

Safety of prophylactic intracameral moxifloxacin 0.5% ophthalmic solution in cataract surgery patients

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PURPOSE: To determine the safety of prophylactic intracameral moxifloxacin 0.5% ophthalmic solution (Vigamox) in patients having cataract surgery.

SETTING: American Eye Center, Manila, Philippines.

METHODS: Preoperative and 1-month postoperative anterior chamber reaction, corneal endothelial cell density, and corneal thickness were assessed in 65 eyes that had cataract surgery with intracameral moxifloxacin. All eyes received 0.1 mL intracameral moxifloxacin 0.5% ophthalmic solution containing 500 µg of moxifloxacin as the last step of phacoemulsification. Different ophthalmologists conducted the postoperative evaluation in an observer-masked fashion. A *P* value less than 0.05 was considered significant.

RESULTS: All 65 eyes completed the study. The mean age was 69.5 years \pm 9.13 (SD) (range 48 to 84 years). All eyes had a postoperative best corrected visual acuity of 20/30 or better. All eyes had trace to +2 cells and flare anterior chamber reaction only on the first day after surgery. The mean endothelial cell count was 2491.52 cells/mm² preoperatively and 2421.58 cells/mm² postoperatively. The mean difference was 70 cells/mm², which not statistically significant (*P* = .737). The increase of 17.80 µm in postoperative pachymetry 1 month after surgery was not statistically significant (*P* > .65).

CONCLUSION: Intracameral Vigamox 0.5 mg/mL appeared to be nontoxic in terms of visual rehabilitation, anterior chamber reaction, pachymetry, and corneal endothelial cell density.

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The use of prophylactic antibiotics in elective cataract surgery remains controversial. Despite a lack of evidence that these agents prevent postoperative infection, many cataract surgeons routinely administer intracameral antibiotics to avert the potentially devastating outcomes of endophthalmitis. Among the antibiotics given intracamerally, cefuroxime and vancomycin are the most commonly used.¹

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Before the introduction of moxifloxacin ophthalmic solution 0.5% (Vigamox), we used intracameral vancomycin at the conclusion of phacoemulsification surgery as part of the prophylactic regimen. Although anecdotal and retrospective analyses were appealing and the risk for endophthalmitis was reduced with vancomycin,^{2–4} there was no strong proof that vancomycin prevents endophthalmitis. In addition, Axer-Siegel et al.⁵ showed that vancomycin increased the risk for clinically significant cystoid macular edema (CME) as well as CME seen on fluorescein angiography 1 month and 4 months after cataract surgery. Moreover, because of its potency, vancomycin has generally been reserved for treatment of infections that are not efficiently treatable by other drugs. Issues have been raised regarding the emergence of vancomycin-resistant enterococci, an increase in intermediate resistance to vancomycin in coagulase-negative staphylococci, and methicillin-resistant *Staphylococcus aureus*. These issues and the lack of scientific proof of vancomycin's efficacy in preventing

endophthalmitis led to a joint statement by the American Academy of Ophthalmology and the U.S. Centers for Disease Control discouraging the routine prophylactic use of vancomycin in ocular surgery.^{6,7}

In contrast, in a preliminary report of the ESCRS Endophthalmitis Study Group,^{8,9} intracameral cefuroxime was shown to significantly reduce the risk for developing endophthalmitis after phacoemulsification cataract surgery. However, like vancomycin, cefuroxime is available in a systemic preparation that must be reconstituted using saline solution before it can safely be delivered to the eye. Reconstituting the drug for intracameral use may increase the risk for toxic anterior segment syndrome (TASS) because an undesired concentration of the drug may be inadvertently injected if a mistake occurs during the preparation or dilution process. It is well known that incorrect drug concentration, incorrect pH, and incorrect osmolality can cause TASS.¹⁰

Endothelial toxicity leading to corneal decompensation is another severe complication of cataract surgery. Often iatrogenic as a result of mechanical or chemical insult to the endothelium, endothelial toxicity is related to the chemical composition, concentration, pH, and osmolality of substances that come in contact with the endothelium and may lead to irreversible corneal edema. Some cases of TASS also result in localized corneal endothelial damage.

