Ocular Infection

Effectiveness of Levofloxacin Eye Drops – A Microbiological Perspective

a report by

Michael Kresken, Thomas C Kreutzer and Herminia Miño de Kaspar

1. Antiinfectives Intelligence GmbH; 2. University Eye Hospital, Ludwig Maximilian University, Munich; 3. Department of Ophthalmology, School of Medicine, Stanford University

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Levofloxacin is a later-generation antibacterial agent of the fluoroquinolone class that exhibits a broad spectrum of in vitro activity. It has been demonstrated to be effective in the treatment of a wide range of community- and hospital-associated infections. This review presents a microbiological perspective of the use of levofloxacin for topical treatment of bacterial external ocular infections, presenting in vitro, pharmacokinetic and clinical trials data. Levofloxacin eye drops were launched in several European countries in 2002. The widespread use of levofloxacin in ophthalmology can be attributed to its appropriate antibacterial spectrum and good corneal penetration. The main indications for treatment are bacterial blepharitis and conjunctivitis, bacterial keratitis – especially when associated with contact lenses – and endophthalmitis, where it is provided as an additional therapeutic agent. Furthermore, levofloxacin eye drops are used as prophylaxis to reduce the bacterial conjunctival flora prior to intraocular surgery. In a healthy eye the conjunctival bacterial flora primarily consists of Staphylococcus spp. (mainly S. epidermidis), Corynebacterium spp. and, to a lesser degree, Streptococcus spp. and various Gram-negative rods. The predominant bacterial organisms isolated from patients with acute bacterial conjunctivitis are S. aureus, S. pneumoniae and Haemophilus influenzae, the latter being frequently recovered from children. S. aureus is also considered the primary pathogen of chronic blepharoconjunctivitis. The leading organisms causing bacterial keratitis are Staphylococcus spp., Streptococcus spp., Pseudomonas aeruginosa and enteric Gram-negative rods. Gram-negative bacilli account for most cases of contact-lens-associated bacterial keratitis.

Pharmacodynamic Properties of Levofloxacin

Levofloxacin is the L-isomer of the racemic drug ofloxacin. The antibacterial activity of ofloxacin resides almost entirely in the L-isomer. Therefore, levofloxacin is, by its nature, twice as active as ofloxacin per unit of mass.

Mechanism of Action

Like other fluoroquinolones, levofloxacin acts by inhibiting two bacterial enzymes that control the topological state of DNA: DNA gyrase, encoded by the genes gyrA and gyrB, and topoisomerase IV, encoded by the genes parC and parE (grlA and grlB) in S. aureus. Both type II DNA topoisomerase enzymes are essential for bacterial growth. The primary target of levofloxacin in Gram-negative bacteria such as Escherichia coli and Neisseria gonorrhoeae is DNA gyrase, while topoisomerase IV is the primary target in Gram-positive cocci such as S. aureus and S. pneumoniae. The antimicrobial action of levofloxacin, like that of other fluoroquinolones, is characterised by concentration-dependent bactericidal activity and the ability to induce a post-antibiotic effect against a range of bacteria.

Antibacterial Spectrum

Levofloxacin has broad-spectrum in vitro antibacterial activity against Gram-positive and Gram-negative aerobes, as well as so-called ‘atypical’ bacteria such as Chlamydia trachomatis, but has limited activity against anaerobic bacteria. Figure 1 shows the cumulative distributions of minimum inhibitory concentrations (MICs) of levofloxacin in comparison with ciprofloxacin and moxifloxacin for wild-type populations of four aerobic bacterial pathogens known to cause external ocular infections. A microorganism is defined as wild-type for a species by the absence of acquired and mutational resistance mechanisms to the corresponding drug. Clinical MIC breakpoint definitions for levofloxacin against staphylococci, β-haemolytic streptococci, H. influenzae, Moraxella catarrhalis, members of the Enterobacteriaceae family and P. aeruginosa, as suggested by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), are ≤1mg/l and >2mg/l separating susceptible from intermediate susceptible organisms and intermediate susceptible from resistant organisms, respectively, while those against S. pneumoniae are ≤2mg/l and >2mg/l, respectively. Levofloxacin displays good activity against wild-type strains of P. aeruginosa (0.063–2mg/l) and is highly active against wild-type strains of H. influenzae (0.008–0.031mg/l), M. catarrhalis (0.016–0.063mg/l) and the Enterobacteriaceae, including Citrobacter spp., Enterobacter spp., E. coli, Klebsiella pneumoniae and Proteus mirabilis (0.016–0.25mg/l). In general, levofloxacin is more active than moxifloxacin (a newer fluoroquinolone), but less active than ciprofloxacin (an earlier fluoroquinolone) against these Gram-negative species. Levofloxacin also shows good in vitro activity against wild-type strains of a range of Gram-positive bacterial species, with MIC values of 0.064–0.5 for S. aureus, 0.5–2mg/l for S. pneumoniae and 0.25–2mg/l for S. pyogenes. In contrast, ciprofloxacin is less active against Gram-positive bacteria, while moxifloxacin has higher in vitro activity.
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**Resistance**

