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A Risk-Benefit Assessment of Levofloxacin in Respiratory, Skin and Skin Structure, and Urinary Tract Infections

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Abstract

As a class, the quinolone antibacterials can no longer be assumed to be both effective and relatively free of significant adverse effects. Recent safety issues with newer generation fluoroquinolones, and concerns regarding drug-use associated bacterial resistance have made all drugs in this class subject to intense scrutiny and further study. Levofloxacin is a second generation fluoroquinolone with a post marketing history of well tolerated and successful use in a variety of clinical situations.

Quinolones as a class cause a variety of adverse effects, including phototoxicity, seizures and other CNS disturbances, tendonitis and arthropathies, gastrointestinal effects, nephrotoxicity, prolonged QT_c interval and torsade de pointes, hypo- or hyperglycaemia, and hypersensitivity reactions. Levofloxacin has been involved in only a few case reports of adverse events, which include QT_c prolongation, seizures, glucose disturbances, and tendonitis.

Levofloxacin has been shown to be effective at dosages of 250mg to 500mg once-daily in clinical trials in the management of acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, skin and skin structure infections, and urinary tract infections. There are data suggesting that levofloxacin may promote fluoroquinolone resistance among the *Streptococcus pneumoniae*, and that clinical failures may result from this therapy. Other data suggest that fluoroquinolones with lower potency against *Pseudomonas aeruginosa* than ciprofloxacin, such as levofloxacin, may drive class-wide resistance to this pathogen.

Levofloxacin is an effective drug in many clinical situations, but its cost is significantly higher than amoxicillin, erythromycin, or first and second generation cefalosporins. Because of the propensity to select for fluoroquinolone resistance in the pneumococcus and potentially other pathogens, levofloxacin should be an alternative agent rather than a drug-of-choice in routine community-acquired respiratory tract, urinary tract, and skin or skin structure infections. In areas with increasing pneumococcal β-lactam resistance, levofloxacin may be a reasonable empiric therapy in community-acquired respiratory tract infections. Similarly, in patients with risk factors for infectious complications or poor outcome, levofloxacin may be an excellent empiric choice in severe community-acquired respiratory tract infections, urinary tract infections, complicated skin or skin structure infections, and nosocomial respiratory and urinary tract infections. Better clinical data are needed to identify the true place in therapy of the newer fluoroquinolones in common community-acquired and nosocomial infections. Until then, these agents, including levofloxacin, might best be reserved for complicated infections, infection recurrence, and infections caused by β-lactam or macrolide-resistant pathogens.

As a class, the fluoroquinolones can no longer be assumed to be both effective and relatively free of significant adverse effects. However, among the many fluoroquinolone compounds available throughout the world today, there are marked differences in structure-associated adverse effect profiles and drug interactions. Levofloxacin is the *L*-isomer of the *D,L*-racemate ofloxacin. Levofloxacin was launched on world markets in the later half of the 1990s under several trade names, including Levaquin®, Levoxacin®, Cravit®, Elequine®, and Tavanic®. Since that time, levofloxacin has been extensively used throughout the world in a variety of clinical circumstances, and against a multitude of

Table I. Quinolone classification

First generation
Nalidixic acid
Oxolonic acid
Cinoxacin
Piromedic acid
Pipemedic acid
Second generation
Norfloxacin
Ciprofloxacin
Enoxacin
Lomefloxacin
Ofloxacin
Levofloxacin
Rufloxacin
Third generation
Temefloxacin
Sparfloxacin
Grepafloxacin
Gatifloxacin
Pazufloxacin
Tozufloxacin
Forth generation
Trovafloxacin
Clinafloxacin
Moxifloxacin
Sitafloxacin
Gemifloxacin

bacterial pathogens. There have been few significant adverse events reported despite the wide spread exposure of this agent.

This review will focus on the risk-benefit ratio of levofloxacin in the treatment of respiratory tract, skin and skin structure, and urinary tract infections in adults. An overview of general toxicities of the fluoroquinolone class is provided, with an emphasis on information relating to levofloxacin. A general review of levofloxacin pharmacokinetics, pharmacodynamics, *in vitro* activity and clinical efficacy is also provided.

1. Quinolone Classification

According to the quinolone classification scheme proposed by Andriole,[1] levofloxacin is a second generation fluoroquinolone similar to ofloxacin and ciprofloxacin (table I). This classification scheme for the quinolones parallels the cefalosporins generation classification in that it is based on potency and spectrum against 'problem' pathogens.

First generation agents are generally nonfluorinated 4-quinolone structures, with adequate activity against Gram-negative aerobes, but ineffective tissue penetration or unacceptable toxicity.[2]

Second generation agents are all fluoroquinolones, the 6-fluoro substitution significantly broadens both Gram-negative and Gram-positive activity, possibly by improving tissue penetration and binding to the DNA gyrase enzyme.[2] Of the second generation agents, ciprofloxacin remains the most potent against *Pseudomonas aeruginosa*, with ofloxacin and levofloxacin minimum inhibitory concentrations (MICs) 1 to 2 tube-dilutions higher.[3] Second generation fluoroquinolones lack clinically significant activity against most streptococci and enterococci, and have experienced noted resistance in the staphylococci, particularly methicillin-resistant *Staphylococcus aureus*.[3]

The third generation agents have increased potency against Gram-positive bacteria, especially the streptococci.[3] These improvements in Gram-positive antibacterial activity came through addition of halogens at the C-8 position, methylation or methoxy-substitution at the C-8 position, or ring substitutions at the C-7 position.[2] The increase in potency against important streptococci, such as *Streptococcus pneumoniae*, is on the order of magnitude of 2 to 6 tube-dilutions lower in MICs than ciprofloxacin.[4] Third generation fluoroquinolones also have increased anaerobic activity over the earlier generations.[5] The half-lives of most third generation fluoroquinolones are significantly longer than those of earlier generations, and these agents are all administered once-daily.[6]

Fourth generation agents also generally have extended half-lives and once-daily administration and are the most potent against streptococci, especially *S. pneumoniae*.[3] These drugs possess the greatest anaerobic activity of the class.[5]

2. Potential Toxicity Issues: Emphasis on Levofloxacin

The late 1990s have brought an end to the generally favourable safety profile of the quinolone antibacterial class. With the exception of temafloxacin, which was introduced in the early 1990s but discontinued in 1992 due to drug-induced haemolytic uraemic syndrome, the fluoroquinolones have enjoyed a relatively reliable safety profile until the marketing of sparfloxacin in 1996, and grepafloxacin and trovafloxacin in 1997. A review of safety results from 28 consecutive prospective, randomised, double-blind, placebo- or active-controlled clinical trials demonstrated that in 27 studies, fluoroquinolones were equal or superior to nonfluoroquinolone comparator agents or placebo in terms of percentage of patients experiencing adverse events.[7]

2.1 Phototoxicity

Many adverse events among the fluoroquinolone class can be predicted based on structure-activity relationships (SARs). Among the most noted toxicities is phototoxicity, which is directly related to substitution at the X-8 position on the bicyclic ring.[2] Halogenation at this position causes a marked increase in photoxicity,[2] with fluorine having more toxic activity than chlorine. Unfortunately, halogenation at this position also confers significant Gram-positive antibacterial potency.[2] Fleroxacin, lomefloxacin, and sparfloxacin all possess this fluorine at X-8.[2] Clinafloxacin and sitafloxacin, 2 potent investigational fluoroquinolones, have chlorine at the X-8 position.[2] Fluoroquinolones with a bulky side chain or a methyl group at R-5 may also produce more phototoxicity than would be predicted solely by the X-8 group.[2]

Levofloxacin is a tricyclic, fluorinated carboxyl quinolone; its structure does not suggest potential phototoxicity concerns (see fig. 1). Fewer than 0.1% of patients receiving levofloxacin in clinical trials experienced phototoxicity.[8] No formal case reports of phototoxicity associated with levofloxacin have been reported to date. Boccumini et al.[9]

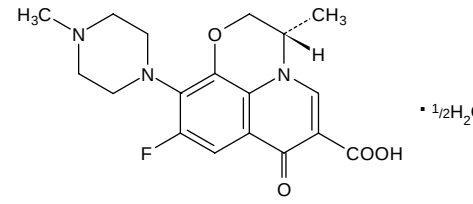

Fig. 1 Chemical structure of levofloxacin.

evaluated the photoreaction potential of levofloxacin in healthy volunteers and found no significant reactions. Study participants were randomised to either oral levofloxacin 500 mg/day or placebo for 5 days. Each participant was exposed to both ultraviolet (UV) A and B light sources. It was noted that UVA exposure was associated with mild reactions in 20 of 24 levofloxacin-treated patients. However, none of these individuals experienced associated symptoms of exposure. Of interest, 3 placebo-recipients also experienced a positive reaction to UVA exposure. All participants had a negative reaction to UVB exposure by investigator assessment. None of the study participants experienced a wheal-flare reaction. While there appears to be little concern for serious phototoxic reactions with levofloxacin, prudence suggests caution should be exercised when prolonged exposure to direct sunlight may occur while taking levofloxacin.

