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REVIEW

Cumulative clinical experience from over a decade of use of levofloxacin in community-acquired pneumonia: critical appraisal and role in therapy

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Abstract: Levofloxacin is the synthetic *L*-isomer of the racemic fluoroquinolone, ofloxacin. It interferes with critical processes in the bacterial cell such as DNA replication, transcription, repair, and recombination by inhibiting bacterial topoisomerases. Levofloxacin has broad spectrum activity against several causative bacterial pathogens of community-acquired pneumonia (CAP). Oral levofloxacin is rapidly absorbed and is bioequivalent to the intravenous formulation such that patients can be conveniently transitioned between these formulations when moving from the inpatient to the outpatient setting. Furthermore, levofloxacin demonstrates excellent safety, and has good tissue penetration maintaining adequate concentrations at the site of infection. The efficacy and tolerability of levofloxacin 500 mg once daily for 10 days in patients with CAP are well established. Furthermore, a high-dose (750 mg) and short-course (5 days) of once-daily levofloxacin has been approved for use in the US in the treatment of CAP, acute bacterial sinusitis, acute pyelonephritis, and complicated urinary tract infections. The high-dose, short-course levofloxacin regimen maximizes its concentration-dependent antibacterial activity, decreases the potential for drug resistance, and has better patient compliance.

Keywords: levofloxacin, community-acquired pneumonia, pharmacodynamics, resistance, pharmacokinetics, clinical use

Information resources

The medical literature published in any language since 1980 on levofloxacin was searched using PuBMed, MEDLINE, and EMBASE. Additional citations were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also obtained from Ortho-McNeil Janssen Scientific Affairs, LLC (Titusville, NJ).

Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of morbidity and mortality in adult populations.[1–4] The severity and incidence of CAP are significant, especially in the elderly and immunocompromised patients.[5–7] CAP affects 6 million people in the US annually.[8] Approximately 20% (1.1–1.3 million) of these patients are hospitalized[9] with estimated cost of about US$25,000 per hospitalization[10] resulting in over US$30 billion annual costs for hospitalizations alone; 12% of patients hospitalized for CAP die.[9] In patients with severe CAP requiring admission to the intensive care unit (ICU), mortality increases to up to 30%.[11–14] The most common cause of CAP is

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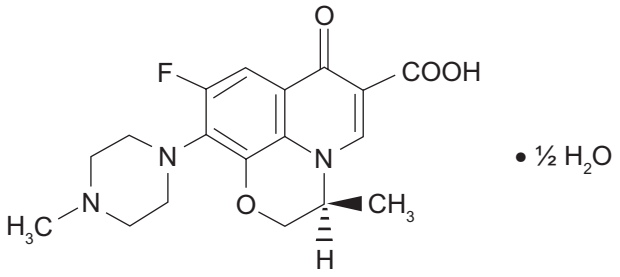
Streptococcus pneumonia.[15–18] Other bacterial causes include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, and the "atypical" CAP pathogens which include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*.[2,17,19–22] Severe CAP, generally requiring admission to the ICU for management, is frequently caused by *Staphylococcus aureus* and Gram-negative bacilli.[13,23–25]

Epidemiologic studies reveal that pathogenic organisms are not recovered in >50% of patients exhibiting clinical signs and symptoms of CAP. Thus, microbiological information is frequently unavailable to refine initial empiric antibiotic treatment of CAP in either hospitalized and outpatient settings.[9,23,25] The guidelines from the Infectious Diseases Society of America/American Thoracic Society recommend initial empiric therapy with a respiratory fluoroquinolone (eg, levofloxacin 750 mg, moxifloxacin, or gemifloxicin) or a β-lactam plus a macrolide. In adults, fluoroquinolones are recommended for the treatment of CAP caused by penicillin-susceptible *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *Legionella pneumophilia*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*. Levofloxacin combination therapy with an antipseudomonal β-lactam (or aminoglycoside) should be considered if *Pseudomonas aeruginosa* infection is a likely cause of pneumonia.[24] Antibiotic resistance in *S. pneumoniae* has been a major problem in the US and worldwide for more than a decade.[26] Furthermore, increasing rates of antibiotic resistance (most notably, penicillin, cephalosporin, and macrolide resistance) observed in bacteria that commonly cause CAP have resulted in increased treatment failures and inferior clinical outcomes for many patients with CAP.[14,15,27–30] Although there are reports of the emergence of resistance to some fluoroquinolones among *S. pneumonia*,[26] the incidence of levofloxacin-resistant organisms has remained steady with resistance rates of <1% worldwide.[31–35]

