time to complete resolution of the symptoms or their return to the baseline severity in the Group 2 (5.1 ± 1.6 vs. 6.9 ± 1.8 ; $P = 0.0001$) (Figure 2).

The incidence of side effects during the treatment with levofloxacin in the Group 1 and Group 2 was similar (12.5% [4/32] vs. 12.9% [4/31]; $P = 0.961$) (Figure 3). Registered side effects (nausea, vomiting, diarrhea, and headache) were mild and self-limited and did not require premature discontinuation of the treatment.

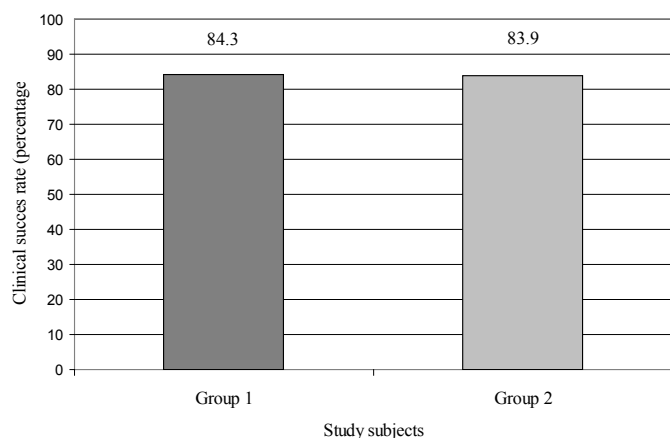


Figure 1. Clinical success rate in the examined groups

Table 1. Characteristics of the study subjects

Variable	Group 1 (n = 32)	Group 2 (n = 31)
Males	19 (59.4%)	18 (58.1%)
Mean age (years)	54.9 ± 9.6	55.7 ± 8.7
Mean duration of COPD after diagnosis (years)	12.8 ± 4.9	13.4 ± 5.3
COPD severity*		
GOLD 2 (50% ≤ FEV ₁ < 80% predicted)	19 (59.4%)	17 (54.8%)
GOLD 3 (30% ≤ FEV ₁ < 50% predicted)	13 (40.6%)	14 (45.2%)
Type of exacerbation**		
Type I	20 (62.5%)	18 (58.1%)
Type II	12 (37.5%)	13 (41.9%)
Increased dyspnea	26 (81.3%)	24 (77.4%)
Increased sputum volume	20 (62.5%)	18 (58.1%)
Increased sputum purulence	32 (100%)	31 (100%)
Smoking status***		
Current smokers	12 (37.5%)	11 (35.4%)
Pack-years smoked	16.5 ± 3.2	14.8 ± 4.1%
Ex-smokers	13 (40.6%)	12 (38.7%)
Passive smokers	16 (46.8%)	14 (45.2%)
Comorbidities		
Arterial hypertension	9 (28.1%)	9 (29.0%)
Depression	5 (15.6%)	4 (12.9%)
Diabetes mellitus type 2	4 (12.5%)	4 (12.9%)

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with certain variable.

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV₁: forced expiratory volume in 1 second.

* COPD severity was defined according to the severity of airflow limitation [1].

** Type of exacerbation was defined according to the Anthonisen, *et al.* [5] classification.

*** Classification of smoking status was done according to the World Health Organization recommendations [16].

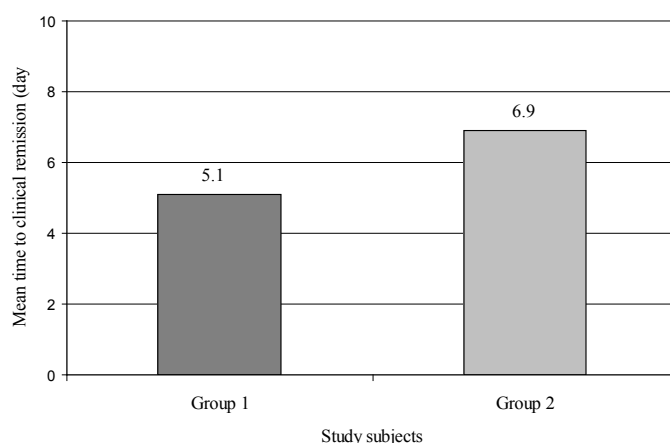


Figure 2. Mean time to clinical remission (days)