2.2 Hepatic and Renal Toxicity

Liver toxicity associated with trovafloxacin and renal toxicity associated with temafloxacin may be linked to the 2,4 di-fluorophenyl substituent at the C-1 position of each of these antibacterials.[10,11] Since 1998, 150 cases of clinically significant liver toxicity have been reported in patients taking trovafloxacin.[12] 14 of these cases reported acute liver failure,[12] with 4 patients requiring liver transplantation, and an additional 5 liver-related deaths. Increases in liver enzyme levels are reported in clinical trials of all fluoroquinolones at rates of 2 to 3%. Liver and renal toxicities have not been reported with levofloxacin.

2.3 CNS Toxicity

CNS disturbances are also a function of quinolone structure, and involve inhibition of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, binding to its $GABA_A$ receptor.[13] This results in CNS stimulation. Substitution at the C-7 position may be responsible for these effects. Derivatives with an unsubstituted piperazinyl ring (e.g. ciprofloxacin, enoxacin, norfloxacin) demonstrate higher GABA-receptor affinity than quinolones with a methylated piperazine ring.[13] Lipophilicity and CNS penetration may also be important in these effects.[2] Clinical symptoms of CNS excitatory disturbances include headache, dizziness, drowsiness, alteration in vision, restlessness, sleep disorders, agitation, confusion, and delirium.[2,14-16] Convulsions and seizures have also been rarely reported, and are more likely to occur with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially fenbufen or its metabolite, biphenyl acetic acid.[17]

Convulsions are uncommon with levofloxacin therapy, but Yasuda et al.[18] recently reported the development of convulsions, involuntary movements (e.g. tremor, myoclonus and chorea-like motion), and visual hallucinations in 2 elderly patients receiving levofloxacin. The only apparent neurological disorder common in these patients (a 67-year-old man and an 85-year-old man) was that of age-related brain atrophy. The authors suggested that levofloxacin may have played a role in these adverse events, but age-related renal and brain impairment may also have been responsible.

Seizures have been reported with ofloxacin therapy.[19,20] Ofloxacin-associated seizures may be a concentration-related phenomenon. Case reports suggest elderly patients receiving full-dosage therapy are at highest risk, and the seizures appear to be temporally-related to maximum serum concentration (C_{max}).[19,20] Dizziness, somnolence, insomnia and nervousness have all been reported with levofloxacin in clinical trials (table II).

2.4 Gastrointestinal Toxicities

Other adverse effects of the fluoroquinolone class are not easily explained by SARs. All agents in the class cause some gastrointestinal (GI) disturbances, which range from nausea, anorexia and dyspepsia to abdominal pain, vomiting and diarrhoea.[15,35] These are the most common adverse events described for the fluoroquinolones, but are typically mild and seldom necessitate discontinuation of therapy.[2] GI disorders were the most common drug-related adverse events in clinical trials with levofloxacin (5.1%). Specific complaints included diarrhoea (1.2%), nausea (1.2%), flatulence (0.5%), abdominal pain (0.3%), dyspepsia (0.3%), taste perversion (0.2%) and vomiting (0.2%)[20,23-27,29-31]

2.5 Nephrotoxicity

Nephrotoxicity is uncommonly reported with most fluoroquinolones, with temafloxacin being the exception.[10] Crystalluria may be associated with fluoroquinolone solubility in urine, which is decreased with alkaline pH.[35] Interstitial nephritis and acute renal failure have been reported with older quinolones, and may be associated with hypersensitivity reactions (as seen with ciprofloxacin) or direct toxicity of the drug (observed with norfloxacin).[15] Elevated serum creatinine levels have been associated with various fluoroquinolones, with ofloxacin having the highest reported incidence (1.3%).[7] Crystalluria, interstitial nephritis, and acute renal failure have not been causally associated with levofloxacin, sparfloxacin, grepafloxacin, or trovafloxacin therapy.[35]

2.6 Cardiovascular Toxicities

Cardiotoxicity has been limited to fluoroquinolone-associated QT_c interval prolongation. This is a class-wide phenomenon, and involves quinolone interference with human ether-a-go-go-related gene (HERG)-mediated potassium channel currents in the myocardium.[36] These myocardial potassium channels are responsible for repolarisation of the ventricle during diastole. Interference with the potassium channels has been associated

Table II. Adverse events associated with intravenous or oral levofloxacin administration[a]

Adverse event	Patients with event/total patients (%)	
	250 mg/day	500 mg/day
Nausea	1/41 (2.4)[21]	6/107 (5.6)[22] 5/297 (1.7)[23] 4/329 (1.2)[24] 6/243 (2.5)[25] 4/187 (2.1)[26] 5/295 (1.7)[27] 3/263 (1.1)[28] 4/136 (3.0)[29] 3/232 (1.3)[30]
Diarrhoea	1/41 (2.4)[21]	4/297 (1.3)[23] 9/329 (2.7)[24] 1/41 (2.4)[21] 4/243 (1.6)[25] 2/187 (1.1)[26] 4/295 (1.4)[27] 4/263 (1.5)[88] 3/230 (1.3)[31] 2/136 (1.5)[29]
Abdominal pain	4/41 (9.8)[21]	2/107 (1.9)[22] 3/297 (1.0)[23] 2/187 (1.1)[26]
Flatulence		5/329 (1.5)[24] 3/187 (1.6)[26]
Digestive	32/281 (11.4)[32]	26/280 (9.3)[32] 520119 (16.7)[33]
Dizziness		3/107 (2.8)[22] 2/195 (1.0)[34]
Somnolence		3/136 (2.2)[29]
Insomnia		2/187 (1.1)[26]
Psychiatric (anorexia, disorientation, insomnia)		5/119 (4.2)[33]
CNS (dizziness, headache)		8/119 (6.7)[33]
Nervous	9/281 (3.2)[32]	10/280 (3.6)[32]
Skin and appendages		3/280 (1.1)[32]
Pruritus		1/41 (2.4)[21]
Oral thrush		1/41 (2.4)[21]
Fungal infection		2/107 (1.9)[22]
Injection site pain		3/295 (1.0)[27]
Cardiovascular	3/281 (1.1)[32]	4 /280 (1.4)[32]
Haematological and lymphatic	5/281 (1.8)[32]	4/280 (1.4)[32]
Metabolic and nutritional	11/281 (3.9)[32]	8/280 (2.9)[32]
Respiratory	7/281 (2.5)[32]	7/280 (2.5)[32]
Vaginitis[b]		2/297 (1.1)[23] 5/243 (2.1)[25] 2/119 (1.7)[33]

a Drug-related adverse events reported in ≥1% of patients and only those assessed by the investigator as being definitely or probably related to study drug are included in this table.

b Vaginitis percentages were calculated from the total number of women in each treatment group.

with the long QT_c syndrome.[37] Prolongation of the QT_c beyond 500 msec may predispose the heart to torsade de pointes.[36] Fluoroquinolone interference with these currents appears to be dose- and concentration-dependent.[36] Affinity for the HERG-mediated channel appears to be greater for sparfloxacin and grepafloxacin, followed by moxifloxacin.[36] At standard therapeutic dosages, sparfloxacin, grepafloxacin, and moxifloxacin (oral) prolong the QT_c by 10 msec, 10 msec, and 6 msec, respectively.[38-40] Levofloxacin, gatifloxacin, and ciprofloxacin appear to have the least affinity for the channel, with QT_c prolongation at standard therapeutic doses of 1 to 4.6 msec.[41] However, these differences are unlikely to translate into clinical differences in ventricular repolarisation of dysrhythmia generation. Quinolone QT_c interval prolongation appears less than that associated with erythromycin (8 to 15 msec), clarithromycin (2 to 5 msec), doxepine (22 msec), or cisapride (6 msec).[42-44]

Levofloxacin-associated QT_c interval prolongation is rare. In preclinical and clinical trials, levofloxacin was not associated with QT_c interval prolongation.[8] One case report and 1 case-series are available. The case involves an 88-year-old woman who was hospitalised with atrial fibrillation, bronchitis and mild congestive heart failure.[45] Her bronchitis was treated with oral levofloxacin 500 mg/day. She also received a single dose of procainamide 500mg at the initiation of levofloxacin but the antiarrhythmic agent was not continued. After receiving her third dose of levofloxacin, her QT_c interval was prolonged (464 *vs* 450 msec at baseline). Following the fourth dose of levofloxacin, her QT_c interval was 568 msec and the patient experienced several nonsymptomatic sustained runs of polymorphic ventricular tachycardia. When measured later in the day, her QT_c interval was 577 msec. Levofloxacin was discontinued, and her QT_c interval returned to baseline (437 msec). A recent case series was reported by Ianinni et al.[46] of QT_c prolongation associated with levofloxacin. 37 patients receiving levofloxacin were studied to determine QT_c intervals before and during antibacterial therapy. Prolongation of QT_c < 30 msec was found

in 16 patients, >30 msec in 8, >60 msec in 1, and total QT_c > 500 msec in 4 patients. No change or a decrease in QT_c was observed in 12 patients. A single patient who also received amiodarone developed torsade de pointes. QT_c was prolonged by an average of 4.6 msec but the range was -47 to +92 msec.