Considering the possible complications with vancomycin and cefuroxime, moxifloxacin seems to be the better choice of antibiotic for endophthalmitis prophylaxis because of its broad-spectrum coverage and mode of action. Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent that is active against a broad spectrum of gram-positive and gram-negative ocular pathogens, atypical microorganisms, and anaerobes.¹¹⁻¹³ (Tables 1 to 3). The ophthalmic solution is isotonic and formulated at pH 6.8 with an osmolality of approximately 290 mOsm/kg (product description, moxifloxacin hydrochloride ophthalmic solution 0.5%, Alcon Laboratories, reference: AAA083-0604); both values are within the compatible range for humans (pH 6.5 to 8.5 and osmolality 200 to 400 mOsm/kg).¹⁴⁻¹⁶ Vigamox is also a self-preserved (no added preservatives) commercial ophthalmic formulation that requires no special preparation for intracameral delivery, reducing the risk for TASS. In addition, early studies of rabbit eyes did not show intraocular toxicity after injection of intravitreal or intracameral moxifloxacin.¹²

To our knowledge, this is the first report of a topical ophthalmic preparation applied through the intraocular route as a prophylactic agent in cataract surgery. Our study evaluated the safety of injecting intracameral Vigamox in human eyes having cataract surgery.

Table 1. Susceptibility of gram-positive species to moxifloxacin.*

| Bacterial Species | MIC ₅₀ (μg/mL) |
|---|---------------------------|
| | Moxifloxacin |
| <i>Staphylococcus aureus</i> | 0.03 |
| <i>Staphylococcus epidermidis</i> | 0.06 |
| <i>Staphylococcus haemolyticus</i> | 0.06 |
| <i>Staphylococcus saprophyticus</i> | 0.03, 0.13 |
| <i>Staphylococcus lugdunensis</i> | 0.13 |
| <i>Staphylococcus hominis</i> | 0.03, 0.06 |
| <i>Staphylococcus simulans</i> | 0.03 |
| <i>Staphylococcus pasteurii</i> | 0.06 |
| <i>Staphylococcus warneri</i> | 0.03, 0.06 |
| <i>Streptococcus pneumoniae</i> | 0.06, 0.13 |
| <i>Streptococcus mitis</i> | 0.13 |
| <i>Streptococcus viridans</i> group | 0.13 |
| <i>Streptococcus pyogenes</i> | 0.13, 0.25 |
| <i>Enterococcus faecalis</i> | 0.19, 0.25 |
| <i>Micrococcus luteus</i> | 0.50 |
| <i>Kocuria</i> species | 0.25 |
| <i>Bacillus cereus</i> | 0.09, 0.13 |
| <i>Bacillus pumilus</i> | 0.13 |
| <i>Bacillus subtilis</i> | 0.16 |
| <i>Corynebacterium accolens</i> | 0.03 |
| <i>Corynebacterium macginleyi</i> | 0.03 |
| <i>Corynebacterium propinquum</i> | 0.25 |
| <i>Corynebacterium pseudodiphtheriticum</i> | 0.25 |

MIC = minimum inhibitory concentration

*From Stroman et al.¹³ (Reproduced with permission from Elsevier.)

PATIENTS AND METHODS

A study conducted from October 2005 to March 2006 had general enrollment criteria of age 45 to 85 years with no ocular pathology other than cataract. Exclusion criteria included glaucoma, retinopathy, maculopathy, media opacity other than cataract (cornea or vitreous), and visual pathway problems that would prevent a postoperative best corrected visual acuity (BCVA) of 20/30 or better. Patients with uveitis, diabetes, corneal endothelial disease, or pseudoexfoliation and those who were taking systemic immunosuppressants or anticoagulants were also excluded. Other exclusion criteria were intraoperative complications or difficulties and prolonged surgery. Only patients with a nuclear density less than NO4/NC4 on the Lens Opacities Classification System III who could be operated on with the standard quick-chop phacoemulsification technique were included.

The preoperative BCVA, refraction, pachymetry, endothelial cell count, and patient age and sex on the day of surgery were recorded using Excel 2004 for Macintosh (version 11.1, Microsoft).

Surgical Technique

Pupils were dilated with a solution of tropicamide 1% and phenylephrine 10%. All surgeries were performed using topical anesthesia of proparacaine (Alcaine) and intracameral lidocaine hydrochloride 1% (Xylocaine) 0.30 mL. Uneventful phacoemulsification was performed in a standardized fashion by 1 of 2 surgeons (C.E., V.C.) through a 2.7 to 3.0 mm clear corneal incision.

