

High-Dose Levofloxacin for the Treatment of Community-Acquired Pneumonia

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A retrospective subgroup analysis of an earlier study compared 750 mg 5-day levofloxacin with a 500 mg 10-day course in patients with Pneumonia Severity Index (PSI) Class III/IV community-acquired pneumonia (CAP). The initial study confirmed that the 750 mg shorter duration regimen was as effective and as well tolerated as the usual 500 mg longer duration course in patients with mild-moderate disease. Results from the subgroup analysis revealed that the higher dose therapy was also as effective and safe in patients with more severe disease. 528 patients were in the original study, with 219 classified as PSI Class III/IV. 101 patients received the 750 mg 5-day treatment, while 118 received the 500 mg 10-day course. 90.8% of the patients receiving 750 mg 5-day therapy achieved a clinical success compared with 85.5% for the 500 mg 10-day group (95% confidence interval [CI]: -5.9 to 5.4). It was also reported that the 750 mg dose was associated with a more rapid resolution of fever and purulent sputum by day 3 of therapy. Microbiological evaluation revealed that eradication rates associated with the higher dose regimen were similar to those achieved by the lower dose therapy (88.9% vs. 87.5%, respectively; 95% CI: -18.3 to 15.6). Safety assessment demonstrated both regimens to be equally well tolerated with comparable safety profiles.

Introduction

Despite continuing improvements in health care, community-acquired pneumonia (CAP) remains a major disease worldwide, associated with significant morbidity and mortality. Although multiple antimicrobial strategies have been employed to treat this disease, it continues to be responsible for approximately 1 million hospitalizations in the United States each year, resulting in a huge economic, social, and medical burden (1). Reports on the prevalence of CAP note rates ranging from 1.6 to 9 cases per 1,000 of the general adult population per year, with 8–51% requiring admission to hospital, and a 4–15% mortality rate in this group (2). To reduce the number of unnecessary admissions, treatment guidelines provide recommendations for appropriately screening patients for hospitalization (1, 3).

Short-course antibiotic therapy may provide new means to reduce healthcare costs. Because of its documented efficacy in respiratory tract

infections (RTIs) ranging from CAP to bronchitis and acute exacerbations of chronic obstructive pulmonary disease (AECOPD), levofloxacin represents an established agent that merits study with novel dosing strategies designed to optimize microbiologic and clinical outcomes. Recent evidence also confirms the efficacy of levofloxacin in managing RTIs, with a therapeutic outcomes model study demonstrating levofloxacin to be one of the most clinically effective agents in mild-moderate AECOPD and severe AECOPD (4). Each of these prior analyses, though, employed the well accepted 500 mg regimen. There is less data available comparing the efficacy of different dosing strategies for managing hospitalized CAP patients. A higher dose 750 mg once daily strategy is now advocated in some situations, particularly for more complicated infections. Supporting this approach are the potential benefits of reduced treatment duration and less risk of developing resistance with the higher levofloxacin dose.

