Review Article

Levofloxacin: A Broad Spectrum Potent Antibiotic
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ABSTRACT
Levofloxacin is a third generation fluoroquinolone antibacterial agent with a broad spectrum activity against Gram-positive, Gram-negative bacteria and atypical pathogens. It shows its bacteriocidal activity by inhibiting topoisomerase IV and DNA gyrase. Levofloxacin has shown strong antibacterial action against *Staphylococcus* species, *Streptococcus pyogenes*, *Streptococcus pneumoniae*. *Staphylococcus haemolyticus*, *Enterobacter* species, *Escherichia coli*, *Salmonella* species *Klebsiella* species *Serratia* species, *Enterococcus* species, Proteus. Species, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Neisseria gonorrhoea*. Moreover, levofloxacin has shown antifungal activity against *Chlamydia trachomatis*. It is also active against penicillin-resistant *Streptococcus pneumoniae*. It also possesses lethal effect on resistant mycobacteria like *Mycobacterium tuberculosis* and *Mycobacterium leprae* causing tuberculosis and even *Mycoplasma* species of HIV infection. Levofloxacin is indicated in the treatment of urinary tract infection, respiratory tract infection, biliary tract infection and other infection with clinical efficacy of 80-92%.

INTRODUCTION
Antibiotics are among the most frequently prescribed medications in modern medicine, they cure disease by killing or inhibiting bacteria. The first antibiotic was penicillin, discovered accidentally from a penicillium notatum. Today, over 100 different antibiotics are available to physicians to cure minor discomforts as well as life-threatening infections.

Although antibiotics are useful in a wide variety of infections, it is important to realize that antibiotics not only treat bacterial infections but are also used in the prevention of infection. Antibiotics were once considered as “wonder drugs” may have been used for decades to effectively treat a number of bacterial infections. Unfortunately, due to the overuse and misuse of antibiotics, the resistant of bacteria may develop that has become a fire alarm to healthcare professionals.

Quinolones and Fluoroquinolones
With the increasing number of available quinolone antibiotics, prescribing these drugs has become a challenge. Compared with older quinolones such as norfloxacin and ciprofloxacin, the newer agents have an expanded antimicrobial spectrum and new indications. The most recently released agents have significant antimicrobial activity against Gram-negative, atypical pathogens and anaerobes. The new classification of quinolone antibiotics by generation can help family physicians to prescribe these agents appropriately and evaluate new drugs as they are introduced.

The fluoroquinolones are broad-spectrum antibiotics with a particular activity against Gram-negative organisms, especially *Pseudomonas aeruginosa*. These agents are well absorbed when given orally. Because tissue and fluid concentrations often exceed the serum drug concentration, these antibiotics are particularly useful for certain infections, such as pneumonia. The original quinolone antibiotics included nalidixic acid, cinoxacin and oxolinic acid. The addition of fluoride to the original quinolone antibiotic compounds yielded a new class of drugs, the fluoroquinolones, which have a broader antimicrobial spectrum and improved pharmacokinetic properties. Levofloxacin belongs to the third generation of quinolones.

Mode of Action
Physical studies have shown that the mode of action of quinolones involves interaction with their principal target, DNA gyrase. The binding of quinolones to the DNA forming gyrase-DNA complex suggests two possible binding sites of differing affinities. Mutations in either the gyrase A gene (gyrA) or the gyrase B
gene (gyrB) that affect quinolones susceptibility also affect drug binding, with resistance mutations causing decreased binding and hypersusceptibility mutations causing increased binding. Regulation of expression of membrane efflux transporters may contribute to quinolone susceptibility in both Gram-positive and Gram-negative bacteria. The fluoroquinolone are bactericidal antibiotics that act by specifically targeting DNA gyrase. In contrast to amino glycosides and beta lactams, some fluoroquinolones are active against dormant and replicating bacteria. Fluoroquinolones exhibit a post-antibiotic effect following bacterial exposure to inhibitory concentrations. The antibacterial effect continues for approximately two to three hours after the bacteria are exposed to these drugs, despite subinhibitory concentrations. The duration of the post-antibiotic effect may be increased with longer bacterial exposure and higher drug concentrations.

LEVOFLOXACIN
Levofoxacin is the optical S-(-) isomer of ofloxacin which has been developed by the Daiichi Seiyaku Pharmaceutical Co. Ltd, Japan. Ofloxacin is a racemic mixture, but the S-isomer has antibacterial activity 32- to 128-fold more potent than the R-isomer – hence most of the antibacterial activity of ofloxacin is due to the S or L-isomer. Levofoxacin has been developed to take advantage of this antibacterial potency while requiring only about half the usual dose of ofloxacin to achieve similar efficacy, but potentially with an improved toxicity profile.