Table 2. Susceptibility of gram-negative species to moxifloxacin.*

| Bacterial Species | MIC ₅₀ (µg/mL) |
|-------------------------------------|---------------------------|
| | Moxifloxacin |
| <i>Aeromonas caviae</i> | 0.13 |
| <i>Citrobacter koseri</i> | 0.03 |
| <i>Enterobacter aerogenes</i> | 0.06, 0.25 |
| <i>Enterobacter cloacae</i> | 0.03, 0.13 |
| <i>Enterobacter hormaechei</i> | 0.13 |
| <i>Escherichia coli</i> | 0.008, 0.06 |
| <i>Klebsiella oxytoca</i> | 0.03, 0.25 |
| <i>Klebsiella pneumoniae</i> | 0.03, 0.13 |
| <i>Morganella morgagnii</i> | 0.06, 0.50 |
| <i>Pantoea agglomerans</i> | 0.03, 0.06 |
| <i>Proteus mirabilis</i> | 0.06, 0.50 |
| <i>Serratia marcescens</i> | 0.25, 0.50 |
| <i>Achromobacter xylosoxidans</i> | 2.0, 4.0 |
| <i>Acinetobacter baumannii</i> | 0.03, 0.13 |
| <i>Acinetobacter calcoaceticus</i> | 0.016, 0.06 |
| <i>Acinetobacter johnsonii</i> | 0.16, 0.13 |
| <i>Acinetobacter junii</i> | 0.06 |
| <i>Acinetobacter genospecies 3</i> | 0.016, 0.06 |
| <i>Chryseobacterium indologenes</i> | 0.25 |
| <i>Chryseomonas luteola</i> | 0.13 |
| <i>Stenotrophomonas maltophilia</i> | 0.13, 1.0 |
| <i>Pseudomonas aeruginosa</i> | 0.50, 2.0, 4.0 |
| <i>Pseudomonas oryziabibans</i> | 0.13 |
| <i>Pseudomonas stutzeri</i> | 0.25 |
| <i>Haemophilus influenza</i> | 0.016, 0.03, 0.39 |
| <i>Moraxella catarrhalis</i> | 0.03, 0.047, 0.06 |
| <i>Moraxella osloensis</i> | 0.13 |
| <i>Neisseria perflava</i> | 0.03 |

MIC = minimum inhibitory concentration

*From Stroman et al.¹³ (Reproduced with permission from Elsevier.)

Sodium hyaluronate 3.0%–chondroitin sulfate 4.0% (Viscoat) and sodium hyaluronate 1.0% (Provisc) were used for intraocular lens (IOL) implantation. An AcrySof SA60AT, SN60AT, or SN60WF IOL (Alcon) was implanted.

Prophylactic Regimen

Preoperatively, patients received 1 drop of topical Vigamox every 15 minutes at least 4 times. Povidone–iodine 0.5% was instilled into the cul de sac.

At the start of the operating day, the contents of a newly opened bottle of Vigamox was aspirated by a scrub nurse into a sterile 10 cc syringe and set aside. With a tuberculin syringe, a volume slightly in excess of 0.1 mL (0.3 to 0.5 mL) of the pure moxifloxacin 0.5% ophthalmic solution was then aspirated from the 10 cc syringe. No solution, including saline, was added to dilute the commercial preparation. The excess amount was discarded, leaving 0.1 mL in the tuberculin syringe ready for injection into the anterior chamber. This volume contained 0.5 mg of the nonpreserved moxifloxacin with a pH of 6.8 and an osmolality of approximately 290 mOsm/kg. The solution prepared in the syringe was injected using a 27-gauge cannula through the side port

Table 3. Susceptibility of atypical and anaerobic species to moxifloxacin.*

| Bacterial Species | MIC ₅₀ (µg/mL) |
|-----------------------------------|---------------------------|
| | Moxifloxacin |
| Atypical | |
| <i>Mycobacterium avium</i> | 3.2 |
| <i>Mycobacterium marinum</i> | 0.4 |
| <i>Mycobacterium chelonae</i> | 1.6, 8.0 |
| <i>Mycobacterium abscessus</i> | 8.0 |
| <i>Mycobacterium fortuitum</i> | 0.06 |
| <i>Mycobacterium kansasii</i> | 0.06 |
| <i>Chlamydia trachomatis</i> | 0.03 |
| Anaerobe | |
| <i>Propionibacterium acnes</i> | 0.25 |
| <i>Bacteroides fragilis</i> | 0.25 |
| <i>Clostridium perfringens</i> | 0.50 |
| <i>Peptostreptococcus</i> species | 0.25 |

MIC = minimum inhibitory concentration

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into the capsular bag as the last step of cataract extraction and IOL implantation.