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Specifically, the rationale for high-dose levofloxacin schedule is based upon pharmacodynamic (PD) aspects of the fluoroquinolone class. PD and pharmacokinetic (PK) studies demonstrate fluoroquinolones to be concentration-dependent agents, and as such their efficacy is likely to increase as their dosage increases. The PD parameters most useful in predicting whether treatment with a fluoroquinolone will achieve clinical or microbiological success include the ratio of area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) and the ratio of peak plasma concentration (C_{max}) to MIC. Studies assessing the PD target attainment against *Streptococcus pneumoniae* using different dosages of levofloxacin in elderly patients with CAP found that levofloxacin 750 mg once daily had a 98.1% probability of achieving a free drug $AUC_{(0-24)}/MIC$ ratio of 30 in plasma and 98.6% in epithelial lining fluid (ELF). In those aged under 65 years the probability of attaining a free drug $AUC_{(0-24)}/MIC$ ratio of 30 in plasma and ELF was 89.9% and 94.1%, respectively. This 30 breakpoint is key in *S. pneumoniae* infection. Researchers concluded that levofloxacin 750 mg once daily results in a high probability of PD target attainment and potentially improved bacteriological outcomes against *S. pneumoniae* in CAP patients (5). This improved PD of 750 mg levofloxacin has also been reported for atypical pathogens, with an assessment by Garrison comparing levofloxacin to ciprofloxacin and gatifloxacin against two clinical *Pseudomonas aeruginosa* isolates (6). He reported that while all agents achieved 3-log reductions in activity against one of the pathogens, re-growth was the greatest with gatifloxacin. Levofloxacin was the only regimen that approached the desired AUC/MIC ratio of greater than 100–125 and which achieved the targeted peak/MIC ratio of ≥ 8 . Therefore by increasing the dose of levofloxacin the peak drug concentration is increased, providing the option for shorter course of treatment with no lessening of therapeutic effect. Increasing the dosage needs to be tempered with maintaining tolerability. Even at higher doses it appears that levofloxacin is well tolerated. Clinical studies investigating the safety of higher-dose levofloxacin have confirmed this hypothesis not only in CAP, but in other RTIs as well. One of the most recent trials compared the 500 mg dose with the 750 mg dose for the treatment of acute bacterial sinusitis, confirming the higher dose regimen was as safe as the lower dose (7).

Patients and methods

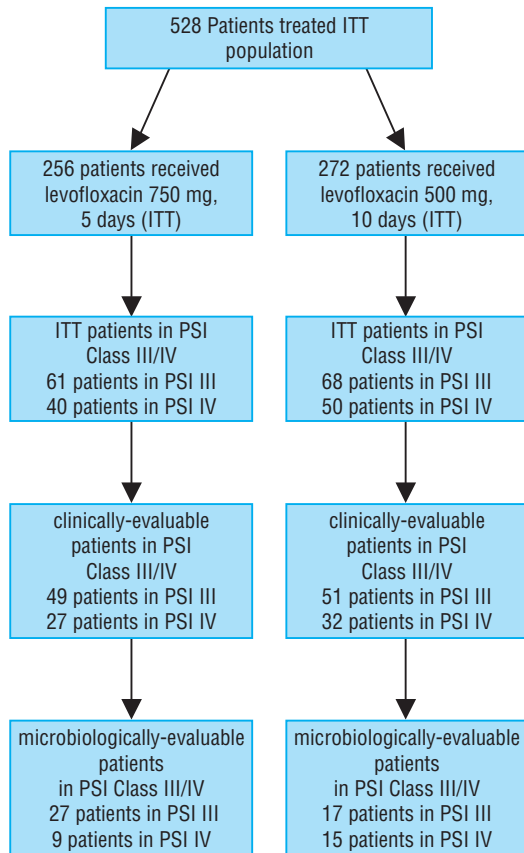
This study investigated a subgroup of patients

from an earlier multicenter, randomized, double-blind trial of patients aged 18 years or older that compared levofloxacin dosages of 750 mg per day for 5 days with 500 mg per day for 10 days for the treatment of mild to severe CAP (8). In the earlier study the clinical success rate of levofloxacin 5-day high-dose therapy was 92.4% (183/198) compared to 91.1% (175/192) for the 500 mg 10 day treatment. Microbiological eradication rates were similar for both groups (93.2% for the 750 mg group and 92.4% for the 500 mg treatment). This study demonstrated that the shorter duration of therapy with a high-dose levofloxacin schedule of 750 mg once daily was at least as effective as the longer duration of 500 mg for 10 days.