Coadministration of drugs known to prolong the QT interval with fluoroquinolones, especially those with higher affinities for the HERG receptor, should be avoided. Other cardiovascular effects of fluoroquinolones include hypotension and tachycardia following rapid intravenous infusion. Some of these effects may be histamine mediated.[46]

2.7 Tendon and Joint Toxicities

Quinolones as a class interfere with the epiphyseal-articular complex in immature mammalian joint cartilage, particularly beagle dogs.[47,48] Doses needed to induce damage in this animal model are similar to those used therapeutically. Since this is not observed in adults, the contraindication for fluoroquinolone use in children and adolescents is based on their potential to cause cartilage toxicity.[47,48] Despite this restriction, fluoroquinolones, especially ciprofloxacin, have been used in millions of infants and children, mostly for the treatment of pulmonary infection in cystic fibrosis, as well as salmonellosis and shigellosis. The data from compassionate use and a few clinical studies suggest that ciprofloxacin and to a lesser extent ofloxacin are effective in treating certain infections in the paediatric population and that the safety profiles appear to be similar to those in adults.[49] However, further studies are needed to clearly determine fluoroquinolone safety in children.

Tendonitis and tendon ruptures have been reported in adults during fluoroquinolone exposure. Levofloxacin, ciprofloxacin, sparfloxacin, norfloxacin, enoxacin, and pefloxacin have been associated with this event.[50-54] The Achilles tendon appears to be at highest risk, but hand and shoulder tendonitis has also been reported.[51]

In pre-marketing clinical testing, 1 case of tendonitis occurred among 3460 patients treated with levofloxacin.[55] Two reports of tendonitis have been reported recently. The first occurred in an 83-year-old woman after the third day of a 10-day course of levofloxacin 500 mg/day.[50] The patient completed the 10-day course, but 2 weeks after completing therapy she was seen by her physician and podiatrist for severe ankle pain and bruising. She was diagnosed with bilateral Achilles tendonitis with possible rupture of the left Achilles tendon, and treated with ibuprofen, ankle immobilisation and rest. At follow-up, 3 weeks later the pain and bruising had improved. Her condition had significantly improved after 10 weeks but had not completely resolved.

The second case was reported in the Spanish literature.[56] A 55-year-old man with a history of hypertension, ulcer disease, and renal transplantation with immunosuppression was treated with levofloxacin for a post-operative urinary tract infection. The patient developed supraspinal tendonitis bilaterally, and the drug was discontinued. The tendonitis pain resolved. Levofloxacin was restarted, and the tendonitis pain subsequently returned. Pain resolved following final discontinuation of the fluoroquinolone antibacterial.

Other arthropathies occurring in adults appear at a rate approximating 1% of patients.[57] These are found mostly in adults under 30 years of age, and symptoms include extremity stiffness, with joint pain and inflammation.[57,58] The effect is usually self-limiting, and resolves with treatment discontinuation.

2.8 Endocrine Toxicity

Quinolones may have adverse effects on glycaemic control, especially in patients with diabetes mellitus. Although both hyper- and hypoglycaemia have been reported, hypoglycaemia appears to be the more serious event. Levofloxacin is reported to cause symptomatic hyper- and hypoglycaemia, usually in patients with diabetes mellitus receiving concomitant treatment with an oral hypoglycaemic agent or with insulin.[8]

2.9 Hypersensitivity

Hypersensitivity reactions to the quinolones occur at a rate of 0.6 to 1.4%.[35] An evaluation of the use of levofloxacin for chronic osteomyelitis included the report of a single patient who experienced an allergic reaction, characterised by a rash and swollen tongue.[59] An ampicillin-like rash associated with infectious mononucleosis was reported for levofloxacin in a 22-year-old woman with no prior history of drug allergy.[60] The patient had presented to the emergency room with a temperature of 38.3°C, generalised body aches, headaches and loin pain. In addition, physical examination revealed enlarged tender cervical lymph nodes with bilateral renal angle tenderness. The only significant laboratory findings were from a urine analysis, which demonstrated trace leucocytes, bacteria 2+, and 10 to 22 white blood cells per high power field. The patient was admitted and started on oral levofloxacin. Her temperature remained elevated and repeat laboratory tests showed thrombocytopenia and elevated transaminase levels. On hospital day 2 the patient developed an erythematous maculopapular rash on her trunk and upper extremities. Levofloxacin was discontinued and the rash subsided 2 days later. A monospot test was found to be positive and lymphocytosis with atypical lymphocytes on peripheral smear was noted. The diagnosis of infectious mononucleosis was made. While the rash presented in a similar manner to that of ampicillin, the exact mechanism is not understood. A review of the literature revealed no additional reports of similar rash with fluoroquinolones. Of interest, it is not clear whether patients who develop ampicillin-associated rash during the course of infectious mononucleosis should be considered sensitive to ampicillin. From this case, the same question remains for levofloxacin.

2.10 Adverse Events in the Patients with HIV Infection

In pharmacokinetic and safety evaluations of levofloxacin use in patients who are HIV-positive, a high rate of adverse events has been reported.[61,62] Piscitelli et al.[61] evaluated the use of high doses of levofloxacin for extended intervals in patients who were HIV-positive. 31 patients were randomly assigned to 1 of 3 study groups: oral levofloxacin 750 mg/day for days 1 to 14 followed by 1000mg 3 times weekly for days 15 to 26; oral levofloxacin 750 mg/day for days 1 to 14 followed by 750mg 3 times weekly for days 15 to 26; or a placebo group. High rates of adverse events were noted, ranging in frequency from 70% in the 1000mg 3 times weekly group to 95% in the 750 mg/day group. These included nausea, diarrhoea, flatulence, fatigue, fever, headache, pruritis and rash. The rate of adverse events was also high in the placebo group (71%).

The pharmacokinetics and safety of levofloxacin has been evaluated in 10 patients with HIV infection.[62] Patients randomly received a single dose of levofloxacin 350mg or placebo on day 1. Starting on day 3, the patients received the same study therapy on a daily basis through to day 10. All study participants experienced adverse events, including those receiving placebo. The most commonly reported adverse events were GI symptoms (9 patients in each group), CNS symptoms and headache (3 patients in each group), haematologic (3 in the levofloxacin group, none in the placebo group) and dermatological symptoms (2 patients in the levofloxacin group and 4 in the placebo group).

3. Fluoroquinolone Drug Interactions

Drug interactions may also be categorised by the predictability from SARs. All quinolones chelate divalent metals found in antacids, iron and calcium supplements, sucralfate and dairy products.[63] This is caused by the 3-carboxy and 4-oxo substitutions.[64] Binding of divalent cations at these positions interferes with oral quinolone absorption. This effect is observed with all the available quinolones.

The quinolone-theophylline interaction is predominantly mediated by the C-7 side chain, but C-1 and X-8 substitutions may also play a role.[64] Interactions involve quinolone interference with theophylline metabolism via the cytochrome P450 isozyme 1A2, and lead to an increase in serum theo-

phylline concentrations.[64] The strongest interactions occur for small nonbulky substituents, with piperazine > pyrrolidine > substituted pipeazine or pyrrolidine or aromatic side chains.[35] The interaction is strongest with enoxacin, and then grepafloxacin, ciprofloxacin, and pefloxacin.[64] The quinolone-theophylline interaction is unlikely to occur with lomefloxacin, ofloxacin, levofloxacin, trovafloxacin, sparfloxacin, gatifloxacin or moxifloxacin.[65]

NSAIDs, particularly fenbufen, may increase the quinolone affinity for $GABA_A$ receptors, thus increasing the risk of seizures.[66] Quinolones, particularly enoxacin interfere with *R*-warfarin hepatic metabolism and may prolong the *R*-isomer elimination half-life ($t_{1/2}$) of the anticoagulant.[63] The *R*-isomer is 5 to 8 times less potent that the unaffected *S*-isomer, but there are reports of increased anticoagulant effect of warfarin after addition of quinolone therapy.[63] There appear to be no interactions between levofloxacin and warfarin metabolism.[67] However, this interaction must be considered for any patients beginning quinolone therapy while maintained on warfarin.

Probenecid, and to a lesser extent, cimetidine, interfere with renal tubular secretion for quinolones primarily excreted by the renal route, such as ciprofloxacin, lomefloxacin, ofloxacin, levofloxacin, gatifloxacin and fleroxacin.[63] Probenecid and cimetidine increase the area under the concentration versus time curve (AUC) for levofloxacin by 27 to 38%, prolong the $t_{1/2}$ by 30%, and decrease its plasma and renal clearance by 21 to 35% in healthy volunteers.[8] However, these changes do not warrant a dosage adjustment when these agents are coadministered. Levofloxacin does not alter the disposition of digoxin.[68] There appear to be no interactions between levofloxacin and cyclosporin or zidovudine.[69,70]

4. Overview of Levofloxacin

4.1 Mechanism of Action

The mechanism of action of levofloxacin, like that of other fluoroquinolones, is to bind to and inhibit topoisomerases II (DNA gyrase) and IV.[71] This results in disruption of DNA supercoiling and decatenation, leading to rapid cell death. Mutations in the topoisomerase genes, particularly *gyrA* and *gyrB*, which encode for DNA gyrase, and *parC* and *parE*, which encode for topoisomerase IV, modify levofloxacin targets and produce decreasing potency and increasing resistance.[71] In addition, low-level resistance due to efflux or permeability factors is also observed.[71] Resistance arises in a step-wise manner, and the mutations observed are species specific. Each mutation may increase the MIC by 2 to 4 serial 2-fold dilutions. In some species, first step-mutations occur in *gyrA* and occasionally *gyrB*, while in others they occur in *parC* and less often in *parE*.[72] Second, third and fourth-step mutations usually occur in *gyrA* and *parC*, depending on the bacterial species.