Postoperative antibiotics included oral ciprofloxacin 500 mg, 1 tablet twice a day for 5 days, and topical Vigamox every 2 hours while awake on the day of the surgery. The Vigamox was reduced to 4 times a day until the bottle was empty. Topical prednisolone acetate 1% (Pred Forte) was also given postoperatively using the same dosage schedule used for Vigamox.

Patient Examinations

The patients were scheduled for follow-up 1 day, 1 week, and 1 month after surgery. Visual acuity, endothelial cell counts, corneal pachymetry, and anterior chamber cells and flare were recorded on the day of surgery and at every postoperative follow-up.

Specular endothelial microscopy of the central cornea was performed with a noncontact specular microscope (Noncon Robo, Konan Medical). Quantitative corneal endothelial cell analysis was done using the variable-frame analysis method. Three images were taken, and the image with the best technical quality was analyzed. At least 50 well-defined endothelial cells were marked for analysis. Central corneal thickness was measured using the Noncon Robo.

Anterior chamber reaction, expressed as cells and flare intensity, was graded by an independent observer using the Hogan system.¹⁷ All observations were done using a biomicroscope (Topcon or Haag-Streit slitlamp) 1 day and 1 and 4 weeks after surgery. The BCVA was checked each visit and recorded 4 weeks after surgery.

Statistical Analysis

Data were recorded and analyzed using the Student paired *t* test data analysis tool in Excel 2004 for Macintosh (version 11.1). The null hypothesis was that the preoperative and postoperative endothelial cell counts and pachymetry are equal. A *P* value less than 0.05 was considered significant.

RESULTS

Sixty-five patients (65 eyes) completed the study. All patients were Asian. The mean age of the 43 women and 22 men was 69.5 years ± 9.13 (SD) (range 48 to 84 years).

All eyes had postoperative BCVA of 20/30 or better; 86% had visual acuity of at least 20/20 (Figure 1). No eye had corneal edema on the first day postoperatively. All eyes had trace to +2 cells and flare only on the first day after cataract surgery (Figure 2). All had quiet anterior chambers at subsequent follow-up examinations. All eyes had a lower endothelial cell at 1 month than preoperatively except for 21 eyes, which gained endothelial cell density.

The mean endothelial cell count was 2491.52 cells/mm² preoperatively and 2421.58 cells/mm² postoperatively (Figure 3). The mean difference was 70.06 cells/mm², which not statistically significant (*P* = .737, *t* test). The mean pachymetry was 548.42 μm preoperatively and 566.22 μm postoperatively. The increase of 17.80 μm in postoperative pachymetry 1 month after surgery was not statistically significant (*P* > .65).

DISCUSSION

Endophthalmitis cases after cataract surgery increased from 1994 to 2001, with a reported incidence of 2.15 per 1000 cases¹⁸ (T.P. O'Brien, MD, "Vigamox Protects Against Staph Isolates in Cataract Surgery Patients," EyeWorld, October 2005, 10[suppl]). Thus, there is a need for protective antibiotics to combat the rise and to better treat patients, especially in the light of increasing antibacterial resistance among causative organisms.

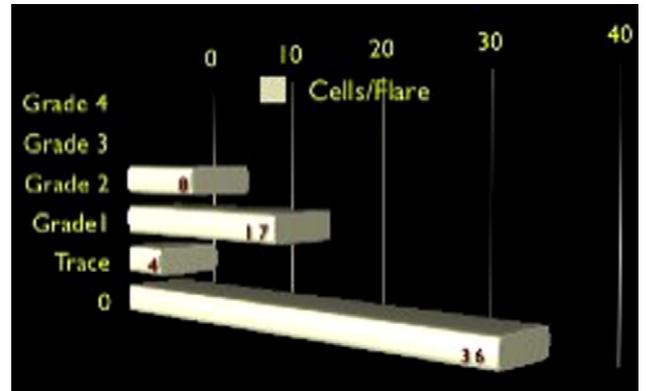


Figure 2. Anterior chamber reaction, observed as cells and flare, 1 day postoperatively.