Mechanism of Action
The mechanism of action of levofoxacin involves inhibition of DNA gyrase, an enzyme required for DNA replication, transcription, repair and recombination. Levofoxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Antibacterial Activity
Levofoxacin is a broad-spectrum antibacterial agent against Gram-positive and Gram-negative bacteria including anaerobes. Levofoxacin has shown strong antibacterial activities against Staphylococcus species, Streptococcus pyogenes, Streptococcus pneumoniae. Staphylococcus haemolyticus, Enterobacter species, Escherichia coli, Salmonella species Klebsiella species Serratia species, Enterococcus species, Proteus species and other glucose non fermentive Gram-negative rod Pseudomonas aeruginosa, Haemophilus influenzae and Neisseria gonorrhoea. More over levofoxacin has shows antibacterial activity against Chlamydia trachomatis.

Gram-Negative Bacteria
Levofoxacin is about two-folds more active than ofloxacin and generally two to four fold less active than ciprofloxacin against most Enterobacteriaceae and P.aeruginosa. The MIC\textsubscript{90} of levofoxacin against P.aeruginosa is generally 4-8 mcg per ml. Similar, levofoxacin is comparable with, or one-or two dilutions inferior to ciprofloxacin in its activity against H. influenzae, N. gonorrhoeae and Moraxella catarrhalis, with MIC\textsubscript{90} values of 0.015 -0.06 mcg per ml\textsuperscript{18-21}. Similar levofoxacin activity has been noted against Gram-negative pathogens isolated from cancer patients a clinical setting in which levofoxacin may have a future role\textsuperscript{22}. Levofoxacin has good activity against both Pasteurella species and Eikenella corrodens with MIC\textsubscript{90} values of 0.015 mcg per ml\textsuperscript{22}. The MIC\textsubscript{90} of levofoxacin against Legionella pneumophila is 0.125 mcg per ml, compared with 0.25 mcg per ml for ofloxacin\textsuperscript{23}.

Levofoxacin is slightly more active against Bacteroides fragilis than ciprofloxacin with an MIC\textsubscript{90} 2 mcg per ml; but in general, levofoxacin can only be considered to have low activity against anaerobes Fusobacterium species are resistant (MIC\textsubscript{90} 64 mcg per ml).\textsuperscript{18, 24}

Gram-Positive Bacteria
Levofoxacin is about two fold more active than ciprofloxacin against penicillin-susceptible and resistant S. pneumoniae (MIC\textsubscript{90} 2 mcg per ml) and two to four fold more active against methicillin-susceptible Staphylococcus aureus (MIC\textsubscript{90} 0.5mcg per ml) Activity
against methicillin-resistant *S. aureus* (MRSA) is less impressive with MIC\(_{90}\) 16 mcg per ml. Concentrations of 1-2 mcg per ml inhibit 90% of *Streptococcus*, while the MIC\(_{90}\) against *Enterococcus faecalis* is generally no better than 2 mcg per ml. Indeed,\(^\text{25}\) found only 39% of vancomycin-susceptible and 11% vancomycin-resistant strains of *Enterococcus* were susceptible to <2 mcg per ml levofloxacin. Levofloxacin has variable activity against *Listeria monocytogenes* (MIC\(_{90}\) 2-8 mcg per ml) and is poorly active against *Corynebacterium jeikeium* (MIC\(_{90}\) > 64 mcg per ml).\(^\text{19-21, 26-28}\) Levofloxacin has variable activity against Gram-positive anaerobes, with MIC\(_{90}\) 8 mcg per ml against *Peptostreptococcus* species and broadly similar activity against *Clostridium* species.\(^\text{18, 22, 24}\)

**Mycobacteria**
In vivo studies of *Mycobacterium tuberculosis* suggest that levofloxacin activity is comparable with that produced by two-folds greater dosage of ofloxacin, although the MIC\(_{90}\) values for both drugs are similar at 1 mcg per ml. Sparfloxacin has better activity with MIC\(_{90}\) 0.5 mcg per ml.\(^\text{29}\) Several workers have found similar findings in vitro.\(^\text{30, 31}\) Rifampicin and isoniazid were more active than levofloxacin in a murine model of tuberculosis, but there was little difference in activity between levofloxacin and ethambutol or pyrazinamide.\(^\text{32}\) Levofloxacin (MIC\(_{90}\) 0.75 mcg per ml) has two fold greater bactericidal activity against *Mycobacterium leprae* than ofloxacin.\(^\text{33}\)

**Mycoplasma**
Levofloxacin is active against *Mycoplasma fermentans*, the Mycoplasma species isolated in patients with HIV infection, with MIC\(_{90}\) 0.078 mcg per ml.\(^\text{34}\)

