ERDEY EYE GROUP
Vision For Life

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Fourth Generation Ophthalmic Fluoroquinolones

Since their introduction nearly thirty years ago, Fluoroquinolone antibiotics have served as an excellent tool in the fight against virulent bacteria; they possess a broad spectrum of activity and an excellent safety profile. Fluoroquinolone agents exert their anti-microbial effect by binding to and inhibiting DNA gyrase (topoisomerase II), an essential bacterial enzyme that is a critical catalyst in the duplication, transcription, and repair of bacterial DNA. Until recently there were three major topical fluoroquinolone agents available for ophthalmic use in the United States: **ofloxacin** (Ocuflox; Allergan), **ciprofloxacin** (Ciloxan, Alcon) and **levofloxacin** (Quixin, Santen). Based on chemical structure, spectrum of action and clinical indications, all three agents are classified as "second-generation" fluoroquinolones.

However, the widespread use of fluoroquinolones has led to a growing emergence of resistant strains of bacteria, particularly among the gram-positive organisms. Resistance to ofloxacin and ciprofloxacin among coagulase-negative Staphylococcus, for example, has been demonstrated in recent studies to range between 52% and 85%. Resistance evolves in bacteria through genetic mutation, and this process can be accelerated by the overuse of antibiotics. The three primary mechanisms of bacterial resistance to fluoroquinolones involve reducing cell wall permeability, altering enzymes that block the antibiotic complex, and using efflux pumps that remove the antibiotic molecules from the cell. A single mutation in the gene that codes for the bacteria's DNA gyrase enzyme can establish resistance to a second generation fluoroquinolone. This increased resistance to second-generation fluoroquinolones has spurned the development of newer and more potent fluoroquinolones. Recently two new fluoroquinolones were introduced; **gatifloxacin** (Zymar, Allergan), and **moxifloxacin** (Vigamox, Alcon). Both are considered as "fourth generation" because they gain their anti-microbial effect by binding not only to DNA gyrase but also to topoisomerase IV; a bacterial enzyme involved in partitioning chromosomal DNA during bacterial cell division. In addition to this dual mechanism of action, both gatifloxacin and moxifloxacin are considerably more potent than their predecessors and in turn have a decreased MIC (minimum inhibitory concentration). Fourth generation fluoroquinolones, require mutations affecting both enzymes for effective resistance. As a result, **the probability of resistance is one in ten million for a second generation fluoroquinolone but increases to one in ten trillion for the fourth generation!** This difference was illustrated by a recent study demonstrating two ciprofloxacin-resistant strains of S. pneumonia were susceptible to both moxifloxacin and gatifloxacin.

History has taught us that it is a matter of when, not if, bacteria will develop resistance to any class of antibiotic. Nonetheless, the addition of newer fluoroquinolones is an exciting development in the eye care field, and has particular promise in the treatment of ocular infections and in the prevention of post-surgical endophthalmitis.

- **Fluoroquinolones have Served as an Excellent Tool in the Fight Against Virulent Bacteria.**
- **Fluoroquinolone Antibiotics have Both a Broad Spectrum of Activity and an Excellent Safety Profile.**
- **The Probability of Fluoroquinolone Resistance:**
  Second Generation: One in Ten Million
  Fourth Generation: One in Ten Trillion

Erdey Eye Group
5965 East Broad Street
Suite 490
Columbus OH 43213
Voice: 614.863.3937
Fax: 614.863.5010
Richard A Erdey MD
Medical Director
Gregory D Searcy MD
Ophthalmologist
Patrick A Janson OD
Clinical Director
Kasey J Eppley OD
Director of Education
Matthew U Neal OD
Staff Optometrist
Douglas J Bosner OD
Refractive Team Director
Jill A Conklin OD
Optometric Resident
Pamela J Andrews
Administrator

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Email Address: bestvision@erdeyeyegroup.com