4.2 Pharmacokinetics

Levofloxacin, like other fluoroquinolones, has excellent bioavailability, a high volume of distribution (Vd), and extensive tissue penetration. Bioavailability approaches 100%, with a C_{max} from a 500mg oral dose of 5.19 mg/L.[73] The oral route can effectively be used whenever possible, as time to C_{max} (T_{max}) and C_{max} are similar for both oral and intravenous routes of administration. Levofloxacin Vd ranges from 1.09 to 1.26 L/kg, with approximately 47 to 52% protein binding to serum albumin.[73] Levofloxacin penetrates most tissue well, especially bronchial mucosa, lung, gallbladder, kidney, prostate and genital tract. Bone penetration is generally adequate for clinical use in osteomyelitis, but penetration into the CNS and cerebral spinal fluid (CSF) is poor.[73] In humans, CSF concentrations for ofloxacin of approximately 21% of simultaneous serum concentrations have been reported.[74] All quinolones penetrate extensively into phagocytic cells, producing high intracellular concentrations. Concentrations significantly above those in serum are attained in the kidney, prostate, liver and lung.[73] Tissue concentrations are consistently higher in infected tissues than in uninfected ones, because of drug accumu-

lation in white blood cells that are recruited into infected tissue.[73] Target-site levofloxacin concentrations often exceed the MIC of bacterial pathogens by several fold.[73] The $t_{1/2}$ of the compound is similar to ofloxacin (6 to 8 hours); however, levofloxacin is only administered once-daily. This is possible because of the increased C_{max} achieved with levofloxacin compared with ofloxacin. The drug follows a typical linear, 2-compartment open pharmacokinetic model, with first order elimination.[73] Levofloxacin is mainly eliminated unchanged in the urine via glomerular filtration, with some active tubular secretion. Concomitant administration of levofloxacin with probenecid or cimetidine, which compete for binding sites at the organic acid transport system in the proximal tubule, results in a 24 and 35% decrease in renal clearance, respectively, and prolongation of the terminal $t_{1/2}$ of the antibacterial.[73] Limited hepatic metabolism of levofloxacin to desmethyl and *N*-oxide metabolites also occurs.[73]

The elderly may have reduced clearance of levofloxacin; up to 32% reduction in total clearance in Japanese individuals older than 65 years has been demonstrated, even after adjustment for renal function was made.[75] This same reduction has been noted in a study conducted in North America, with 31 and 37% reductions in renal clearance for men and women, respectively, and 29 and 38% reductions in total body clearance reported for men and women, respectively.[75] These findings correlate with reductions in creatinine clearance. Dosage adjustments should be based on calculated creatinine clearance rather than age. Levofloxacin is not efficiently removed by haemodialysis or peritoneal dialysis.[8]

Ortho McNeil has recently marketed a levofloxacin 750 mg/day dosage. The pharmacokinetic parameters following administration of doses of levofloxacin 750mg were similar to those obtained with 500mg doses, except expected dose-related differences. Mean C_{max} and AUC_{0-24} (values ± standard deviation) with a single 750mg dose were 7.13 ± 1 .44 μg/ml and 71.3 ± 10.3 μg • h/ml, respectively. At steady state, C_{max} and AUC_{0-24} (values ± standard deviation) were 8.60 ± 1.86 μg/ml and 90.7 ± 17.6 μg • h/ml, respectively.[76] In a human volunteer study, 3 of 10 volunteers who received the 750mg dose, and 4 of 10 volunteers who received the 1000mg dose complained of adverse effects related to levofloxacin.[76] However, the effects were generally mild, and similar adverse effects were observed in a placebo control group. Most complaints were of nausea and headache.

4.3 Pharmacodynamics

Like other fluoroquinolones, levofloxacin is concentration-dependent in its bactericidal effects. Preston et al.[77] demonstrated that C_{max} : MIC is a better predictive variable than AUC : MIC in explaining clinical and microbiological outcome in patients enrolled in phase III clinical trials.[77] Both clinical success and microbiological eradication success rates were maximal for patients achieving a C_{max} : MIC ratio of >2.2. The AUC : MIC ratio was also predictive of effect; C_{max} : MIC and AUC : MIC were highly correlated (r = 0.942). Others have suggested AUC : MIC is predictive of efficacy for ciprofloxacin versus primarily Gram-negative respiratory pathogens.[78] Against *S. pneumoniae*, an AUC : MIC ratio of 30 to 50 is suggested to predict clinical success for the fluoroquinolones.[79,80]

4.4 *In vitro* Antimicrobial Activity

The *L*-isomer of ofloxacin is approximately 8 to 128 times more potent than the *D*-isomer against Gram-positive and Gram-negative bacteria.[81] Levofloxacin activity against Gram-positive bacteria is greatly enhanced compared to ciprofloxacin. Recent *in vitro* MIC data are shown in table III. Although all of the newer fluoroquinolones have significantly increased potency against *S. pneumoniae*, levofloxacin is the only fluoroquinolone approved by the US Food and Drug Administration for use in penicillin-resistant pneumococcal infections.[8]

Table III. Levofloxacin *in vitro* antibacterial activity

Organism (n)	N	Levofloxacin MIC_{90} (mg/L)	Reference
Staphylcoccus aureus methicillin sensitive	434	0.25	82
S. aureus methicillin-resistant	457	16	82
S. epidermidis methicillin sensitive	214	4	82
S. epidermidis methicillin-resistant	436	8	82
Streptococcus pneumoniae	6549	1	83
S. pyogenes	a	1	3
Enterococcus faecalis	230	16	82
E. faecium	175	>16	82
Acinetobacter species	428	16	82
Citrobacter feundii	109	2	82
Enterobacter aerogenes	192	16	82
E. cloacae	378	2	82
Escherichia coli	a	0.03	3
Haemophilus influenzae	859	0.015	83
Klebsiella pneumoniae	445	0.5	82
Moraxella catarrhalis	388	≤ 0.03	83
Neisseria gonorrhoeae	185	≤0.008	82
Proteus mirabilis	319	4	82
P. vulgaris	39	0.12	82
Pseudomonas aeruginosa	615	>16	82
Salmonella species	326	0.06	82
Serratia marcescens	211	2	82
Stenotrophomonas maltophilia	106	2	82
Bacteroides fragilis	39	16	82
Clostridium difficile	143	4	82
Peptostreptococcus species	35	4	82
Prevotella species	12	4	82

a Quantity tested unknown.

MIC = minimum inhibitory concentration.

5. Clinical Data with Levofloxacin

Data from pre-marketing and recent post-marketing clinical trials are reviewed. Tables IV to VIII summarise efficacy data and table II summarises adverse events associated with levofloxacin use.

5. 1 Respiratory Tract Infections

5.1.1 Acute Bacterial Sinusitis

The efficacy and safety of levofloxacin in the treatment of acute sinusitis has been compared with clarithromycin and amoxicillin-clavulanic acid in 2 multicentre, randomised studies.[22,23] Compared with clarithromycin, levofloxacin therapy resulted in a similar clinical success rate as defined as a cure or improvement in symptoms (96% for clarithromycin *vs* 93% for levofloxacin).[22] Symptomatic relapse occurred in 4.1% (4 out of 97) of levofloxacin-treated patients and in 7.2% (6 out of 83) of clarithromycin-treated patients. In safety assessments, 14% (15 out of 107) of patients in the levofloxacin group and 23.2% (25 out of 109) in the clarithromycin group reported at least 1 adverse event considered to be treatment-related. Most of these complaints involved the GI system and taste perversion, both of which were more common with clarithromycin.[22] In a similar study by Lasko et al.,[33] approximately 94% of the clinically evaluable patients in both clarithromycin and levofloxacin group were considered cured or improved. At 1-month post therapy, 5 patients in the levofloxacin group and 7 patients in the clarithro-

Table IV. Therapeutic efficacy of levofloxacin in adult patients with acute sinusitis

Reference	Study design	Dosage and duration	No. of patients	Clinical success (%)[a]	Bacteriological eradication/no. of patients (%)
Adelglass et al.[22]	Multicentre, investigator-blinded, randomised	LEV 500mg PO qd × 14d CLA 500mg PO bid × 14d	101 89	97 (96.0) 83 (93.3)	NA
Lasko et al.[33]	Double-blind, randomised	LEV 500mg PO qd × 10-14d CLA 500mg PO bid × 10-14d	98 93	92 (93.9) 87 (93.5)	NA
Adelglass et al.[23]	Multicentre, randomised, open-label	LEV 500mg PO qd × 10-14d Amox/Clav 500/125mg PO tid × 10-14d	267 268	236 (88.4) 234 (87.3)	NA
Sydnor et al.[24]	Multicentre, open-label	LEV 500mg PO qd × 10-14d	300	265 (88.3)	127/138 (92.0)

a Clinical success includes clinical cure as well as improvement at 2 to 5 days, 5 to 7 days, or 5 to 14 days post-therapy.[22,23,33]

Amox/Clav = amoxicillin/clavulanate; **bid** = twice a day; **CLA** = clarithromycin; **LEV** = levofloxacin; **NA** = not available; **PO** = oral; **qd** = once a day; **tid** = 3 times a day.

mycin group reported reoccurrence severe enough to return to their physician and all but 1 patient received a second course of antibacterial therapy. In this study, levofloxacin was associated with a higher incidence of CNS effects than clarithromycin (6.7 *vs* 4.3%, respectively). However, the rates of GI symptoms (16.7 *vs* 33.3%) and taste perversion (0.8 *vs* 7.7%) were lower with levofloxacin therapy.