Decreased susceptibility to levofloxacin (and other fluoroquinolones) can develop through two major mechanisms, namely alterations in the drug’s target and alterations that affect the intracellular concentration of the drug. Target-site alterations are linked to mutations in the quinolone-resistance-determining region (QRDR) of the \textit{gyrA} and \textit{parC} genes.\textsuperscript{7,10} Such mutations usually result from errors during chromosome replication, but can also be acquired via horizontal gene transfer, which has been observed in \textit{S. pneumoniae}\textsuperscript{13,14} and viridans group streptococci.\textsuperscript{13,14} A high level of resistance to levofloxacin requires mutations in more than one gene.\textsuperscript{15}

The second main mechanism of resistance, which is associated with a decrease in the intracellular concentration, results from changes in the outer membrane of bacteria (limited to Gram-negative bacteria) and/or drug efflux.\textsuperscript{7} Recently, plasmid-mediated quinolone resistance genes (\textit{qnr}) have been described in \textit{E. coli}\textsuperscript{16} and other \textit{Enterobacteriaceae} species.\textsuperscript{16} The Qnr proteins are capable of protecting DNA gyrase from quinolones. Increasing levels of resistance to fluoroquinolones have been reported worldwide over the past 10–15 years. For example, among German \textit{E. coli} isolates recovered in the surveillance studies conducted by the Paul Ehrlich Society (PEG) between 1995 and 2004, resistance to fluoroquinolones (ciprofloxacin, levofloxacin) increased from 5 to 22%.\textsuperscript{17} However, the data from the PEG studies were mainly recorded at tertiary care hospitals with a high proportion of nosocomial pathogens. Therefore, the rates of resistance found here may not be interpreted as representative of the outpatient sector.

**Prevalence of Resistance Among Ocular Pathogenic Bacteria**

\textit{Staphylococcus aureus}: The rates of susceptibility and resistance to the fluoroquinolones (including levofloxacin) often resemble those of methicillin-susceptible \textit{S. aureus} (MSSA) and methicillin-resistant \textit{S. aureus} (MRSA). Most of the MSSA are susceptible to fluoroquinolones, while the majority of MRSA are resistant. Data from Ocular TRUST 1, a prospective multicentre surveillance study conducted in the US between October 2005 and June 2006, show that the rates of levofloxacin resistance were 18.9 and 78.8% among the MSSA isolates (\textit{n}=164) and MRSA isolates (\textit{n}=33), respectively.\textsuperscript{18} According to data from a German prospective surveillance study conducted in 2004 evaluating 436 \textit{S. aureus} isolates recovered from patients with external ocular infections in 35 laboratories, the level of resistance to levofloxacin was 5% among the MSSA (\textit{n}=380) and 53.6% among the MRSA (\textit{n}=56).\textsuperscript{19}

\textit{Streptococcus pneumoniae}: The emergence of fluoroquinolone-resistant strains of \textit{S. pneumoniae} has been reported in recent years in some parts of the world, in particular in South-east Asia.\textsuperscript{20,21} However, the overall incidence of fluoroquinolone resistance among pneumococci seems to remain low. All 49 isolates collected during Ocular TRUST 1 were levofloxacin-susceptible. In addition, all archived 760 ocular isolates collected during the longitudinal TRUST surveillance programme between 1996 and 2006 were susceptible to levofloxacin, except one.\textsuperscript{18} The German surveillance study found that 184/187 (98.4%) were susceptible.\textsuperscript{19}
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Haemophilus influenzae: All isolates collected during Ocular TRUST 1 (n=32) were susceptible to levofloxacin, as were 355/356 (99.7%) of the archived isolates from TRUST, regardless of β-lactamase production.14 The German surveillance study found that all 164 isolates examined showed susceptibility to levofloxacin.19

Other ocular pathogens: Data from the German resistance surveillance study for ocular organisms indicated that none of the 46 E. coli isolates and 6/45 (13.3%) of the P. aeruginosa isolates were resistant to levofloxacin,19 five of which were isolated from hospitalised patients.

