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# Pharmacogenetics and Pharmacokinetic Topical Levofloxacin on Cataract Surgery

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**ABSTRACT**

The fluoroquinolones (FQs) have proven to be successful for treating ocular infections because the introduction of ciprofloxacin and ofloxacin; the improvement in ofloxacin to levofloxacin, the active l-isomer of ofloxacin; and the targeting of Gram-positive bacteria by moxifloxacin and gatifloxacin with a dual mechanism of action. The in vitro testing of the FQs has determined that moxifloxacin and gatifloxacin are more potent anti-infectives with lower minimum inhibitory concentrations (MICs) to Gram-positive bacteria than the earlier generations of FQs, but no real advantage for in vitro susceptibility has been noted among the FQs for Gram-negative bacteria. The objective of this review is to outline the pharmacogenetics, pharmacokinetics, and efficacy of levofloxacin along with the impact on patients' life. Such particular approach, being the foundation of personalized medicine, increases efficacy and safety of timolol while reducing costs by using targeted doses.

## 1. Introduction

Cataract still is a leading cause of visual impairment worldwide Despite the fact that 90% of cataracts in the world are reported in developing countries, its social, physical and economic impact is still substantial in the developed world. Cataract is a common cause of visual impairment in the elderly that is often noticed by patients at an early stage, and surgery is often effective in restoring vision. Nevertheless, cataract surgery still remains a major healthcare cost in Europe and other Western countries. Progressive ageing of the European population is linked to the increase of incidence and prevalence of cataract. As an example, the general population of Denmark is expected to increase by 10%, the proportion of the population aged 70 or older is predicted to double from 10.5% (2009) to 20.40% (2050), and the number of cataract surgeries is projected to correspondingly increase from 46 000 in 2004 to 86 000 in 2050 The increased demand for cataract surgery may be hard to meet in the future unless preventative actions are taken .Therefore, a review of modifiable risk factors of cataract and the evaluation of aspects that affect total costs of cataract surgeries is needed.

Cataract is a multifactorial disease associated with age, female sex, genetic predisposition, smoking, diabetes mellitus, drug intake and environmental exposure to UVB radiation Previous reviews were often focused on one of the aspects of cataract epidemiology, such as common risk factors, the cost-effectiveness of different treatment approaches and their comparison between different countries in Europe. Several epidemiological studies report on cataract as a possible adverse effect of widely used drugs nevertheless, this aspect of cataract aetiology was not reviewed previously. This literature review was undertaken to provide an overview of cataract epidemiology, cataract risk factors and cataract-related economic burden as well as to evaluate the potential for cataract prevention in Europe.

**Pharmacogenetics and pharmacokinetics levofloxacin**

Fluoroquinolone (FQ) antibiotics are compounds that contain a keto-carbonyl group that binds divalent ions, including magnesium. In addition to their antimicrobial activity, FQs are endowed with immunomodulatory properties, but the mechanism underlying their anti- inflammatory activity remains to be defined. The aim of the current study was to elucidate the molecular mechanism of these compounds in the TLR4/NF-κB inflammatory signaling pathway.

In recent years, many antibacterial agents, including fluoroquinolones (i.e., 7-fluoro-4-oxo-1,4-dihydroquino- line-3-carboxylic acid) (FQs), one of the most important and commonly prescribed classes of synthetic antibiotics[19], have been shown to exert immunomodulatory ac- tivities by decreasing the production and release of in- flammatory-associated cytokines, both in vitro and in vivo, in addition to their classical antimicrobial activity[20-25]. Several underlying mechanisms of the immuno- modulatory activity of FQs have been proposed, includ- ing the inhibition of phosphodiesterase and transcription factors, such as activator protein-1, nuclear factor of ac- tivated T cells, nuclear factor-IL-6, and NF-Kb[22]. However, to date, the precise cascade of events and, most important, the primary target for the anti-inflam- matory properties of FQs have not been defined. Al- though the interference of FQs with cellular receptors, such as TLRs, has been hypothesized[21,26], there is still no evidence showing any interactions of these drugs with TLRs or other cell membrane receptors associated with inflammatory signaling.

By molecular modeling simulations, we first characterized the putative binding mode of five FQs [ciprofloxacin (CPFX), levofloxacin (LVFX), moxifloxacin (MXFX), ofloxacin (OFX), and delafloxacin (DLFX)] to the TLR4–MD-2 complex. Next, we examined the effect of CPFX and LVFX, two of the most largely prescribed antibiotics, on LPS-induced microglia activation and sought to identify their molecular targets in the TLR4 signaling pathway (i.e., TLR4–MD-2 complex and NF-κB activation), using primary microglial cells and Ba/F3 cells, a murine interleukin-3 dependent pro-B cell line. We found that CPFX and LVFX reduced the re- lease of pro-inflammatory cytokines by LPS-activated microglia. They also inhibited LPS-induced activation of NF-κB, one of the major transcription factors im-plicated in TLR4 signaling. Finally, we showed that the two FQs prevented the engagement of LPS to TLR4–MD-2 complex and its dimerization, indicat-ing that the binding between LPS and the receptor complex is the target for the anti-inflammatory properties of CPFX and LVFX.