Levofloxacin 500 mg/day was compared with amoxicillin-clavulanic acid 500mg 3 times daily for acute bacterial sinusitis.[23] The clinical success rate for the levofloxacin group was comparable with the amoxicillin-clavulanic acid group (88.4 vs 87.3%, respectively). Relapse occurred in 2.1% (5 out of 233) of levofloxacin-treated patients and 3.9% (9 out of 231) of amoxicillin-clavulanic acid–treated patients. Drug-related adverse events were reported in 7.4% of patients treated with levofloxacin and in 21.2% of patients treated with amoxicillin-clavulanic acid. Most of these were assessed as mild to moderate in severity. Commonly reported adverse events included nausea, abdominal pain, diarrhoea and vaginitis. All adverse events were higher in the amoxicillin-clavulanic acid group.

The efficacy and safety of levofloxacin therapy in the treatment of acute sinusitis was also evaluated in a noncomparative, prospective, multicentre study.[24] Levofloxacin 500mg once-daily administered for a median duration of 14 days resulted in a clinical success rate of 88% and microbiological eradication rate of 92%. Treatment was unsuccessful in 35 of the 300 patients (11.7%). In this study, eradication for *S. pneumoniae* was 100% and for *Haemophilus influenzae* it was 97%. Adverse events were reported by 9% (29 out of 322) of patients. Diarrhoea occurred in 2.9% of patients, followed by abdominal pain (1.5%) and nausea (1.2%).

5.1.2 Acute Exacerbation of Chronic Bronchitis

The effectiveness of levofloxacin 250 and 500 mg/day has been compared with cefuroxime axetil in the treatment of acute exacerbation of chronic bronchitis (AECB) in 2 trials. A randomised, double-blind, double-dummy, 3-arm parallel design, multicentred study reported that the clinical success rate for levofloxacin 250 mg/day was similar to levofloxacin 500 mg/day (78 *vs* 79%, respectively).[32] Clinical success rates for both levofloxacin groups were significantly higher than for a cefuroxime axetil 500 mg/day comparator arm (66%). Bacteriological eradication rates were 69% with levofloxacin 250 mg/day, 77% with levofloxacin 500 mg/day, and 60% with cefuroxime axetil. The higher eradication rate in the levofloxacin groups occurred as a result of its Gram-negative antibacterial efficacy. The most common persistent pathogens were *S. pneumoniae* and *P. aeruginosa* in the levofloxacin groups and *H. influenzae* and *P. aeruginosa* in the cefuroxime axetil group. Superinfection and relapse rates were less than 2% in all 3 groups. Adverse events which were considered possibly related to the study drug were reported in

20.3% (57 out of 281), 20.4% (57 out of 280) and 18.1% (49 out of 271) of patients treated with levofloxacin 250 mg/day, 500 mg/day, and cefuroxime axetil 500 mg/day, respectively. The most commonly affected body systems were respiratory, digestive, nervous and body as a whole, although the authors did not define these effects. Premature discontinuation of treatment occurred in 42 patients, 14 from each of the 3 study arms. Events associated with the digestive system were the most common.

A second study also compared 2 levofloxacin dosages against cefuroxime axetil 500 mg/day in patients with purulent AECB.[21] The bacteriological eradication rates for levofloxacin 250 mg/day and 500 mg/day were similar (63 *vs* 68%, respectively) but significantly higher than with cefuroxime axetil (48%). These lower eradication rates were attributed to increased severity of illness; most patients had experienced 2 or more AECB episodes in the year prior to study enrollment. Therapy failures in both levofloxacin groups were due to *S. pneumoniae* infections [6 out of 41 (15%) for levofloxacin 250 mg/day and 4 out of 41 (10%) for levofloxacin 500 mg/day], whereas *H. influenzae* was responsible for failures in the cefuroxime axetil group [9 out of 42 (21%)]. Common levofloxacin adverse effects were abdominal pain (9.8% with 250 mg/day), nausea (2.4% with 250 mg/day), diarrhoea (2.4% with both 250 and 500 mg/day), pruritis (2.4% with 500 mg/day) and oral thrush (2.4% with 500 mg/day).

A shorter duration of therapy with levofloxacin 500 mg/day was compared with cefuroxime axetil 500 mg/day for AECB.[25] The mean duration of therapy was 7 days in levofloxacin-treated patients and 10 days in cefuroxime axetil-treated patients. The clinical success rates were similar (96 *vs* 93% for levofloxacin and cefuroxime axetil, respectively). Bacteriological eradication was also similar between the 2 groups (97 *vs* 95% for levofloxacin and cefuroxime axetil, respectively). Microbiological persistence was observed in 5 out of 222 levofloxacin-treated patients (4%) and 10 out of 229 cefuroxime axetil–treated patients (7%). Three patients in the levofloxacin group and 4 patients in the cefuroxime axetil group developed superinfection. A total of 8 pathogens were isolated from these patients and 6 were susceptible to levofloxacin and 5 were susceptible to cefuroxime axetil. Adverse event rates were comparable for the treatment groups. Vaginitis (2.0%), nausea (2.5%), diarrhoea (1.6%) and taste perversion (0.8%) were common adverse effects in levofloxacin-treated patients.

A shorter course of levofloxacin therapy was also compared with cefaclor in the treatment of AECB.[26] The mean duration of treatment was 6.6 days for levofloxacin-treated patients and 8.7 days for cefaclor recipients. Clinical efficacy was 92%

Table V. Therapeutic efficacy of levofloxacin in adult patients with acute exacerbation of chronic bronchitis

Reference	Study design	Dosage and duration	No. of patients	Clinical success (%)[a]	Bacteriological eradication/no. of patients (%)
Davis and Maesen[21]	Randomised, double-blind	LEV 250mg PO qd × 7d	41	NA	26/41 (63.4)
		LEV 500mg PO qd × 7d	41		28/41 (68.3)
		CFX 250mg PO bid × 7d	42		20/42 (47.6)
DeAbate et al.[25]	Multicentre, randomised, open-label	LEV 500mg PO qd × 5 to 7d	222	210 (94.6)	129/134 (96.3)
		CFX 250mg PO bid × 10d	229	212 (92.6)	137/147 (93.2)
Habib et al.[26]	Multicentre, randomised	LEV 500mg PO qd × 5 to 7d	154	141 (91.6)	97/103 (94.2)
		CEF 250mg PO qid × 7 to 10d	155	142 (91.6)	77/89 (86.5)
Shah et al.[32]	Randomised, double-blind	LEV 250mg PO qd x 7 to 10d	156	121 (78%)	88/129 (69%)
		LEV 500mg PO qd x 7 to 10d	137	108 (79%)	82/107 (77%)
		CFX 250mg PO bid x 7 to 10d	134	88 (66%)	68/114 (60%)

a Clinical success includes clinical cure as well as improvement at 5 to 7 post-therapy.[21,25,26]

bid = twice a day; **CEF** = cefaclor; **CFX** = cefuroximeaxetil; **LEV** = levofloxacin; **NA** = not available; **PO** = oral; **qd** = once a day; **qid** = 4 times daily.

Table VI. Therapeutic efficacy of levofloxacin in adult patients with community-acquired pneumonia

Reference	Study design	Dosage and duration	No. of patients	Clinical success (%)[a]	Bacteriological eradication/no. of patients (%)
Fogarty et al.[28]	Multicentre, noncomparative, open-label	LEV 500mg IV/PO qd × 7 to 14d	234	222 (94.9)	129/136 (94.9)
File et al.[27]	Randomised, double-blind, multicentre	LEV 500mg IV/PO x 7 to 14d CXN 1 to 2g IV qd to bid, then CFX 500mg PO bid 7 to 14d[b]	226 230	NA (96%) NA (90%)	128/NA (89%) 144/NA (85%)

a Clinical success includes clinical cure as well as improvement at 5 to 7 days post-therapy.[27,31]

b CXN and CFX were 1 treatment group (IV CXN to PO CFX).

bid = twice daily; **CFX** = cefuroximeaxetil; **CXN** = ceftriaxone; **IV** = intravenous; **LEV** = levofloxacin; **NA** = not available; **PO** = oral; **qd** = once a day.

in both groups. Four patients in the cefaclor group and no patients in the levofloxacin group required hospitalisation because of antibacterial failure. Microbiological eradication rates were 94% for levofloxacin-treated group and 87% for cefaclor-treated patients. Seven superinfections developed in 6 cefaclor-treated patients [*H. influenzae* (n = 2), *Haemophilus parainfluenzae* (2), *Escherichia coli* (1), *Moraxella catarrhalis* (1)], in contrast to no superinfections among levofloxacin-treated patients. 13 patients (7%) in the levofloxacin group and 9 cefaclor-recipients (4.9%) had drug-related adverse events. Among levofloxacin-treated patients, nausea (2.1%), flatulence (1.6%), insomnia (1.1%), abdominal pain (1.1%) and diarrhoea (1.1%) were the most common drug-related adverse events.