**PHARMACOKINETICS**

**Absorption**
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg oral dose of levofloxacin is approximately 99%.\(^\text{2}\) Levofloxacin pharmacokinetics is linear and predictable after single and multiple oral dosing regimens. Steady state is reached within 48 hours following a 500 mg once-daily regimen. The peak and through plasma concentrations attained following multiple once-daily oral 500 mg regimens were approximately 5.7 and 0.5 mcg/ml, respectively.\(^\text{35}\) Oral administration with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin can be administered without regard to food. The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/ml) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.\(^\text{36-38}\)

**Distribution**
The mean volume of distribution of levofloxacin generally ranges from 89 to 112 L after single and multiple 500 mg doses, indicating widespread distribution into body tissues. Penetration of levofloxacin into blister fluid is rapid and extensive.\(^\text{2}\) Levofloxacin also penetrates well into the lung tissues. Lung tissue concentrations were generally two to five folds higher than plasma concentrations and ranged from approximately 2.4 to 11.3 mcg/ml over a 24 hour period after a single dose of 500 mg oral dose.\(^\text{39, 40}\) Levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. It is mainly bound to serum albumin in humans and the binding is independent of the drugs concentration.\(^\text{41-45}\)

**Metabolism**
Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin.\(^\text{16}\) Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours.\(^\text{2}\)
Excretion
Levofoxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofoxacin ranges from approximately six to eight hours following single or multiple doses of levofoxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 ml/min and 95 to 142 ml/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofoxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofoxacin renal clearance, respectively, indicating that secretion of levofoxacin occurs in the renal proximal tubule.

Therapeutic Uses
Therapeutically, Levofoxacin is used for urinary tract infection, sinusitis, and chronic bronchitis. Uncomplicated mild to moderate infection of skin and skin structure including abscesses, cellulitis and wound infection, acute mild to moderate pyelonephritis against a variety of aerobic Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Enterococcus faecalis* are only moderately susceptible. Levofoxacin is also administered topically as 0.5% eye drop for the treatment of bacterial conjunctivitis.

Urinary Tract Infections and Prostatitis
Various Japanese studies of levofoxacin, 100-200 mg thrice daily for 3-14 days, suggest rates of clinical efficacy of 85-100% in the treatment of uncomplicated and complicated urinary tract infections. Levofoxacin administration in 250 mg daily for 10 days has similar efficacy of either ciprofloxacin 500 mg twice daily for 10 days, or lomefoxacin 400 mg daily for 14 days, in the treatment of acute pyelonephritis. Levofoxacin is used in the treatment of acute and chronic prostatitis, epididymitis and gonococcal and chlamydial urethritis. In a small open study of 23 patients with acute epididymitis treated with levofoxacin 100 mg two or three times daily for 14 days, overall clinical efficacy was 100%. A 5-day course of 300 mg per day levofoxacin was effective in a small study of gonococcal urethritis.

Respiratory Tract Infections
Levofoxacin is effective in the treatment of respiratory tract infections when used in doses ranging from 200 mg once daily to 200 mg thrice daily. In one study, treatment of 12 patients with various lower respiratory tract infections with levofoxacin 200 mg once-daily for 7-14 days resulted in 100% efficacy. Other studies using various regimens, including 100-200 mg thrice-daily, have found less satisfactory results with approximately only 50% patients classified as having a 'good' or 'excellent' clinical outcome. As might be expected, knowing the in vitro activity of levofoxacin, the rate of *P. aeruginosa* eradication was low in the 300 mg per day group, but approached 75% in patients receiving 200 mg thrice daily. In one of the largest studies the efficacy of either 300 or 600 mg per day in 87 patients who were managed either as outpatients (300 mg per day for 3 days) or as inpatients (200 mg thrice-daily for 7 days) was examined. Eradication of responsible pathogens was noted in 80% cases by day 7, and among patients with, pneumonia, clinical efficacy was noted in about 89% cases. A 7- to 14 day course of levofoxacin 500 mg once-daily appears to be as effective as cotrimoxazole (I-2 g per day)/cefuroxime (500 mg twice-daily) for community-acquired pneumonia, and cefaclor 250 mg twice-daily for acute exacerbations of chronic bronchitis.

Biliary Tract Infections
Among 11 patients with biliary tract infections (six cholecystitis; three cholangitis; cholecystocholedocholithiasis and liver abscess) treated with levofoxacin 100-200 mg thrice daily for 3-14 days, clinical outcome was good in eight patients (73%) and in the remainder.