Pharmacokinetic and Toxicological Properties

After a single drop of 0.5% levofloxacin opthalmic solution applied to each eye of healthy volunteers, drug concentrations in the tear fluid remained above 2μg/ml for at least six hours.22 Following topical administration, the drug has also been demonstrated to effectively penetrate the cornea, and if the drug is frequently given over one hour, concentrations achieved in the anterior chamber of the eye were above the MICs of most ocular bacterial pathogens.23-25 When combined with orally administered levofloxacin, adequate drug levels were also achieved in the vitreous cavity of the eye.26 Topically applied fluoroquinolones have been considered to be more toxic to the corneal epithelium than other antibiotic agents.27,28 However, in a recently published study levofloxacin did not negatively influence epithelial wound healing.29 Moreover, levofloxacin was shown to be less cytotoxic on human corneal keratocytes and epithelial cells than other fluoroquinolones, including gatifloxin, moxifloxacin, ciprofloxacin and ofloxacin.30

Pharmacokinetic/Pharmacodynamic Relationships

The ratio between the 24-hour area under the serum concentration curve and MIC (AUC24/MIC) and the peak concentration/MIC (Cmax/MIC) for unbound drug are thought to be predictors of clinical and bacteriological efficacy. However, the magnitude of the pharmacokinetic/pharmacodynamic (PK/PD) index needed seems to vary according to the type of quinolone, bacterial species and immune status. A Cmax/MIC ratio of >10 is a dynamic (PK/PD) index needed seems to vary according to the type of infection between levofloxacin and placebo did not reach statistical significance, although the dosing regimen was met with some criticism (low dose and late time-point of post-operative prophylaxis), and an unexpected high incidence of post-operative infections was observed in the placebo arm.44

Conclusions

Despite the long-term extensive use of fluoroquinolones for the treatment of local and systemic infections, levofloxacin-resistant ocular isolates of S. pneumoniae and H. influenzae remain uncommon. Also, based on the data of the German surveillance study, the treatment of superficial ocular infections caused by E. coli and P. aeruginosa with levofloxacin still have a high likelihood of success. In contrast, levofloxacin, like other fluoroquinolones, is not indicated if MRSA is suspected as a pathogen. Due to its high corneal penetration, levofloxacin represents one of the most valuable antibacterial agents for topical use in ophthalmology, especially for the treatment of fulminant bacterial keratitis. However, its role as a prophylactic regimen in ophthalmic surgery needs to be further elucidated.
Oftaquix® is a broad spectrum topical antibiotic that acts fast to kill bacteria without inhibition of wound healing. In fact, hard-hitting Oftaquix has been the anti-infective eye drops of choice in the ESCRS endophthalmitis study and the ESCRS Guidelines.

Oftaquix (Levofloxacin) Abbreviated Prescribing Information

Please refer to the full Summary of Product Characteristics before prescribing.

Presentation: One ml Oftaquix eye drop solution contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg of levofloxacin. Indications: Oftaquix is indicated for the topical treatment of bacterial external ocular infections in patients ≥1 year of age caused by levofloxacin susceptible microorganisms. Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Posology: Instil one to two drops in the affected eye(s) every two hours up to 8 times per day while awake for the first two days and then four times daily on days 3 through 5.

Contraindications: Hypersensitivity to the active substance levofloxacin, to other quinolones or to any of the excipients, e.g. benzalkonium chloride.

Precautions/Warnings: Oftaquix must not be injected sub-conjunctivally. The solution should not be introduced directly into the anterior chamber of the eye. Systemic fluoroquinolones have been associated with hypersensitivity reactions, even following a single dose. If an allergic reaction to levofloxacin occurs, discontinue the medication. As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Oftaquix 5 mg/ml eye drops in multi-dose bottles contains benzalkonium chloride, which may cause eye irritation. Oftaquix should be used during pregnancy and lactation only if the potential benefit justifies any potential risk to the foetus or the nursing child. Adverse Reactions: Approximately 10% of patients can be expected to experience adverse reactions. The reactions are usually graded as mild or moderate, are transient, and are generally restricted to the eye. The following undesirable effects assessed as definitely, probably or possibly related to treatment were reported during clinical trials and post-marketing experience with Oftaquix: Eye disorders Common (>1/100, <1/10): Ocular burning, decreased vision and mucous strand. Uncommon (>1/1,000, <1/100): Lid matting, chemosis, conjunctival papillary reaction, lid oedema, ocular discomfort, ocular itching, conjunctival injection, conjunctival follicles, ocular dryness, lid erythema, and photophobia. No corneal precipitates were observed in clinical studies. Immune system disorders Rare (>1/10,000, <1/1,000): extra-ocular allergic reactions, including skin rash. Very rare (< 1/10,000), <including isolated reports>: anaphylaxis. Nervous system disorders Uncommon (>1/1,000, <1/100): headache Respiratory, thoracic and mediastinal disorders Uncommon (>1/1,000, <1/100): rhinitis. Very rare (< 1/10,000), <including isolated reports>: laryngeal oedema. Storage precautions: Multi-dose bottle: After first opening to be used within 28 days. Single-use containers: After first opening the pouch to be used within 3 months, after first use discard the opened single-use container with any remaining solution. Pack sizes: 5 ml white LDPE bottle with a LDPE dropper tip and a tam HDPE screw cap. Oftaquix unpreserved unit-doses in LDPE single-dose containers as strips of ten containing 0.5 ml each, packed in a paper-coated aluminium-PE foil pouch. Pack sizes country specific. Prescription only medicine. Last text revision: July 2006. Santen Oy, 33721 Tampere, Finland.