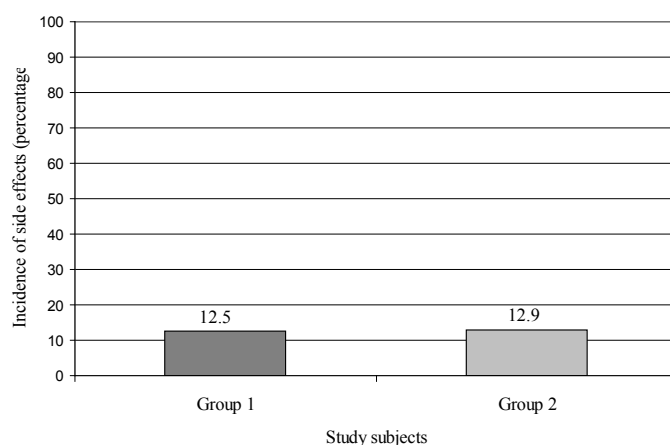


Figure 3. Incidence of side effects during the treatment with levofloxacin

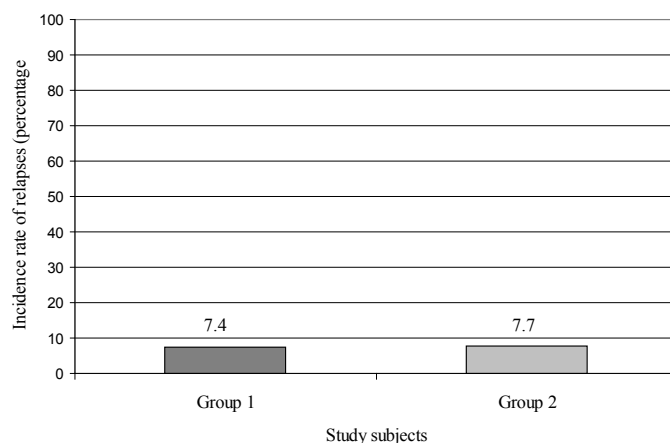


Figure 4. Incidence rate of relapses during 20-day follow-up period

The incidence of relapses in the study subjects with clinical remission of the exacerbation during a 20-day follow-up period was similar in both groups (7.4% [2/27] vs. 7.7% [2/26]; $P = 0.968$) (Figure 4).

Discussion

COPD exacerbations substantially contribute to the overall burden of the disease. The goals of treatment of COPD exacerbations are to minimize the negative impact of current exacerbation and to prevent the development of subsequent effects. Antibiotics, when indicated,

can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration [17-19].

In the present study we compared efficacy and tolerability of levofloxacin 750 mg and levofloxacin 500 mg in the treatment of moderate COPD exacerbations in outpatient setting. Study population was divided in two groups, i.e. the Group 1 the subjects of which were treated 7 days with levofloxacin 750 mg once a day and the Group 2 the subjects of which were treated 10 days with levofloxacin 500 mg once a day. Following current recommendations, levofloxacin in these subjects was administered after treatment failure with antibiotics considered as a first-line treatment of bacterial COPD exacerbations probably due to bacterial resistance. In addition, levofloxacin in these patients was prescribed empirically, i.e. without microbiological evaluation of the sputum as they did not meet recommended criteria [1,7,20].

Demographic and other characteristics of the study subjects from Group 1 and Group 2 were similar. In both groups there were a high percentage of subjects who still did not quit smoking, as well as a high percentage of subjects exposed to environmental tobacco smoke. This finding reflected findings from our previous studies of high prevalence of smoking in our country in all population sub-groups and still non-effective anti-smoking strategies [21,22].