Levofloxacin (Figure 1) is a light yellowish-white crystal or crystalline powder with a molecular weight of 370.38 g/mol. It interferes with critical processes in the bacterial cell, such as DNA replication, transcription, repair, and recombination, by inhibiting bacterial topoisomerases. Human cells lack these topoisomerases, which are essential for bacterial DNA replication, providing specificity against bacterial DNA topoisomerases that are responsible for separating the strands of duplex bacterial DNA, inserting another strand of DNA through the break, and then resealing the originally separated strands.[36,37] Levofloxacin is active against a broad range of Gram-positive, Gram-negative, and cell-wall-deficient (atypical) bacteria that may be causative pathogens in community-acquired and nosocomial infections. Levofloxacin is a well-established treatment option for respiratory and urinary tract infections (UTI), particularly since levofloxacin is active against some penicillin – and macrolide-resistant species (eg, *S. pneumoniae* – the most common causative pathogen for community-acquired bacterial respiratory infections).[31–34,38,39] The incidence of penicillin- and macrolide-resistance in many bacterial species is both high and widespread.[40] In the US, a high-dose, short-course regimen of levofloxacin (750 mg once daily for 5 days) is approved for the treatment of adults with CAP, acute bacterial sinusitis (ABS), complicated UTI, and acute pyelonephritis (AP). The use of levofloxacin, including some data on the high-dose, short-course treatment regimen, has been reviewed previously.[39] This review focuses on the pharmacology of levofloxacin in the treatment of CAP.



Levofloxacin

Figure 1 Structure of levofloxacin.

Pharmacodynamic properties

Spectrum of activity

Levofloxacin is the *L*-isomer of the racemic fluoroquinolone ofloxacin.[39,41] Topoisomerase IV is the main target for levofloxacin in Gram-positive bacteria and DNA gyrase (topoisomerase II) is the target in Gram-negative bacteria.[42] Levofloxacin has a broad spectrum of antibacterial activity that includes several Gram-positive and Gram-negative aerobes and cell-wall-deficient (atypical) bacteria. The minimum inhibitory concentrations (MIC) of levofloxacin required to inhibit the growth of 90% of clinical isolates (MIC_{90}) are used as assessments of the in vitro activity of levofloxacin. The levofloxacin MIC breakpoints for *S. pneumoniae* defined by the Clinical and Laboratory Standards Institute are: ≤2 mg/L (susceptible), 4 mg/L, (intermediate), and ≥8 mg/L (resistant).[41,43] Also, levofloxacin generally demonstrates good in vitro activity against penicillin-resistant *S. pneumoniae* strains. *S. pneumoniae* with reduced susceptibility to penicillin commonly cause CAP. The levofloxacin MIC_{90} for penicillin-susceptible, -intermediate,

and -resistant isolates of *S. pneumoniae* was 1 mg/L in multiple studies, with >97% of isolates testing susceptible to the drug.[31–34,38,44]

Levofloxacin has variable activity against *S. aureus*, depending on methicillin susceptibility. Levofloxacin had MIC_{90} values of 0.25–4.0 mg/L against methicillin-susceptible *S. aureus* isolates, whereas methicillin-resistant *S. aureus* isolates exhibited levofloxacin resistance, MIC_{90} values ranging from >4 to ≥64 mg/L.[38,44–46] The in vitro activity of levofloxacin against *Enterococcus faecalis* was limited (MIC_{90} of 8 to ≥32 mg/L in vancomycin-susceptible and -resistant strains). Although levofloxacin has limited activity against coagulase-negative staphylococci (>4 mg/L, 54.1%).[45] It has demonstrated good in vitro activity against a range of other Gram-positive bacteria, such as *Streptococcus pyogenes* (1 mg/L, 99.9%)[32,33] and other β-hemolytic streptococci (0.5–1 mg/L, 99.1%–100%).[47]