Oral levofloxacin 300 mg/day and 600 mg/day was evaluated in patients with either diffuse panbronchiolitis (n = 5) or bronchiectasis (5) caused by *P. aeruginosa*.[85] The patients were treated for a mean duration of 10 days (range 3 to 14 days). The clinical efficacy rate was reported to be 40% in the 300 mg/day group and 80% in the 600 mg/day group. *H. influenzae* was isolated in 1 patient, *P. aeruginosa* in 8 patients and *Proteus vulgaris* in 1 patient. Levofloxacin 300 mg/day was ineffective against *P. aeruginosa*, but the 600 mg/day dose was effective in eradication of 75% of the isolates treated. No adverse reactions or abnormal laboratory findings were noted during or after levofloxacin therapy.

A prospective, randomised study was performed to compare the efficacy of oral levofloxacin 300mg twice a day or intravenous ceftazidime 1g 3 times daily for 10 days in patients with acute exacerbation of bronchiectasis.[86] 17 patients in the levofloxacin group and 18 patients in the ceftazidime group completed the study. One patient from each group withdrew from the study because of clinical deterioration and severe haemoptysis. All other patients in both groups achieved clinical success. *P. aeruginosa* and *H. influenzae* were the most frequently isolated sputum pathogens. Only 1 pathogen in each group was found to be resistant to the respective antibacterials (*Mycobacterium chelonei* in the ceftazidime group and *P. aeruginosa* in the levofloxacin group). Eradication was achieved in 69 and 57% of ceftazidime and levofloxacin treatment groups, respectively. Three ceftazidime-treated patients complained of dizziness and dyspepsia and 4 levofloxacin-treated patients reported dizziness, insomnia and mild skin rash.

5.1.3 Pneumonia

The therapeutic efficacy of levofloxacin was compared with ceftriaxone and/or cefuroxime, in the treatment of mild to moderate community-acquired pneumonia (CAP).[27] 22% (50 out of 230) of the patients receiving β-lactam antibacterials also received erythromycin or doxycycline. The most common bacterial pathogens were *S. pneumoniae* and *H. influenzae*. A total of 150 isolates of atypical bacteria were also identified (101 *Chlamydia pneumoniae*, 41 *Mycoplasma pneumoniae*, 8

Legionella spp.). The clinical success rates were comparable: 96% for levofloxacin versus 90% for the β-lactams. A 20% failure rate was observed in cefalosporin-treated patients with *H. influenzae* infections. There were no treatment failures in patients with *H. influenzae* treated with levofloxacin therapy. The pathogen associated with clinical failures included atypical bacteria in 1 patient receiving levofloxacin, 2 receiving ceftriaxone and/or cefuroxime axetil, and 3 receiving cefalosporins plus erythromycin or doxycycline. Relapse rates were low for both groups (<3%), as were rates of superinfection (<2%). All adverse events were reported to be mild in severity and GI symptoms were the most common in both groups. The events were reported in 5.8% of patients receiving levofloxacin and 8.5% receiving ceftriaxone/cefuroxime.

An economic analysis of outpatient results from the clinical trial conducted by File et al.[27] was reported for those who received oral levofloxacin or oral cefuroxime axetil as initial primary treatment for CAP.[87] In comparison with cefuroxime, the mean duration of treatment was shorter (11.7 *vs* 12.3 days) and the percentage of patients who received the intravenous formulation was smaller (5.8 *vs* 17.6%) with levofloxacin therapy. In addition, approximately 14% of patients receiving the cefalosporin therapy also received erythromycin or doxycycline for an average of 11.3 days. Overall, according to this analysis, the total cost of levofloxacin treatment was 24% lower than that for cefuroxime axetil which equated to a total cost advantage of US$169 in 1997.

The efficacy and safety of levofloxacin was also evaluated in patients with mild to moderate and severe CAP.[28] In this multicentre, noncomparative, open-label study, 78% of patients were cured and 17% of patients were improved at the post-therapy visit. The most common pathogens were *H. influenzae, S. pneumoniae,* and *C. pneumoniae*. Treatment failure occurred in 5% of patients treated with levofloxacin and 1.7% of the patients experienced a relapse of infection. Bacterial eradication occurred in 94% of patients with mild to moderate infections and 97% of those with severe infections. 14 out of 263 patients (5.3%) experienced adverse events related to levofloxacin therapy. Commonly reported adverse events included diarrhoea (1.5%) and nausea (1.1%). All drug-related adverse events were considered mild or moderate in intensity.

The clinical efficacy of levofloxacin was determined in acute pneumonia or bronchitis, or in patients with chronic respiratory disease who developed secondary infection.[88] Outpatients received levofloxacin 100mg 3 times daily and inpatients received 200mg 3 times daily. The duration of treatment was 3 days for outpatients and 7 days for inpatients. The clinical efficacy rate in patients with pneumonia was 89%. In patients with acute exacerbations of chronic respiratory diseases clinical efficacy was 69% at day 7. Bacteriological efficacy was 50% at day 3 and 80% by day 7. The organisms that persisted were *S. aureus, Pseudomonas* spp., and *Candida* spp. Epigastric discomfort was reported in 1 patient, but no significant adverse events occurred.

Levofloxacin 200mg 3 times daily was also evaluated in the treatment of bacterial lower respi-

Table VII. Therapeutic efficacy of levofloxacin in adult patients with skin and skin-structure infections

Reference	Study design	Dosage and duration	No. of patients	Clinical success (%)[a]	Bacteriological eradication/no. of patients (%)
Nichols et al.[31]	Multicentre, randomised, open-label	LEV 500mg PO qd × 7 to 10d	182	162 89.0)	153/157 (97.5)
		CIP 500mg PO bid × 7 to 10d	193	168 (87.0)	135/152 (88.8)
Nicodemo et al.[29]	Multicentre, randomised, double-blind	LEV 500mg PO qd × 7d	129	124 (96.1)	93/100 (93.0)
		CIP 500mg PO bid × 10d	124	116 (93.5)	87/97 (89.7)

a Clinical success includes clinical cure as well as improvement at 2 to 7 days,[31] 1 to 10 days[29] post-therapy.

bid = twice a day; **CIP** = ciprofloxacin; **LEV** = levofloxacin; **PO** = oral; **qd** = once a day.

Table VIII. Therapeutic efficacy of levofloxacin in adult patients with complicated urinary tract infections

Reference	Study design	Dosage and duration	No. of patients	Clinical success (%)[a]	Bacteriological eradication/no. of patients (%)
Richard et al.[84]	Multicentre, randomised, double-blind	LEV 250mg PO qd × 10d	126	116 (92.0)	115 (90.5)
		CIP 500mg PO bid × 10d	133	101 (89.4)	105 (92.9)
Kilmberg et al.[30]	Multicentre, randomised, open-label	LEV 250mg PO qd × 7 to 10d	171	159 (93.0)	163 (95.3)
		LMF 400mg PO qd × 14d	165	146 (88.5)	152 (92.1)

a Clinical success includes clinical cure as well as improvement at 5 to 9 days post-therapy.[30,84]

bid = twice a day; **CIP** = ciprofloxacin; **LEV** = levofloxacin; **LMF** = lomefloxacin; **PO** = oral; **qd** = once a day.

ratory tract infections.[89] A total of 16 patients were enrolled into the study (13 patients with bronchopneumonia, 1 patient with a lung abscess, 1 with panbronchiolitis and 1 with pyothorax). However, 1 of the patients with bronchopneumonia was excluded because of discontinuation of levofloxacin therapy because of an adverse event (headache), and the patient with pyothorax was excluded because of rifampicin use. Clinical success was achieved in the 12 patients diagnosed with bronchopneumonia, the patient with a lung abscess and the patient with diffuse panbronchiolitis. All 7 isolated prior to the initiation of drug treatment were believed to be the causative bacteria and 100% eradication rate was achieved with levofloxacin [*S. pneumoniae* (n = 2), *H. influenzae* (1), *Klebsiella pneumoniae* (1), *P. aeruginosa* (1), *M. catarrhalis* (1) and *Prevotella melaninogenica* (1)]. One patient complained of moderate headache while receiving levofloxacin but no adverse events were observed in the remaining patients.