CPFX, LVFX, MXFX, OFX, and DLFX structures were built using the "Builder" module of MOE, and each compound was docked into the presumptive binding sites (LPS binding site) using flexible MOE-Dock meth- odology. The purpose of MOE-Dock is to search for favorable binding configurations between a small, flex- ible ligand and a rigid macromolecular target. Searching is conducted within a user-specified 3D docking box, using the "tabù search"[29] protocol and the MMFF94 force field[30]. Charges for ligands were imported from the MOPAC program[31] output files. MOE-Dock per-forms a user-specified number of independent docking runs (50 in the present case) and writes the resulting conformations and their energies to a molecular data-base file. The resulting ligand/protein complexes were subjected to MMFF94 all-atom energy minimization until $-1\ -1$ the rms of conjugate gradient was < 0.1 kcal mol Å. GB/SA approximation[32] has been used to model the electrostatic contribution to the free energy of solvation in a continuum solvent model. The interaction energy values were calculated as the energy of the complex minus the energy of the ligand, minus the energy of the protein: $\Delta E_{inter} = E(complex) - (E(L) + E(Protein))$.

## 2. Results

A molecular docking study was carried out to characterize the putative binding mode to TLR4–MD-2 complex of five largely prescribed FQs, CPFX, LVFX, MXFX, OFX, and DLFX. Interestingly, and similarly to what has already been described for curcumin and its analogues18, the five docked FQs showed the

propensity to bind the TLR4–MD-2 complex in two different modes: occupying the canonical LPS recognition site in the MD-2 structure, and binding at the interface between MD-2 and TLR4 complex where a Mg2+ ion is coordinated by LPS, as de- tected in the crystallographic structure coded by PDB as 3FXI10,18. Considering the analogies in the binding modes of all the docked FQs, the CPFX structure was used as an example for a more detailed description of the two binding modes with the TLR4–MD-2 complex. Firstly, as shown in Fig. 1 and in Additional file 1: Figure S1, CPFX in its zwitterionic form could be accommodated into the large binding pocket of MD-2, occupying a relevant portion of the LPS binding site and assuming different binding modes. Among all generated binding modes of each ligand, the en- ergetically more stable were those that showed important interactions to MD-2, such as charge-charge interactions or hydrogen bonding, engaged with residues Arg90, Glu92, and Tyr102. Secondly, CPFX in its zwitterionic form can also coordinate the Mg2+ ion through its carbonyl and carboxyl groups in neighboring positions. The Mg2+ coord- ination could prevent the stabilization of the LPS binding to MD-2, interfering with the TLR4 dimerization process. Based on the in silico analysis, the two most popular FQs CPFX and LVFX were used with the aim of characterizing the molecular mechanism involved in the regulation of microglia inflammatory response.

## 3. Discussion

That the resistance of the bacterial flora of the conjunctival sac of patients undergoing cataract surgery with 1 month of topical levofloxacin administration. The diversity of bacterial flora in the conjunctival sac, ie lost after topical levofloxacin administration, resolved 3 months after the last levofloxacin treatment. Levofloxacin MICs from S epidermidis showed transient symptoms but significantly improved after treatment; However, P acnes did not change in terms of the mean levofloxacin MIC over time. Recovery of the levofloxacin MIC of the S epidermidis in the conjunctival sac after the last levofloxacin treatment takes more than 6 months after the last levofloxacin treatment.

The predominance of S epidermidis and P acnes and the presence of various strains prior to topical levofloxacin treatment are consistent with the results obtained previously with aerobic and anaerobic microbiological analyzes and suggest that the patients in this study were healthy. Several studies have reported the long-term effects of antibiotics in healthy patients. Levofloxacin resistance is based on serum standards for systemic treatment, and there is no standard antibiotic breakpoint for topical antibiotic therapy. In this study, levofloxacin-resistant S epidermid clones increased in 6 months after topical levofloxacin[6-9]

Administration and decreased thereafter. These findings are consistent with the presence of fluoroquinoloneresistant bacteria in the conjunctival sac of a patient with a history of topical fluoroquinolone at 3 months.16 We recently reported that antibiotic-resistant S epidermidis was less frequent after perioperative administration of topical levofloxacin for 1 week than after administration during 1 month.10 This suggests that the diversity and antibiotic susceptibility of the ocular surface flora is not very high affected by ophthalmological procedures in the United States and Europe, where antibiotics are usually given for 1 week or less.

## 4. Conclusion

The post-cataract surgery management is as important as the preparatory procedure before cataract surgery and the cataract surgery procedure itself. Good post-surgical management will result in maximum cataract surgery results according to the specified target. Patients must know how to care for the eye after cataract surgery to get maximum surgery results.

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