Generally, levofloxacin has good in vitro activity against Gram-negative bacteria including the common respiratory tract pathogens *H. influenzae*.[31,35,38,44,48–50] *Haemophilus parainfluenzae*,[50] and *M. catarrhalis*[31,35,44,48–50] as well as urinary tract pathogens (*K. pneumoniae*,[38,44,51] *Enterobacter cloacae*,[38,44,51–53] and *Proteus mirabilis*[38,45,48]). The values of MIC_{90} for levofloxacin against isolates of *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* were ≤0.06 mg/L with nearly 100% susceptibility rates. Levofloxacin was also highly active against β-lactamase-positive isolates of *H. influenzae*[31–34,38] and *M. catarrhalis,*[31,44,48–50,54,55] However, the activity of levofloxacin is variable against *Escherichia coli* and *P. aeruginosa*. The MIC_{90} of levofloxacin against *E. coli* ranged from ≤0.06 mg/L (susceptible) to >8 mg/L (resistant).[38,44,45,51,56] Levofloxacin showed lower levels of activity against isolates of *P. aeruginosa*, MIC_{90} values ranging from 0.5 mg/L to 64 mg/L and susceptibility rates of 71%–94%.[38,44,45,48,51] Levofloxacin also had limited activity against extended-spectrum β-lactamase-producing *K. pneumoniae* (MIC_{90} of >8–32 mg/L).[45] Levofloxacin has good activity against the cell-wall-deficient (atypical) organisms *C. pneumonia.*[57–60] *L. pneumophila*,[38,44,48,57,61,62], and *M. pneumonia*,[48,57,63–65] MIC_{90} values being ≤2 mg/L.

Bactericidal activity

The bactericidal activity of levofloxacin is concentration-dependent,[66] and the minimum bactericidal concentration (MBC) of levofloxacin was ≤4× the MIC against the majority of isolates for a number of causative pathogens of respiratory tract infections.[59,60,64,65,67] The MBC_{90} of levofloxacin was 1–4× the MIC against the majority of *M. pneumoniae* isolates (MBC of ≤0.5–1.0 mg/L), as reported by multiple authors.[59,60,63–65,67] The MBC of levofloxacin was 1–2× the MIC (≤0.06–4 mg/L) against *K. pneumoniae*, *P. aeruginosa*, *E. coli*, and *E. cloacae.*[51] Levofloxacin has a post-antibiotic effect (PAE) of 2.0–4.5 hours depending on the pathogen.[39] The PAE of levofloxacin against *S. pneumoniae* was up to 4.5 hours at 10× the MIC. Furthermore, levofloxacin has shown PAEs against methicillin-susceptible *S. aureus* (MSSA), *K. pneumoniae*, *L. pneumophila*, and anaerobes[39] as well as against erythromycin-resistant and -susceptible strains of *L. pneumophila*.[61]

Resistance

Resistance to antibacterial drugs in *S. pneumoniae* has been a major problem in the US for more than a decade.[26] The primary cause of reduced susceptibility of bacteria (particularly *S. pneumoniae*) to fluoroquinolones is at least one mutation in the *parC* and *parE* genes that code for DNA topoisomerase IV or *gyrA* and *gyrB* genes that code for DNA gyrase.[68,69] Another fluoroquinolone resistance mechanism involves active drug efflux through mutation in the efflux regulatory genes *mexR* and *nfxB*.[68,70] Although there are reports of the emergence of fluoroquinolone resistance among *S. pneumoniae*,[26] the incidence of levofloxacin-resistant organisms has remained stable to date at ≤1% worldwide.[31–35]

In the worldwide PROTEKT surveillance program between 1999 and 2000, levofloxacin-resistant isolates of *S. pneumoniae* were identified; 94% of these isolates had at least one mutation in the genes coding for topoisomerase IV as well as in the genes coding for DNA gyrase.[69] The SENTRY surveillance program (1997–2005) identified fluoroquinolone-resistant isolates of β-hemolytic *Streptococcus* spp. as having significant mutations in the *parC* or *gyrA* gene, or both. Only mutations in *parC* were associated with lower MIC values.[47] A report of an in vitro pharmacodynamic model simulating the concentration of levofloxacin in the epithelial lining fluid (ELF) after once daily administration of 500 mg revealed that all five isolates of *S. pneumoniae* containing the first-step *parC* mutation had levofloxacin resistance within 48 hours (≥16-fold increase in MIC) and four of the isolates acquired a second-step (*gyrA*) mutation.[71] The acquisition of a second-step mutation appeared to be related with an area under the concentration–time curve (AUC):MIC ratio of ≤256; this indicates that to prevent levofloxacin resistance from being acquired in isolates with a first-step *parC* mutation, the AUC:MIC ratio target should be >256.[71] When the range of free AUCs (*f*AUCs) of levofloxacin and other fluoroquinolones were simulated, the