Of the prophylaxis methods for cataract surgery, only povidone-iodine received intermediate clinical recommendation, as discussed by Ciulla et al.¹⁹ in a literature review of endophthalmitis prophylaxis. In addition, Isenberg et al.²⁰ found that povidone-iodine reduces conjunctival flora by 91% for colony-forming units and 51% for species when applied alone to the eye just before surgery; when applied in conjunction with a topical antibiotic, it produced a synergistic effect that led to sterilization of 83% of the eye. Although antiseptic agents such as povidone-iodine are effective for ocular surface decontamination, antibiotics with favorable pharmacodynamic properties are required to deliver ocular protection.

Fluoroquinolones were introduced for treatment of corneal and conjunctival infections; however, these

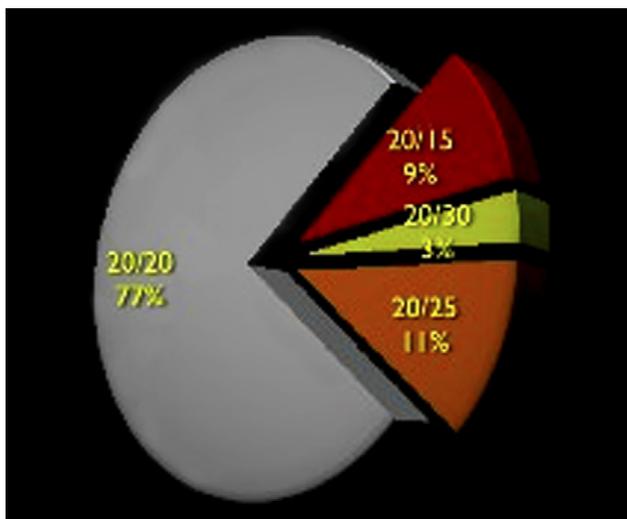


Figure 1. Best corrected visual acuity weeks after phacoemulsification with intracameral Vigamox.

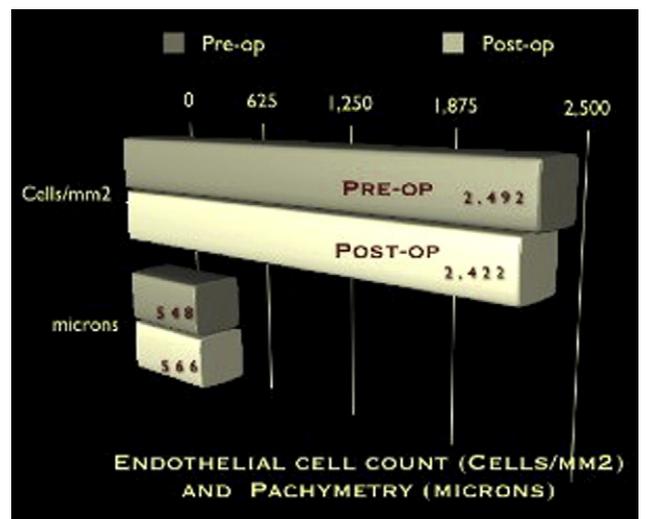


Figure 3. Mean preoperative and postoperative endothelial cell count (cells/mm²) and pachymetry (μm).

antibiotics found a greater role in prophylaxis before surgery to prevent endophthalmitis. New generations of fluoroquinolones were introduced to counteract resistance to the second-generation agents. These include third-generation (levofloxacin) and fourth-generation (moxifloxacin and gatifloxacin) fluoroquinolones.¹¹

Several studies^{11,13,21,22} found moxifloxacin, a fourth-generation antibiotic, to be superior in terms of potency. It has the lowest mean inhibitory concentration (MIC) for most bacterial endophthalmitis isolates¹³; thus, it seems to be a better choice for prophylactic antibiotic. The moxifloxacin injection we used was a commercially available ophthalmic solution labeled for topical use with the brand name Vigamox. Vigamox does not contain preservatives, which in addition to its broad-spectrum activity, led us to investigate its intraocular use. Vigamox has a pH of 6.8 and an osmolality of 290 mOsm/kg; both values are within the compatible range for humans.¹⁴

We addressed concerns about biocompatibility of the antibiotic by observing its effects on the cornea (endothelial cell count and pachymetry) and blood–aqueous barrier (BAB) (aqueous flare) and whether it caused inflammation in the anterior chamber (aqueous cells). We also excluded patients with corneal problems and ocular pathology other than cataract to avoid confounding the postoperative findings. We found no statistical evidence of reduced endothelial cells or increased corneal thickness in our patients as early as 4 weeks postoperatively compared to preoperatively. The 3% endothelial cell loss in our study group is comparable to that in most studies, which report a mean reduction in endothelial cells after cataract surgery ranging from 4% to 15%.²³ In addition, we found no proof that Vigamox causes increased BAB disturbance or secondary inflammation, which would have caused raised aqueous flare levels and raised cell levels, respectively. All eyes had 0 cells and flare at the 1-week postoperative visit. No eye lost a line of BCVA from the preoperative acuity.