The question then arose of whether there was any difference in response according to the severity of the patient's disease. To answer this, we performed a retrospective analysis of subgroups in the initial study according to the severity of their CAP, based upon their Pneumonia Severity Index (PSI), developed by Fine et al (3). The PSI score has been used in a number of studies to identify patients at greater risk of death, and has been used in critical pathways to help in providing more cost-effective management strategies (9). In this study two groups were evaluated: those with PSI Class III (Score > 70 but ≤ 90) and a second group of patients with more severe disease, PSI Class IV (> 90 but ≤ 130). All patients with an initial PSI score of $> 70 \leq 130$ were treated as inpatients for at least 24 hours. The patients treated with 750 mg levofloxacin received a placebo for Days 6–10. Patients were assessed on Day 3 following initiation of therapy, at 7–14 days after receipt of the last dose of active drug, and a late follow-up visit at day 31–38 after study entry. Clinical response following treatment was defined as cure, improvement, and failure or unable to evaluate. Microbiologic response was evaluated in all patients with an identifiable pathogen at study entry (either respiratory or blood). Response was defined as eradicated, persisted or unknown. All patients were evaluated for the development of any adverse events, including both clinical and laboratory results. Figure 1 outlines the study protocol (10).

Results

528 patients were enrolled in the original intent-to-treat (ITT) population, with 219 (41.5%) belonging to PSI Class III or IV. Of these 101 patients were treated with 750 mg levofloxacin and 118 patients received the 500 mg dosage. Analysis of the patients by subgroup revealed that patient demographics were similar for both the ITT and clinically evaluable (CE) groups. The

Figure 1. Patient populations

Abbreviations: ITT = intent-to-treat, PSI = pneumonia severity index.

mean age for the 750 mg and 500 mg groups was 66.0 ± 11.6 and 68.2 ± 12.0 , respectively. Assessment of the clinically evaluable patients demonstrated a mean overall PSI score of 87.6 for the

750 mg group and 88.6 for the 500 mg group. Comparison of the PSI scores for those with PSI Class III versus Class IV revealed a mean score of 78.7 and 79.2 for the 500 and 750 mg groups respectively in Class III, and 103.7 and 103.8 for Class IV. Patients with a PSI Class III and IV combined achieved an overall cure rate of 88.1% which was lower than the 94.7% reported for those with less severe disease (PSI Class I/II) (8).

In the moderate to severe CAP patients the 500 mg and 750 mg dosage strategies achieved similar cure rates, although the 750 mg shorter duration therapy did achieve a slightly higher rate overall (90.8% vs. 85.5%; 95% confidence interval [CI]: -15.9 to 5.4). Assessment of microbiological eradication rates revealed that both treatment regimens achieved similar results (88.9% for the 750 mg group and slightly lower 87.5% for the 500 mg course; 95% CI: -18.3 to 15.6). The eradication rates were also analyzed according to individual pathogens, with the 750 mg and 500 mg regimens achieving comparable eradication rates against the identified respiratory and serological pathogens (Table 1). In regard to the serological results, an additional aspect of the study included assessment of microbiological results in nine patients with bacteremia (5 patients received 750 mg and 4 received 500 mg). Three of the high-dose therapy group had an *Escherichia coli* infection, all of which were eradicated, while the other two were infected with *S. pneumoniae*. The latter two were assumed to persist, although cultures were not available to confirm this. In the 500 mg group all bacteremias were due to *S. pneumoniae*, with 3 out of 4 being eradicated.

The development of adverse events was

Table 1. Microbiologic eradication rates^a at posttherapy by pathogen of primary interest identified in PSI Class III/IV microbiologically evaluable patients

	n/N (%) of patients		95% CI ^b
	750 mg (N = 36)	500 mg (N = 32)	
Total patients	32/36 (88.9)	28/32 (87.5)	-18.3-15.6
Respiratory cultures (typical pathogens)			
<i>Haemophilus influenzae</i>	6/7 (85.7)	4/5 (80.0)	
<i>Haemophilus parainfluenzae</i>	3/3 (100)	4/5 (80.0)	
<i>Streptococcus pneumoniae</i>	6/7 (85.7)	6/8 (75.0)	
Serologies (atypical pathogens)			
<i>Chlamydia pneumoniae</i>	5/6 (83.3)	4/4 (100)	
<i>Legionella pneumophila</i>	4/4 (100)	2/2 (100)	
<i>Mycoplasma pneumoniae</i>	9/10 (90.0)	10/11 (90.9)	

^a Eradication rates include eradicated and presumed eradicated.