results demonstrated that *f*AUC:MIC ratios of ≤82 and ≤86 for levofloxacin were associated with a first-step *parC* mutation and second-step *gyrA* mutation in *S. pneumoniae*. These resistance breakpoints for levofloxacin were significantly higher ($P \leq 0.001$) than those for other tested fluoroquinolones (gatifloxacin, gemifloxacin, and moxifloxacin) using post hoc analysis. Furthermore, the higher the *f*AUC:MIC ratio for each fluoroquinolone, the more delay in the development of first- or second-step mutations was observed.[72]

In the SENTRY (worldwide, 1997–2004),[47] PROTEKT (US and Canada, 1999–2002),[32–34] and TRUST (US, 1998–2002)[35] surveillance programs, the overall levofloxacin resistance rate in *S. pneumoniae* isolates was ≤1%; in penicillin-resistant isolates, the overall rate of levofloxacin resistance was 0.9%–2.7%.[31,34,35] In the TRUST surveillance program from 2001 to 2005, the rate of *S. pneumoniae* resistance to levofloxacin changed from 0% to 0.5% and the resistance of these isolates to penicillin resistance increased from 27.4% to 28.9%. Amoxicillin/clavulanic acid resistance increased from 6.5% to 12.9%, and clindamycin resistance increased from 12.1% to 18.6%.[73] The levofloxacin 750 mg dose has been directly compared to imipenem–cilastatin in the treatment of nosocomial pneumonia. The average age of the patients was 55 years and 438 patients were randomized. Forty-two percent of patients in the levofloxacin arm were ≥65 years of age. The clinical success rate in the intention-to-treat population was 66.2% in the levofloxacin arm vs 69.4% in the imipenem arm. In the clinically evaluable population, the success rates were 59.3% and 62.5% for levofloxacin and imipenem, respectively.[74] Other data from 1998 and 2005 revealed that the levofloxacin-resistant isolates of *H. influenzae* or *M. catarrhalis* could not be identified in large worldwide surveillance studies.[32–34,49,54,55] However, surveillance studies have demonstrated resistance to levofloxacin in MSSA and methicillin-resistant strains of *S. aureus* (MRSA) (3.4%–10.1% and 76.6%–79.2%, respectively) and *P. aeruginosa* (24.7%).[45,46,56]

Pharmacokinetics and metabolism

Levofloxacin is rapidly absorbed after oral administration and shows linear pharmacokinetics for both single- and multiple-dose (once daily) regimens. The oral solution and tablet formulations are bioequivalent to the intravenous formulation.[41] The mean pharmacokinetic parameters obtained in different studies of intravenous and oral levofloxacin in healthy adults[75,76] are comparable to those reported in the manufacturer's US prescribing information.[41] The peak plasma concentration (C_{max}) after single 750 mg doses of levofloxacin given to healthy volunteers was 11.3 mg/L[75] and 12.1 mg/L for intravenous administration, compared with 7.1 mg/L[76] and 9.3 mg/L[41] for oral administration. When given in multiple doses levofloxacin had C_{max} of 12.1 mg/L and 12.4 mg/L for intravenous administration compared with 8.6 mg/L for oral ones.[41,76] Levofloxacin steady-state conditions were reached within 48 hours of initiating once-daily intravenous or oral 750 mg.[41] After oral administration, the T_{max} of levofloxacin is reached within 1–2 hours with an absolute bioavailability of oral levofloxacin 500 mg and 750 mg of approximately 99%.[41,75,76] Systemic exposure to levofloxacin was similar for the intravenous and oral formulations upon administering equal doses of levofloxacin.[41] The AUC_{24} was 103 mg h/L[75] and 90.7 mg h/L[76] at steady state after intravenous or oral administration of levofloxacin 750 mg once daily, respectively.