Our choice to analyze the data 4 weeks after surgery is supported by observations in previous studies of intracameral instillation of vancomycin, cefuroxime, and cefotaxime.^{3,24–26} Kramann et al.²⁶ report no further postoperative loss of endothelial cells after 4 weeks, which suggests wound healing is complete by then. Cheng et al.²⁷ and Amon et al.²⁸ report that preoperative corneal thickness values were restored within a similar period of time.

Regarding efficacy, the drug level in the target tissue (in this case the aqueous) becomes paramount. Antibiotic concentrations over time should be established and should be above the MIC₉₀ levels of the most common, if not all, endophthalmitis-causing pathogens. We injected 0.1 mL of Vigamox 0.5% solution, or an equivalent of 0.5 mg (500 µg) of moxifloxacin, into the capsular bag. With an IOL positioned in the capsular bag, the

estimated fluid capacity of the combined anterior and posterior chambers after crystalline lens extraction is approximately 0.525 mL.²⁹ Granting that we reestablished this volume with balanced salt solution (BSS) and the 0.1 mL of antibiotic at the conclusion of the surgery, the concentration of moxifloxacin would be 500 µg in 0.525 mL, or 952 µg/mL. The median MIC (in µg/mL) of even moxifloxacin-resistant endophthalmitis isolates has been established to be no higher than 3 µg/mL.¹¹ Therefore, the initial moxifloxacin levels in the anterior chamber after injection in our cases was at least 300 times the median MICs of endophthalmitis-causing organisms.

Development of resistant strains through mutation with the prophylactic use of antimicrobials is another parameter by which to evaluate antibacterial potency. This drug level, called the mutant prevention concentration (MPC), addresses the concern that frequent, suboptimal use of antibiotics increases the chances for and hastens the appearance of resistant mutants. Knowing, and more important achieving, concentrations above these levels more or less ensures prevention of such strains. The MPC of fluoroquinolones is typically 8 to 10 times their MIC.^{30,31} Calculations show that the moxifloxacin concentrations initially achieved in our patients were at least 30 times the estimated MPCs of the antibiotic for endophthalmitis isolates.

Another issue is the antibiotic's concentration in the anterior chamber over time and its effective kill rate. Unfortunately, there is a dearth of data in the literature on the bioavailability of antibiotics after intraocular administration in humans.^{32–34} Furthermore, the data in these studies are not entirely conclusive as a result of unavoidable limitations in aqueous humor sampling. Because of the small volume of aqueous, which prevents repeated extractions, these studies evaluated antibiotic concentrations in different patients at different times. Still, these provide only a general idea of aqueous humor clearance and of the concentrations of intracocularly administered medications over time. One study estimates a decline in aqueous humor antibiotic concentration by a factor of 4 in 1 hour.²⁴ The investigators, however, instilled the antibiotic (cefuroxime) in a nondistended anterior chamber to avoid overfilling the chamber and prevent leakage of the antibiotic solution. The actual half-drop in concentration, however, may be closer to 1 to 2 hours, as reported for irrigation fluid antibiotics.^{32–34} If these data reflect actual circumstances and if presumed constant elimination rates based on available information are to be believed (T.P. O'Brien, MD, "Vigamox Protects Against Staph Isolates in Cataract Surgery Patients," *EyeWorld*, October 2005, 10[suppl]), moxifloxacin levels in the aqueous exceeding MICs for relevant species will persist for a conservatively estimated time of 5 hours. Mutant prevention concentrations, on the other hand, will be maintained until approximately 3 hours after surgery.

CONCLUSION

Vigamox given intracamerally appeared to be nontoxic in terms of visual rehabilitation, anterior chamber reaction, pachymetry, and corneal endothelial cell density. This study established only that Vigamox can safely be given intracamerally; thus, further studies to prove its effectiveness in preventing endophthalmitis are required.

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