Other Infections
Non-comparative studies of levofoxacin 100 mg thrice-daily for soft tissue and skin infections, obstetric and gynecological infections and ear, nose and throat infections (occasionally requiring 200 mg thrice-daily)
have demonstrated overall clinical efficacy in about 80-92% cases.\textsuperscript{13} Levofloxacin 500 mg once daily for 7 days appears to have efficacy comparable with ciprofloxacin 500mg twice-daily for 7 days in the treatment of skin and skin structure infections, with reported rates of cure/improvement in 96.1% versus 93.5% cases, respectively.\textsuperscript{59}

In one Japanese study of 22 patients with obstetric and gynecological infections, the clinical efficacy of levofloxacin, 200-600 mg daily for 3-14 days, was 95%.\textsuperscript{60} In a study of 114 patients with bacterial enteritis levofloxacin 200-300 mg per day for 3-5 days was associated with clinical cure rate of 97% .\textsuperscript{13}

**Toxicity**

Doses of 200-600 mg levofloxacin per day appear to be well tolerated with side effects largely consisting of those noted with all fluorquinolones, such as\textsuperscript{52, 61, 62}

**Shock:**

Since shock symptoms may rarely occur, observe patients carefully if any abnormalities are observed, discontinue the medication and take appropriate measure.

**Hypersensitivity:**

Anaphylactoid symptoms (erythema, chills, dyspnea), edema, urticaria, feeling of warmth or photosensitivity may rarely occur and rash or pruritus may infrequently occur. In the event of such symptoms, discontinue the medication.

**Dermatological:**

It has been reported that ofloxacin may rarely cause Lyell syndrome or stevens johnson syndrome.

**Psychoneurological:**

Convulsion, tremor or numbness may rarely occur, and insomnia, dizziness or headache may infrequently occur.

**Renal:**

An increase in BUN may infrequently occur it has been reported that ofloxacin may rarely cause acute renal failure.

**Hepatic:**

An increase in SGOT, SGPT, Alkaline phosphatase, y-GT or total bilirubin may infrequently occur.

**Hematologic:**

A decrease in leukocytes, erythrocytes, hemoglobin or homatocrit or an increase in eosinophils may infrequently occur. Observe patient carefully, and if any abnormality is observed, discontinue the medication.

**Gastrointestinal:**

Nausea, vomiting, abdominal discomfort, diarrhea, anorexia, abdominal pain or enlarged feeling of abdomen may infrequently occur. Since it has been reported that ofloxacin may rarely cause severe colitis, with blood in the stool, such as pseudomembranous colitis, in the event of abdominal pain or frequent diarrhea take appropriate measures, including discontinuation of the medication.

**Muscular:**

Since rhabdomyolysis with rapid deterioration of renal function characterized by myalgia, weakness, increase in CPK or myoglobin in blood or urine may occur, patient should be cautioned.

**Drug Interactions**

Antacids containing aluminium or magnesium and drugs containing iron may interfere with the absorption of levofloxacin resulting in attenuation of the efficacy of levofloxacin. These agents should be taken at least two hours before or two hours after levofloxacin administration.\textsuperscript{2}

**MODE OF ADMINISTRATION AND DOSAGE**

**Oral Administration**

The optimal dosage of levofloxacin for various patient populations has yet to be determined, but most studies have used 100 mg thrice-daily (occasionally 200 mg thrice-daily) for the treatment of a variety of infections, including respiratory, skin, biliary genitourinary,
obstetric/gynecology and eye infections. The usual duration of treatment is single-dose therapy for women with uncomplicated cystitis, 3-5 days for other urinary tract sepsis or gonococcal urethritis and 7-14 days therapy for most other indications except for prostatitis, when longer courses may be needed.\(^3\)

Patients with Renal Failure
Since levofloxacin is mainly excreted unchanged in the urine. Serum levels are sensitive to changes in renal function. Thus, dosage reduction is required in patients with renal impairment. In Japanese patients, doses are reduced as follows; glomerular filtration rate (GFR) 40-70 ml per min, 100 mg twice-daily; GFR 20-40 ml per min, 100mg daily; GFR <20 ml per min, 100mg every 48 hours.\(^3,6^3\) No information is available regarding the need for any dosage adjustment in the elderly or in patients with hepatic failure.

CONCLUSIONS
Levofloxacin is a broad-spectrum antibiotic that possesses activity against Gram-positive and Gram-negative and atypical microbes. Due to its lethal action on microorganisms, it has been widely prescribed in respiratory tract infections, biliary tract infections and urinary tract infections with a clinical efficacy of 80-92%. It shows its bactericidal action on atypical pathogens like Mycobacteria species and Mycoplasma species. It also possesses its action on resistant bacteria like penicillin-resistant S. pneumoniae, Salmonella species Pseudomonas aeruginosa, Haemophilus influenzae. Levofloxacin is well tolerated, and is associated with minimum side effects.

REFERENCES
Application number 020635.
34. Hayes MM, Foo HH, Kotain H et al. In vitro antibiotic susceptibility testing of different strains
of Mycoplasma fermentans isolated from a variety of sources. Antimicrob Ag Chemother. 1993; 37:2500