The in vitro studies revealed that 24%–38% of levofloxacin was bound to plasma proteins (mainly albumin) and the binding was independent of levofloxacin concentration.[41] The volumes of distribution obtained in pharmacokinetic studies ranged from 74–112 L after single or multiple doses of levofloxacin 500 mg or 750 mg.[75,76] Levofloxacin is distributed extensively in tissues and fluids throughout the body and accumulates in phagocytic cells.[39] Furthermore, the mean concentrations of levofloxacin in tissues, ELF, alveolar macrophages, polymorphonuclear leukocytes, paranasal sinus mucosa, and urine, surpass the concentration of levofloxacin in the plasma.[39,77–83] It has been reported that the paranasal sinuses mucosa:plasma concentration ratio was 2.56 at T_{max} after a single 500 mg oral dose of levofloxacin. The concentration of levofloxacin in the paranasal sinuses mucosa was generally higher than the MIC_{90} of the common causative pathogens for upper respiratory tract infections (0.008–2.0 mg/L), including penicillin-susceptible, -intermediate, and -resistant isolates of *S. pneumoniae*.[82] In healthy volunteers, oral levofloxacin (500 or 750 mg) had a mean ELF:plasma concentration ratio at steady state of 1.16 using population pharmacokinetic modeling and 3.18 using Monte Carlo simulation.[82] At a lower dosage of levofloxacin (500 mg once daily for 3 days), C_{max} and AUC_{24} values for the drug were significantly ($P < 0.01$) higher in the polymorphonuclear leukocytes than in plasma.[84] Reassuringly, the concentrations of levofloxacin in the ELF and alveolar macrophages were 1.5- to 6-fold higher than that in the plasma at steady state after receiving levofloxacin 500 mg once daily for 5 days in older patients undergoing diagnostic bronchoscopy with a mean age of 62 years.[80]

Levofloxacin is eliminated mainly through the kidneys, 75%–87% of the dose excreted being unchanged in the urine within 48–72 hours of administering oral levofloxacin 500 or 750 mg; <4% is excreted in the feces.[41,75,76] After a single dose of levofloxacin 750 mg, the mean drug concentration in the urine was 475 mg/L at 4 hours and 186 mg/L at 24 hours;[77] <5% of the dose is excreted in the urine as inactive metabolites of levofloxacin.[41] The mean total body clearance (CL) of levofloxacin in healthy volunteers was reported as 8–9.4 L/h[75,76] and 8.6–13.6 L/h.[41] Levofloxacin appears to undergo glomerular filtration as well as tubular secretion.[41] After single or multiple doses of oral or intravenous levofloxacin 750 mg, the mean terminal plasma elimination half-life ($t_{1/2}\beta$) is 7.5–8.8 hours in pharmacokinetic studies.[75,76] The $t_{1/2}\beta$ of levofloxacin is increased and the CL reduced in patients with impaired renal function (creatinine clearance $CL_{CR} < 50$ mL/min); therefore dosage adjustment is required to avoid drug accumulation as shown in Table 1.[41] Furthermore, levofloxacin is not cleared effectively by hemodialysis or continuous ambulatory peritoneal dialysis.[39,41] The pharmacokinetic properties of levofloxacin are not influenced by age, gender, or race, and they do not show noticeable differences between healthy adults, patients with HIV,[39] or patients with severe community-acquired bacterial infections.[41] Levofloxacin pharmacokinetics in hepatically-impaired patients have not been investigated; however, because of the limited hepatic metabolism of levofloxacin, hepatic impairment is unlikely to have a prominent effect on the drug pharmacokinetics.[41]

Clinical efficacy

The efficacy of levofloxacin 750 mg once daily (intravenous and oral) for 5 days in adults with CAP,[66] ABS,[85] and complicated UTI[86,87] has been assessed in several randomized, double-blind, multicenter, noninferiority trials.[66,85–87] The endpoints were the clinical success rate (proportion of patients showing either a clinical cure or improvement with no need for further antimicrobial therapies in both situations) 1–2 weeks after the end of treatment,[66] or at 2–3 weeks of the study,[85] or the microbiological eradication rate (all pathogens identified in samples at the study entry were eradicated) at 2–3 weeks of the study.[86,87] Levofloxacin indications and dosing for patients with normal renal function are summarized in Table 2.