^b Two-sided 95% CI with continuity correction was calculated around the difference (levofloxacin 500 mg/10-day regimen minus levofloxacin 750 mg/ 5-day regimen).

Abbreviation: CI = confidence interval.

Adapted from reference (10).

Table 2. Incidence of treatment-emergent adverse events ($\geq 2\%$ of either treatment group)

Adverse event by body system	750 mg (<i>N</i> = 101) <i>n</i> (%)	500 mg (<i>N</i> = 116) <i>n</i> (%)
Any adverse event	63 (62.4)	80 (69.0)
Body as a whole		
Edema, peripheral	3 (3.0)	5 (4.3)
Condition aggravated	2 (2.0)	3 (2.6)
Pain	1 (1.0)	5 (4.3)
Cardiovascular		
Hypertension	3 (3.0)	2 (1.7)
CNS		
Headache	3 (3.0)	2 (1.7)
Dizziness	2 (2.0)	0 (0)
Gastrointestinal		
Constipation	4 (4.0)	2 (1.7)
Nausea	4 (4.0)	3 (2.6)
Vomiting	3 (3.0)	0 (0)
Diarrhea	1 (1.0)	4 (3.4)
Metabolic and nutritional		
Hypokalemia	3 (3.0)	2 (1.7)
Myocardial disorder		
Myocardial infarction	2 (2.0)	0 (0)
Platelet, bleeding and clotting		
Epistaxis	2 (2.0)	0 (0)
Psychiatric		
Insomnia	3 (3.0)	10 (8.6)
Respiratory system		
Chronic obstructive airway disease	4 (4.0)	0 (0)
Skin		
Rash	1 (1.0)	3 (2.6)
Rash erythematous	0 (0)	4 (3.4)

Abbreviation: CNS = central nervous system.
Adapted from reference (10).

closely monitored in both groups, with the overall rates of adverse events similar, although a greater percentage of the 500 mg lower dose regimen were recorded as developing at least 1

treatment-emergent adverse events (69% vs. 62%, $p = 0.307$). The most common reported side effects included insomnia, edema, gastrointestinal upsets and pain (Table 2).

Time to resolution of symptoms was evaluated with a significantly greater proportion of those in PSI Class III treated with the 750 mg dose reporting earlier resolution of fever. In this less severe class 66.3% of the high-dose group reported resolution of fever within 3 days compared to 47.7% in the low dose group ($p = 0.008$). This was also true for other variables such as measured temperature (48.4% for the 750 mg group vs. 34.0% for the 500 mg group, $p = 0.046$) and reduction in purulent sputum (48.4% vs. 27.5%, respectively; $p = 0.007$) (Table 3).

Discussion

It is important when treating any patient, but particularly CAP patients, that therapy should be tailored according to the severity of the condition. One must also consider the patient's chronic health state and severity of illness. Patients with more severe disease, poor general health, or multiple risk factors predictive of a potentially worse clinical outcome require an effective treatment strategy that can be initiated rapidly and has a high probability of success. In addition due to the strong economic pressures being faced by physicians around the world, it is important that costs are also minimized. This is of particularly true in treating patients who require hospitalization, as this is associated with a greatly increased economic and medical care burden. Any strategy that can provide effective, well tolerated treatment is useful. When it also provides for a shorter duration of treatment and a possibility for a reduced hospital stay, it has the potential to provide many benefits. High-dose, short-course levofloxacin is such a treatment option.