Results of the present study indicated high clinical success rate in both examined groups (more than 80%). Similar results, i.e. high clinical success rate of levofloxacin 250 mg, 500 mg or 750 mg used for 3-10 days, were obtained in several studies performed in the last 15 years [23-25]. Levofloxacin is considered as a potent antibiotic with low prevalence of bacterial resistance by the most respiratory pathogens (about 1%) [26]. In a German comparative study on levofloxacin versus clarithromycin in COPD exacerbations focused on exacerbation-free interval which included more than 500 study subjects, of the 322 strains isolated at baseline, 34.5% were resistant to clarithromycin and only one strain (*Streptococcus pneumoniae*) showed an intermediate level of resistance to levofloxacin. Of the *Haemophilus influenzae* strains, 35% were resistant to clarithromycin, whereas none were resistant to levofloxacin [27].

The recommendation regarding length of antibiotic therapy (5 to 7 days) in COPD exacerbations originates from the use of levofloxacin 500 mg, which have achieved clinical and bacteriological success as therapy lasting 7 to 10 days [28,29]. However, this evidence was obtained in patients being managed in community as general practice patients and outpatients [30,31]. In the present study the length of the therapy was longer, i.e. 7 days for levofloxacin 750 mg and 10 days for levofloxacin 500 mg, as this treatment was initiated after treatment failure with other antibiotic. The mean time to clinical remission in the group treated with levofloxacin 750 mg was 5.1 days being significantly lower than the mean time to clinical remission in the group treated with levofloxacin 500 mg (6.9 days).

Incidence of side effects probably due to the antibiotic use in the present study was similar in both examined groups. The side effects which occurred with levofloxacin were mild and self-limited and did not require discontinuation of the treatment. As in the case of other antibiotics use in the treatment of COPD exacerbations, the most common side effects were gastrointestinal [32]. On the other side, due to the possibility of occurring severe side effects during the treatment with fluoroquinolones, primarily vascular and osteomuscular, besides these effects are registered rarely (less than one in 10,000 people), they should not be used in situations where other options are available or where the use of antibiotic is questionable [33-35].

Results of several studies indicated that the use of later fluoroquinolones, e.g. levofloxacin, gatifloxacin and moxifloxacin, is associated with fewer relapses and longer exacerbation-free intervals as compared to first-line antibiotics used in the treatment of bacterial COPD exacerbations [36-38]. In the present study, we found low frequency of relapses in the study subjects with clinical remission of the exacerbation during a 20-day follow-up period which was similar in both examined groups.

Results of the present study must be interpreted in context of its limitations. First, the study design, since the study was neither blinded nor randomized and, therefore, can be a subject to possible selection bias. Second, a small number of the study subjects could have certain implications on data obtained and its interpretation. Third, the short follow-up period could also have certain implications on data obtained and its interpretation. On the other hand, the study design may be its strength, as it is documented by other real life-studies. Furthermore, the assessment of efficacy of levofloxacin in different doses in the treatment of COPD exacerbations after the treatment failure with some of the first-line antibiotics could also be strength of the study.

Conclusion

In conclusion, in an observational, non-randomized, open-label study (a real life-study) aimed to compare efficacy and safety of levofloxacin 750 mg and levofloxacin 500 mg in the treatment of moderate COPD exacerbation in outpatient setting after treatment failure with antibiotics considered as a first-line treatment for this purpose we found high efficacy of levofloxacin in both doses, significantly shorter mean time for resolution of the symptoms in the study subjects treated with levofloxacin 750 mg, and similar frequency of mild side effects and relapses over a 20-day following period in both examined groups. Our findings supported the use of levofloxacin 750 mg as an alternative antibiotic in the treatment of COPD exacerbations due to its high efficacy and good tolerability.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. North Macedonia, Skopje gave approval for performing the study and publishing the results obtained (03-0302-572/2 - 12.09.2019).

Competing Interests

All authors hereby have declared that no competing interests exist.

Authors Participations

JM participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB participated in the study design, writing the protocol, managing the analyses of the study, as well as writing all versions of the manuscript. TP managed the literature searches and participated in the managing the analyses of the study. KV performed the statistical analysis and participated in the managing of the analyses of the study. SS and DM participated in the data collection. All authors read and approved the final manuscript.

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