Patients enrolled in the noninferiority trial with CAP were aged ≥18 years and were diagnosed with mild-to-severe CAP. Other inclusion criteria involved one or more signs or symptoms including fever, a white blood cell count of >10,000 cells/mm^3, or hypothermia. The exclusion criteria included the following conditions: patients without a confirmed diagnosis of CAP, patients who did not come to the follow-up visit, patients who increased (>120%) or reduced (<80%) the scheduled doses, and patients who had additional antimicrobial therapy during treatment with levofloxacin.[66] Patients with mild-to-severe CAP received 750 mg levofloxacin (intravenous or oral) once daily for 5 days or 500 mg once daily for 10 days. Subjects receiving the higher dosage of levofloxacin were given a placebo for the last 5 days of the 10-day treatment regimen.[66] Levofloxacin susceptibility testing of the causative pathogens was performed, but initial treatment was empirical. The noninferiority criteria were established as the upper limit of the 2-sided 95% CI for the between-group difference in the clinical success rate <15%, if both treatment groups had a clinical success rate of 80%–90%, or <10%, if both treatment groups had a clinical success rate of ≥90%.[66] The results revealed that levofloxacin 750 mg once daily for 5 days was noninferior to 500 mg once daily for 10 days in the treatment of mild-to-severe CAP in the overall patient population,[66] as well as for patients with CAP caused by atypical organisms (*C. pneumoniae* or *M. pneumoniae*),[88] and for elderly patients aged ≥65 years.[89]

Table 1 Dosing in patients with diminished renal function

Renal status	Initial dose	Subsequent dose
CL_{CR} ≥ 50 mL/min	500 mg	500 mg q24h
CL_{CR} 20–49 mL/min	500 mg	250 mg q24h
CL_{CR} 10–19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
CL_{CR} ≥ 50 mL/min	750 mg	750 mg q24h
CL_{CR} 20–49 mL/min	750 mg	750 mg q48h
CL_{CR} 10–19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h

Abbreviations: CL_{CR}, creatinine clearance; CAPD, chronic ambulatory peritoneal dialysis; q, every.

Table 2 Levofloxacin indications and dosing for patients with upper respiratory tract infections and with normal renal function

Type of infection	Dose	Frequency	Duration
Community acquired pneumonia	500 mg	q24h	7–14 days
Community acquired pneumonia	750 mg	q24h	5 days
Nosocomial pneumonia	750 mg	q24h	7–14 days
Acute bacterial exacerbation of chronic bronchitis	500 mg	q24h	7–14 days
Acute bacterial sinusitis	500 mg	q24h	10–14 days
Acute bacterial sinusitis	750 mg	q24h	5 days

Abbreviation: q, every.

In patients receiving either the levofloxacin 750 mg or 500 mg regimen, baseline characteristics were similar and overall microbiological eradication rates were similar in both groups.[66] The eradication rates for both the 750 mg and 500 mg regimens were high for subgroups of microbiologically evaluable patients infected with aerobic Gram-positive (82.8% vs 85.3%) and Gram-negative (96.2% vs 90.7%) pathogens, as well as other pathogens (93.8% vs 96.2%). Eradication rates for *S. pneumoniae*, *H. influenzae*, and *H. parainfluenzae* in the corresponding post-therapy visit were 86.4% vs 85%, 92.3% vs 85.7% and 100% vs 90%, respectively.[66] Retrospective analysis revealed that the clinical success rates in patients with CAP caused by *H. influenzae*, *H. parainfluenzae*, or *S. pneumoniae* were also similar between the levofloxacin 750 mg and 500 mg treatment groups (92.3% vs 92.9%, 100% vs 90%, and 90.9% vs 90%, respectively).[66]