Table 3. Resolution of CAP symptoms by day 3 of therapy (PSI Classes III and IV ITT patients)

	<i>n/N</i> ^a (%) of patients		<i>p</i> value ^b
	750 mg	500 mg	
Purulent sputum	46/95 (48.4)	30/109 (27.5)	0.007
Fever (patient reported)	63/95 (66.3)	52/109 (47.7)	0.008
Fever (measured)	44/91 (48.4)	36/106 (34.0)	0.046
Pleuritic chest pain	34/95 (35.8)	28/109 (25.7)	0.135
Shortness of breath	31/95 (32.6)	29/109 (26.6)	0.419
Chills	51/95 (53.7)	54/109 (49.5)	0.571
Cough	15/95 (15.8)	15/109 (13.8)	0.736

^a Total number of patients assessed who had a response documented at both baseline and Day 3. For each symptom analysed, $n =$ (number of patients reporting "yes" at baseline and "no" at Day 3) – (number of patients reporting "no" at baseline and "yes" at Day 3).

^b *p* value was calculated from a two-sample McNemar's test.

Abbreviations: CAP = community-acquired pneumonia, PSI = pneumonia severity index, ITT = intent-to-treat.
Adapted from reference (10).

In the initial Dunbar study that this sub-analysis is taken from, an important finding was that the high-dose short-course levofloxacin regimen was associated with a faster resolution of symptoms, including fever and sputum production. Measured fever was reduced in almost 50% of high-dose patients by Day 3, compared to 38% in the 500 mg group. Fever as reported by patients was reduced in 67% of the 750 mg group compared to 54% of the 500 mg group and purulent sputum reduced in 40% of the high-dose group compared to 30% of the lower dose regimen. This is a key benefit both in terms of the patient's well being as well as from a cost-effective perspective. Many infectious disease management strategies are now streamlined using symptomatology to help manage patients in a more clinically effective and economically beneficial way. As such the reduction of fever is often used as a marker to initiate a change from intravenous to oral therapy, and the reduction in symptoms also allows patients to be discharged sooner, both of which are associated with significant cost and medical manpower savings. This was documented in another sub-analysis of the Dunbar study performed by File et al which looked at 232 patients from the ITT population and 168 from the clinically evaluable group who were initially given parenteral therapy (11). In the ITT group, those patients receiving 750 mg moved from intravenous to oral therapy within a median of 2.35 days, compared to 2.75 days for the lower 500 mg dose. The results for the clinically evaluable patients were similar with a greater percentage of the 750 mg patients switching to oral therapy by both Day 3 and Day 4 of therapy.

Although antimicrobial therapy is crucial in CAP, no new agents have been introduced for several years. One reason for this is the problem with resistance. Fluoroquinolones have been shown to be more useful in this regard than macrolides and penicillins. These agents face significant resistant rates worldwide. A recent

report by Morrissey et al assessed resistance rates in *S. pneumoniae* worldwide in 2003 and found that the highest resistance was to clarithromycin (34.1%) followed by penicillin (22.1%) (12). This report noted that fluoroquinolone resistance rates remain low, but due to concern over treating fluoroquinolone-susceptible isolates with a high MIC it may be useful to lower the currently accepted fluoroquinolone breakpoint values.

Using high doses of quinolones with shorter total duration of treatment may help slow or prevent the emergence of antibacterial resistance. For example the 5 day 750 mg regimen requires less total antibiotic exposure (e.g., 3.75 gm) than the traditional approach (5 gm). A recent meta-analysis examined twelve studies that compared the development of resistance as a function of the dosage used fluoroquinolones (13). The authors noted that there was no difference across these trials. However, a major limitation of this analysis is that not all the included trials followed patients to look for emergence of resistance. Additionally, emergence of resistance on therapy is a rare event so the meta-analysis was rather underpowered to examine this issue.

Irrespective of controversies regarding the prevention of potential emergence of resistance, a shorter duration of therapy is beneficial. Not only is patient compliance likely to be enhanced since fewer days of therapy are needed (which may in turn help prevent antibiotic abuse) but faster symptom resolution has important implications for resource use. Beyond that, faster symptom resolution may allow patients to return to work earlier.

In conclusion this study is pivotal in drawing attention to the potential benefits of a high-dose, short course levofloxacin therapy for the treatment of moderate-severe CAP. While clinical cure rates were similar because of the studies non-inferiority design, it is apparent that the higher dose was associated with a faster resolution of symptoms.

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