The efficacy of levofloxacin in the treatment of hospitalised patients with pneumonia was compared with ceftriaxone in a multinational, multicentre, open-label, randomised study.[90] Patients randomised to levofloxacin received 500mg twice daily for a median duration of 9 days (intravenous for 4 days and oral for 5 days). In comparison, the patients treated with ceftriaxone received 4g intravenously once-daily for a median duration of 8 days. The clinical success rates in 266 patients with a proven bacteriological infection at baseline (130 levofloxacin recipients and 142 ceftriaxone recipients) were similar for levofloxacin (87%) and ceftriaxone (86%). In these patients, 30 out of 61 (47%) in the levofloxacin group and 57 out of 142 (40%) of the ceftriaxone patients had an indeterminate bacteriological response. Of those patients who were analysed for bacteriological response, 57 out of 69 (83%) patients in the levofloxacin group and 71 out of 85 (83%) ceftriaxone patients had organism eradication. Three pathogens (*S. pneumoniae*, Group A beta-haemolytic streptococcus, *S. aureus*) persisted in 2 patients receiving levofloxacin, and 2 pathogens (*P. aeruginosa, Acinetobacter baumannii*) persisted in 2 patients receiving ceftriaxone. Adverse events associated with levofloxacin therapy included cardiovascular (1.9%), digestive (4.8%), haematological/lymphatic (5.4%), injection site reactions (2.9%), metabolic/nutritional (6.1%), nervous system (2.2%), skin/appendages (1.9%), and special senses complaints (1%).

5.2 Skin and Skin Structure Infections

Levofloxacin has been shown to be as efficacious as ciprofloxacin in the treatment of skin and skin-structure infections in 2 multicentre, randomised studies.[29,31] Nichols et al.[31] compared the 2 antibacterials in patients with mild to moderate cellulitis. Clinical success occurred in 89% of patients treated with levofloxacin and 87% with ciprofloxacin. Therapy failed in 4 patients (2.2%) in levofloxacin group versus 11 in the ciprofloxacin group (5.7%). The microbiological eradication rates were higher in the levofloxacin group than in the ciprofloxacin group (98 and 89%, respectively). *S. aureus* was the most prevalent pathogen. Levofloxacin had 100% eradication against *S. au-*

reus, compared with 87% for ciprofloxacin. Overall, the nature and frequency of treatment-emergent adverse events were comparable between treatment groups. 13 (6%) patients treated with levofloxacin and 12 (5%) treated with ciprofloxacin experienced treatment-emergent adverse events that were mild in severity and considered by the investigator to be drug-related. The most common adverse events in both groups were diarrhoea, nausea, and headache.

In the second study by Nicademo et al.[29] the most common diagnoses in the levofloxacin treatment group were abscess (22%), impetigo (21%), and cellulitis (14%), and in the ciprofloxacin treatment group they were abscess (19%), furuncle (17%), cellulitis (15%) and impetigo (15%).[29] The clinical success rates between the levofloxacin and ciprofloxacin groups were similar (96 and 94%, respectively). The microbiological eradication rates were 93% for levofloxacin-treated patients and 89.7% for ciprofloxacin recipients. The eradication rate for *S. aureus* was 66 out of 70 (94%) for levofloxacin and 70 out of 75 (93%) for ciprofloxacin. Five levofloxacin-treated patients [*S. aureus* (n = 3), *Enterococcus faecium* (1), *Klebsiella oxytoca* (1), and *Enterobacter cloacae* (1)] and 3 patients treated with ciprofloxacin [*S. aureus* (n = 1), *Streptococcus* spp. (1), and *P. aeruginosa* (1)] developed superinfection. Levfloxacin compared favourably with ciprofloxacin in terms of drug-related adverse events. 12 (8.9%) patients in the levofloxacin group and 11 (8.2%) patients in ciprofloxacin group experienced drug-related adverse events associated with drug use. Nausea (3%), dizziness (2.2%) and diarrhoea (1.5%) were reported for levofloxacin.

A comparative trial of oral levofloxacin 750mg once-daily for complicated skin structure infections reported overall clinical success of 84% with the higher levofloxacin dosage, versus 80% for the ticarcillin-clavulanic acid and amoxicillin-clavulanic acid comparators.[91] Few adverse events were seen with this higher levofloxacin dose. GI complaints including constipation, nausea, and dyspepsia were most common.

5.3 Urinary Tract Infections

Levofloxacin was as efficacious as ciprofloxacin and lomefloxacin, in the treatment of complicated urinary tract infections. Richards et al.[84] compared levofloxacin and ciprofloxacin and found similar clinical (92 and 89%, respectively) and microbiological (91 and 93%, respectively) responses at 5 to 9 days post-therapy. Greater than 90% eradication rates were achieved in both groups against the common pathogens, *E. coli* and *K. pneumoniae*. The eradication rate for *Enterococcus faecalis* was higher in the levofloxacin-treated group than in the ciprofloxacin-treated group (100 and 60%, respectively), but lower with *P. aeruginosa* (64 and 100%, respectively). Treatment failed in 10 (7.9%) patients treated with levofloxacin and 13 (11.5%) treated with ciprofloxacin. Superinfection developed in 6 patients in each of the levofloxacin and ciprofloxacin treatment arms. 13 patients in the levofloxacin group had infection relapse compared with 10 patients in the ciprofloxacin group. Overall, 3.6% (7 out of 195) of patients in the levofloxacin group and 2.7% (5 out of 185) of patients in the ciprofloxacin group reported adverse events that were considered drug-related by the investigator. All of the drug-related adverse events were considered to be of mild and moderate intensity. The only drug-related adverse event reported 2 or more times was dizziness, which was reported in 2 patients receiving levofloxacin. Two patients in the levofloxacin group (1%) and 1 patient in the ciprofloxacin group (0.5%) withdrew from the study because of drug-related adverse events. These were primarily GI complaints and central/peripheral nervous system symptoms.

Clinical success rates for levofloxacin (93%) and lomefloxacin (89%) were similar in another study of complicated urinary tract infections.[30] Six patients (1.5%) treated with levofloxacin and 12 patients (7.3%) treated with lomefloxacin had superinfections at the post-therapy visit. Both levofloxacin and lomefloxacin were well tolerated, and most adverse events were of mild or moderate severity. Overall, 10 patients (4.3%) in the levofloxacin group and 18 (7.9%) in the lomefloxacin

group reported adverse events that were considered drug-related by the investigator. The only adverse event reported by greater than 1% of patients treated with levofloxacin was nausea (1.3%).

5.4 Other Infections

Levofloxacin 500mg twice daily was compared with imipenem-cilastatin 1g 3 times daily in the treatment of patients with suspected bacteraemia/sepsis in an open-label, randomised trial.[92] The clinical response rates were 89% (125 out of 144) for the levofloxacin arm and 85% (125 out of 164) for the imipenem-cilastatin arm. Although not statistically different, a greater bacteriological response rate was observed for imipenem-cilastatin (97%) than for levofloxacin (87%). The bacteriological eradication rates were similar for *S. pneumoniae*, *K. pneumoniae*, *E. coli*, and *H. influenzae*. The adverse events related to the most commonly affected body systems were similar in both groups (levofloxacin *vs* imipenem-cilastatin): nausea (5.0 *vs* 8.5%), vomiting (2.9 *vs* 3.8%), headache (1.7 *vs* 3.5%), insomnia (2.5 *vs* 2.3%) and anxiety (2.5 *vs* 1.5%).

Levofloxacin safety following an extended treatment period was evaluated in a study of lomefloxacin, levofloxacin and ciprofloxacin for the treatment of chronic osteomyelitis. 27 patients with documented infection with fluoroquinolone-sensitive organisms were followed.[59] 15 patients were treated with oral levofloxacin 500 mg/day, and the mean duration of therapy was 60.6 days. Levofloxacin was effective in 9 out of 15 (60%) patients. No adverse events were reported with levofloxacin therapy, other than an allergic reaction (rash and tongue swelling) which prompted discontinuation of the drug in 1 of the 15 patients.

6. Resistance

6.1 *Streptococcus pneumoniae*

The enhanced activity of the fluoroquinolones against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, Enterobacteriaceae, and atypical pneumonia pathogens has prompted wide use of these agents in both outpatient and hospital settings. This dramatic increase in usage over the decade of the 1990s has been followed by emergence of resistance in *S. pneumoniae*, the most common cause of community-acquired infections.[93,94] According to the SENTRY Antimicrobial Surveillance Program, high-level fluoroquinolone resistance in *S. pneumoniae* has increased from 3% in 1997 to 9% in 1999 in the US.[94] This surveillance report noted that during the 1999 respiratory disease season, levofloxacin resistance was present in 2.3% of the penicillin-intermediate pneumococcal strains and 2.8% in the penicillin-resistant isolates. Others have reported similar increases in pneumococcal resistance throughout Europe, Latin America, and Asia.[95,96] In a 10-year longitudinal study, Chen et al.[93] reported an increasing rate of fluoroquinolone reduced-susceptibility in pneumococcal isolates from Canada. A linear correlation was observed between the number of fluoroquinolone prescriptions in Canada and the increase in pneumococcal resistance. Against 75 clinical isolates of *S. pneumoniae* with defined reduced fluoroquinolone susceptibility (ciprofloxacin MIC >4 mg/L) from this study, the levofloxacin MIC_{90} was 16 mg/L.

Recently 5 levofloxacin treatment failures against *S. pneumoniae* were reported.[97,98] All 5 isolates were resistant to levofloxacin (MIC >4 to >32 μg/ml) by *in vitro* susceptibility testing. Two of the 5 isolates were levofloxacin-resistant at baseline, but penicillin-, macrolide-, and vancomycin-susceptible. Both of these patients had a prior history of recent fluoroquinolone use. Two other isolates were documented to be levofloxacin-susceptible at baseline, and developed levofloxacin resistance during therapy. With this rise in the rates of resistance, clinical failures appear to be an unavoidable consequence of fluoroquinolone use.