The efficacy of the high-dose, short-course of levofloxacin in achieving early resolution of symptoms has been studied.[90] Resolution of purulent sputum, shortness of breath, chills and cough were 40.6% vs 30.7%, 35.1% vs 27.7%, 54.8% vs 54.2%, and 10% vs 10.1% comparing patients who received the levofloxacin 750 mg or 500 mg regimen, respectively. Furthermore, 99.4% of the 158 pathogens isolated at study entry were susceptible to levofloxacin and there was no significant difference between treatment groups in the time of switching from the intravenous administration of levofloxacin to oral administration of the drug.[90] High-dose, short-course of levofloxacin (750 mg once daily for 5 days) also had good efficacy in the subgroup of patients with severe CAP, demonstrating high clinical success rates of >85%. Overall, high microbiological response rates (≥87.5%) were observed in the subgroup of microbiologically evaluable patients receiving levofloxacin regardless of the treatment regimen.[91] In the same study, microbiological eradication was observed in 88.2% of typical pathogens identified from respiratory cultures and 90% of atypical pathogens.[91]

It has been reported that levofloxacin 750 mg once daily for 5 days has good efficacy in patients with CAP caused by atypical organisms.[88] The overall clinical success rate of levofloxacin 1–2 weeks after treating CAP caused by a single atypical pathogen, was >95%. Noninferiority of levofloxacin 750 mg once daily for 5 days compared with the 10-day regimen was also established in this study. The overall clinical success rate of the levofloxacin 750 mg regimen was 94.8% for CAP caused by atypical pathogens, compared with 96.5% for the levofloxacin 500 mg regimen.[88] Furthermore, the clinical success rates at the 1–2 weeks post-treatment visit for patients with *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae* were comparable between the groups receiving the levofloxacin 750 mg and 500 mg dosing regimen (90.9% vs 100%, 100% vs 100%, and 95.3% vs 94.4%, respectively).[88]

Post-marketing surveillance

Post-marketing data demonstrated that levofloxacin simultaneous administered with warfarin may increase the prothrombin time. Therefore, coagulation studies and bleeding should be monitored in patients receiving the two drugs concomitantly.[41] Levofloxacin does not currently have a US Food and Drug Administration approved indication in patients aged <18 years. Like other fluoroquinolones, levofloxacin decreases theophylline metabolism and dosage adjustment for theophylline may be required for concurrent administration of both drugs. Concomitant fluoroquinolone administration with cyclosporin resulted in elevated serum concentrations of ciclosporin, but these alterations were not clinically significant.[41]

Safety and tolerability

Intravenous levofloxacin must be administered slowly as an infusion over a minimum period of 60–90 minutes, depending on the dose. Levofloxacin tablets or oral solution are generally prescribed at dosages of 250, 500, or 750 mg once daily. The tablet formulation of levofloxacin can be taken with or without food; however, the oral solution should be taken 1 hour prior to or 2 hours after meals. In patients receiving levofloxacin, sufficient hydration should be maintained to prevent excessively concentrated urine. Levofloxacin should be administered at least 2 hours apart from some agents such as magnesium- or aluminium-containing antacids, sucralfate, metal cations, zinc-containing multivitamins, or didanosine.

Data from patients aged ≥65 years (phase III clinical trials) demonstrated no difference between elderly and younger patients for safety or effectiveness of levofloxacin. Elderly patients may be more sensitive to levofloxacin, mainly due to the effect of the drug on the QT interval. Thus, caution is required in the simultaneous administration of levofloxacin with drugs that prolong the QT interval such as class IA or class III antiarrhythmics. Although, levofloxacin is a very safe fluoroquinolone, caution and a risk/benefit assessment is required with the use of levofloxacin in the elderly due to the increased risk of severe tendon disorders in this group of patients, particularly if they are receiving corticosteroids.[41] However, it should be stated that there is no evidence that tendon rupture is more likely to occur with levofloxacin than with any other fluoroquinolone.[92] Blood

glucose monitoring is recommended in patients with diabetes mellitus receiving simultaneous hypoglycemic agents and/or insulin, because symptomatic hyperglycemia and hypoglycemia have been reported with levofloxacin administration.[41] Concomitant administration of fluoroquinolones (including levofloxacin) with NSAIDs may increase the risk of central nervous system stimulation and convulsive seizures.[41]