Outbreaks of multiple cases of fluoroquinolone-resistant *S. pneumoniae* have also been reported. Within a 15-month period, 16 cases of fluoroquinolone-resistant *S. pneumoniae* were isolated from patients with AECB and nosocomial pneumonia in a hospital setting.[99] The outbreak occurred

in 2 phases; initially 9 patients presented with pneumococcal strains in which the fluoroquinolone MICs were: ciprofloxacin 4 mg/L; levofloxacin 2 mg/L; and moxifloxacin 0.25 mg/L. The second cluster of 7 patients had *S. pneumoniae* with fluoroquinolone MICs of: ciprofloxacin 16 mg/L; levofloxacin 8 mg/L; and moxifloxacin 2 mg/L. All isolates were serotype 23F, demonstrated a similar pulse field gel electrophoresis pattern, and had mutations at the *parC* and *gyrA* genes. The electrophoresis patterns of the second cluster of isolates were distinct from that of the first cluster, indicating that fluoroquinolone resistance arose independently. Ciprofloxacin therapy failed in all 5 patients. Clusters of fluoroquinolone-resistant *S. pneumoniae* have also been identified at 2 long term care facilities.[100]

All *S. pneumoniae* isolates responsible for clinical failures have been reported to have both *parC* and *gyrA* mutations in the fluoroquinolone-resistant determining region of the bacterial chromosome.[97,98] This double mutation appears to cause resistance to second, third, and fourth generation fluoroquinolones.

The optimal pharmacodynamics for the fluoroquinolones against the pneumococcus are not known, largely due to the paucity of human data evaluating pharmacodynamics. *In vitro* pharmacodynamic models have suggested an AUC : MIC ratio between 30 to 50 will produce a bactericidal effect and minimise regrowth of antibacterial-resistant organisms.[101-103] *In vitro* modelling predicts the average 24 hour AUC : MIC value for levofloxacin against *S. pneumoniae* is 61, which is significantly lower than that of gatifloxacin (146), clinafloxacin (142), and trovafloxacin (122), and equal to that of ciprofloxacin (71), with simulated standard dosing for each drug.[104]

Other *in vitro* modelling work demonstrated that levofloxacin AUC : MIC ratios of > 110 were required for bactericidal activity against *S. pneumoniae* strains.[105] To achieve this AUC : MIC value with standard levofloxacin 500mg once-daily administration, the pneumococcal MIC must be ≤ 0.5 mg/L. When a levofloxacin 500mg twice daily dose was simulated, bactericidal activity was observed for strains with an MIC of 1 mg/L, but not 2 mg/L. The National Committee for Clinical Laboratory Standard susceptibility breakpoint for levofloxacin against *S. pneumoniae* is 2 mg/L. Thus, in this model, pneumococcal strains reported susceptible by MIC testing may not be fully eradicated by levofloxacin 500mg once-daily unless the strain MIC is 0.5 mg/L. Although the relationship of simulated *in vitro* pharmacodynamics, and clinical infection outcomes have not been correlated, the possibility of clinical failure and generation of antibacterial resistance because of under exposure to levofloxacin is an important issue when considering wide-spread use of the compound.

6.2 *Pseudomonas aeruginosa*

Another pathogen of concern for increasing fluoroquinolone resistance is *P. aeruginosa*. In comparison with ciprofloxacin, levofloxacin generally demonstrates MIC values that are 1 to 2 two-fold dilutions higher against *P. aeruginosa*. Despite this lower potency, levofloxacin has been shown to be effective in treating patients with bronchiectasis or diffuse panbronchiolitis infected with *P. aeruginosa*.[85,86,88] This efficacy may be a function of levofloxacin pharmacokinetics. Standard levofloxacin 500mg once-daily administration produces a 4-fold higher AUC than ciprofloxacin 500mg twice daily. MacGown et al.[34] have shown that an AUC : MIC ratio of 125 is predicted in 85.4% of standard levofloxacin administration situations against *P. aeruginosa*, compared with 81.5% for standard ciprofloxacin administration situations. Based on these data, clinical efficacy against *P. aeruginosa* may be attributed to the favourable exposure profile of levofloxacin. However, because of the lower potency of levofloxacin against *P. aeruginosa* when compared with ciprofloxacin, there is a risk for emergence of fluoroquinolone-resistant organisms selected by extensive use of levofloxacin in the hospital setting.

Peterson et al.[106] demonstrated that the susceptibility of *P. aeruginosa* to ofloxacin or ciprofloxacin

floxacin is directly related to the usage patterns of fluoroquinolones in a large inter-city teaching hospital. This group reported a 3-year study of *P. aeruginosa* susceptibilities to fluoroquinolones during a period of changing fluoroquinolone formulary. Resistance to 1 agent highly correlated with resistance to the other. The authors suggested that ciprofloxacin resistance in *P. aeruginosa* may have been caused in part by the use of ofloxacin, which is not as potent against the pathogen. Other reports confirm this correlation.[107,108] This phenomenon has been well documented with aminoglycosides of varying potency.[109]

Levofloxacin clearly has lower potency against *P. aeruginosa* than ciprofloxacin. Whether the selective pressure of levofloxacin exposure in an institution can produce increased fluoroquinolone resistance in this pathogen overall remains to be seen. However, history would suggest this is a significant possibility.

7. Risks Versus Benefits of Levofloxacin Therapy

The place of fluoroquinolones in the management of community-acquired and nosocomial infections remains to be clearly determined. These drugs have excellent bioavailability, extensive tissue penetration and urine concentration, rapid bactericidal activity and favourable pharmacokinetics for ease of use. Recent guidelines for the management of community-acquired pneumonia suggest that antipneumococcal fluoroquinolones may be first-line therapy in both the outpatient and inpatient settings.[110] However, antibacterial resistance issues and a recent track record of serious adverse events complicate therapeutic choices.

For the treatment of respiratory tract, skin and skin structure, and urinary tract infections, oral levofloxacin 500 mg/day administered for 10 to 14 days is equal in efficacy to β-lactam, macrolide or other fluoroquinolone therapies with similar indications. Efficacy rates for any antibacterial in these indications in clinical registry trials ranges from 85 to 100%, with most therapies at 90 to 100%. Thus, it is difficult to select 1 antibacterial over others for any of these 3 conditions based solely on clinical efficacy. However trials conducted for registration purposes generally select only patients with organisms susceptible to the study medications, and often exclude complicated infections or patients who have recurring disease. Registry trials often prove that susceptible organisms are successfully treated with the study antibacterials, but seldom are designed to demonstrate that nonsusceptible organisms are unsuccessfully treated. Neither do they fully describe the limits of clinical success from a duration-of-therapy standpoint, or an administration standpoint. Thus, there may be a role for 1 antibacterial over another in these circumstances, but clinical data are lacking to define these situations. Secondary issues include adverse effects, drug-drug interactions and costs of therapy. Drug toxicities must also include the risk of generating antibacterial and multi-drug resistance because of drug selection. Drug-drug interactions may precipitate morbidity and interfere with control of concomitant chronic conditions. Lastly, cost is a consideration, especially when amoxicillin or erythromycin may be as effective as more costly alternatives at a fraction of the expense.

Given the generally favourable success of inexpensive, nonfluoroquinolone therapies for most community-acquired respiratory tract, urinary tract, and skin- or skin structure-related infections, one must question the widespread use of levofloxacin or other newer fluoroquinolones in the mainstream management of these infectious diseases. However, with the exceptional broad-spectrum and rapid bactericidal action of the fluoroquinolones, one could argue that these drugs should supplant older traditional therapies for these common infections. Thus, the boundaries of this therapeutic debate are drawn.

There is little debate that levofloxacin is a well tolerated and effective agent for the current US FDA-approved indications of acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, complicated skin and skin structure infections, complicated and uncomplicated urinary tract infections, and acute py-

elonephritis. Its significantly higher cost when compared with amoxicillin, erythromycin, cotrimoxazole (trimethoprim-sulfamethoxazole) and cefalosporins, and its propensity to select for fluoroquinolone resistance in the pneumococcus make levofloxacin an alternative agent rather than a drug-of-choice in routine community-acquired respiratory tract, urinary tract, and skin- or soft-tissue-related infections. Local resistance patterns, and the severity of illness are mitigating circumstances in the drug selection process. In areas with increasing β-lactam resistance among the pneumococcus, levofloxacin may be a reasonable empiric therapy for community-acquired respiratory tract infections. Similarly, in patients with risk factors for infection complication or poor outcome, such as the elderly, patients with underlying pulmonary or cardiovascular disease, patients with indwelling urinary catheters, or a history of recurrent infection, levofloxacin may be an excellent empiric choice. Better clinical data are needed to identify the true place in therapy of the newer fluoroquinolones in common community-acquired and nosocomial infections. Until then, these agents, including levofloxacin, might best be reserved for complicated infections, infection recurrence, and infections caused by β-lactam or macrolide-resistant pathogens.

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