Levofloxacin 750 mg once daily for 5 days is a well-tolerated fluoroquinolone for patients with CAP or UTI.[86,87,93] In a pooled analysis of patients with respiratory infections receiving the levofloxacin 750 mg regimen or 500 mg regimen, the results revealed that 4.5% and 4.9% of patients, respectively, had adverse effects during the therapy. The adverse effects in both dosage regimens included nausea, vomiting, diarrhea, dyspepsia, constipation, abdominal pain, headache, insomnia, and dizziness. The incidence of levofloxacin-associated adverse effects was similar between both treatment regimens (8% vs 7.6%).[93]

The use of fluoroquinolones and exposure to the sun or UV light has been associated with photosensitivity reactions.[41] Fluoroquinolones can potentially prolong the QT interval but there are no reported cases of torsade de pointes in any clinical or post-marketing trials.[41,93] It has been reported that levofloxacin is associated with *Clostridium difficile* diarrhea, as are most other antibacterial agents. Severity ranges from mild diarrhea to pseudomembranous colitis.[41] The incidence of drug-related adverse effects in patients with CAP or ABS was similar between the levofloxacin 750 mg and 500 mg dosing regimens.[93]

Regulatory affairs

Levofloxacin is approved for use in the US, Canada, and worldwide in the treatment of CAP, ABS, complicated UTI, and AP.

Conclusion and comments

The respiratory fluoroquinolones are considered to be a substantial component of the anti-infective armamentarium for the treatment of bacterial respiratory infections. Levofloxacin is active against most of the respiratory pathogens and has a good clinical success rate. Its favorable pharmacodynamics, safety, efficacy profile, and tolerability, and also its in vitro activity against the common respiratory pathogens, places levofloxacin among first-line agents for the treatment of community-acquired respiratory tract infections such as CAP.

The Infectious Diseases Society of America/American Thoracic Society guidelines recommend that a respiratory fluoroquinolone (eg, levofloxacin 750 mg) or a β-lactam plus a macrolide be used for the treatment of CAP. The use of fluoroquinolones is a reasonable therapeutic choice for the treatment of respiratory infections caused by penicillin-susceptible *S. pneumoniae,* penicillin-resistant *S. pneumoniae*, *Legionella pneumophilia*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*. Levofloxacin combination therapy with antipseudomonal β-lactam (or aminoglycoside) should be considered if *P. aeruginosa* is likely to be a causative pathogen of the respiratory infection. *S. pneumoniae* resistance to antibacterial drugs has been a major problem in the US and worldwide for more than a decade. Although there are reports of the emergence of resistance to some fluoroquinolones among *S. pneumoniae*, the incidence of levofloxacin-resistant organisms has remained steady at $<1\%$ worldwide. In general, levofloxacin shows good in vitro activity against clinically relevant Gram-positive, Gram-negative, and atypical organisms that cause respiratory infections. Levofloxacin is active against penicillin-susceptible and -resistant strains of *S. pneumoniae*, the Gram-negative species *E. cloacae* and *P. mirabilis*, and the atypical organisms *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae* (MIC_{90} of ≤ 2 mg/L). Levofloxacin is highly active against the Gram-negative species *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* (MIC_{90} of ≤ 0.06 mg/L), including β-lactamase-positive strains of *H. influenzae* and *M. catarrhalis*. Because the activity of levofloxacin is concentration-dependent, the most common predictor of microbiological and clinical efficacy is the AUC:MIC ratio. A ratio of >30 was used in some studies to predict in vivo activity, particularly against *S. pneumoniae*. A higher ratio (>100) is suggested as being predictive of a bactericidal effect, and thus reducing the potential of first-step mutations. Availability of pneumococcal vaccine is decreasing the incidence of pneumococcal infections and decreasing the incidence of infections caused by resistant *S. pneumoniae*.

In the last 5 years, the rate of resistance of *S. pneumoniae* to amoxicillin/clavulanic acid, azithromycin, and tetracycline appears to have increased, but the levofloxacin resistance rate of *S. pneumoniae* remains $\leq 1\%$ worldwide.[94] High-dose, short-term therapy (levofloxacin 750 mg once daily for 5 days) is the standard dosing regimen for levofloxacin in the treatment of CAP worldwide. Increased availability of pneumococcal vaccination programs may decrease the incidence of *S. pneumoniae* as a cause of CAP in adults over time. Other problematic infections with multidrug-resistant organisms will become the main focus of research in the next 5 years.

Disclosure

The authors declare no conflicts of interest in this work.

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