My colleagues and I undertook a study to determine whether the prophylactic use of topical antibiotics could make a difference in ameliorating, or even preventing, the damage from endophthalmitis, that occurs in about 1 in 1,000 cataract cases.

In our study which was recently published in the American Journal of Ophthalmology, we developed a reliable endophthalmitis rabbit model in which we introduced a bacterial isolate into the rabbit’s anterior chamber (n=60).

Obviously, the preferred method to test our hypothesis would have been to do a masked, randomized, prospective human trial, instead of using an animal model. Since endophthalmitis is relatively rare, a proper, prospective study of this complication in patients unfortunately is not feasible. To do this study effectively, in which just one variable is changed, would require an enormous effort with between 50,000 and 70,000 patients.

In the first experiment, we administered four drops of moxifloxacin 0.5% (Vigamox*) starting with a drop beginning one hour prior to introduction of the endophthalmitis-causing bacteria and then continuing every 15 minutes until the procedure. In the control animals we used this same protocol but administered four saline drops.

The bacteria we chose was an actual clinical isolate of Staphylococcus aureus that had caused endophthalmitis in a patient. After we injected 5,000 bacteria into the anterior chambers of these rabbits, we again put in a drop of either moxifloxacin 0.5% (Vigamox) or saline solution.

Following the procedure, the tested agents, either moxifloxacin 0.5% or saline were continued every four hours in each group respectively. At the 24-hour mark we had two ophthalmologists examine the eyes in a masked fashion to look for clinical evidence of endophthalmitis.

The various parameters that we graded in our exams included blepharitis, conjunctivitis, corneal clarity, dilated iris vessels, cell and flare, hypopyon, vitritis, and retinal or choroidal signs of inflammation or infection. The rabbits then had cultures taken from the anterior and posterior chambers. Thus, in addition to clinical signs, we also had a bacteriologic end-point for the study.

Prophylactic protection

Our results were dramatic. We showed that the eyes did best when we administered the prophylactic antibiotic moxifloxacin 0.5% (Vigamox) both before and after the injection. We termed it ‘Full Prophylaxis.’

The evidence from our clinical observations were striking, with 100% of those eyes that received the saline developing obvious clinical signs of endophthalmitis, while none of those eyes that received the moxifloxacin 0.5% (Vigamox) developed the clinical signs. (Figure 1)

Unfortunately we have no current way of knowing whether other antibiotics would have a similar effect. We do believe, however, that there are several reasons why Vigamox may have been able to prevent endophthalmitis in this study.

First of all, moxifloxacin has excellent activity against gram-positive bacteria such as Staphylococcus aureus. Multiple studies have shown that 94% of post-operative endophthalmitis is caused by gram-positive pathogens. Secondly, fluoroquinolones in general, and Vigamox in particular, have an excellent ability to penetrate into ocular tissues. So if you combine those two characteristics in an antibiotic then, potentially, as we have shown, you will be much better able to prevent endophthalmitis.

We believe this study is particularly important because it is the first time that there is evidence, in either a rabbit model or in humans, that antibiotics alone can make a difference in preventing endophthalmitis.

Francis S. Mah, M.D.

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With cataract surgeons more likely than ever to use clear corneal incisions, rates of endophthalmitis appear to be on the rise. Although I. Howard Fine, M.D., first introduced this technique in 1991, it was not until the late 1990s that it was fully adopted. During this period, the incidence of endophthalmitis has been increasing, according to a recent survey conducted by Peter J. McDonnell, M.D., and Emily West, M.D., based on analysis using the U.S. Medicare database of patients undergoing modern cataract surgery.

One important factor linked to the rise in infection appears to relate to leaking corneal wounds that allow inflow of contaminated fluid from the ocular surface. Clear incisions rely on a normal or higher intraocular pressure to close them adequately. If the patient blinks or rubs the eye, an external pressure is applied in the post-operative period that lowers the internal pressure. Fluid contaminated with microorganisms can then enter the eye through the leaking incision and, depending on the inoculum size, exceed the capability of the normal defense mechanisms to clear them from the aqueous humor, thereby increasing the likelihood of endophthalmitis.

In seeking to keep these increasing rates of endophthalmitis under control, together with the potential association with clear corneal incisions, I felt that it was important to consider what role prophylactic treatment with new, fourth-generation fluoroquinolones might play. I was intrigued by the idea of not just decreasing surface contamination pre-operatively, but, for the first time, also being able to eradicate bacteria in the aqueous humor with sufficiently high concentrations of antibiotics from the topically administered route.

Evaluating fluoroquinolone activity

Fluoroquinolones are concentration dependent killers, meaning the greater their levels at the target site, the greater their activity. The degree of microbiological activity can be quantifiably measured in vitro through minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC), and, ultimately, mutant prevention concentration (MPC). The definitions of these parameters are as follows:
- **Minimal Inhibitory Concentration (MIC):** The minimum concentration of antibiotic that is required in order to inhibit the growth of a particular pathogen. The lower the number, the more potent the antibiotic;
- **Minimal Bactericidal Concentration (MBC):** The minimum concentration of antibiotic that is required to not just inhibit, but also to kill pathogens. As for a MIC, the lower the number, the more potent the antibiotic. The relevant literature indicates that a fluoroquinolone’s MBC against a particular bacterium is typically four times its MIC against that pathogen.
- **Mutant Prevention Concentration (MPC):** The actual concentration that is required to prevent the survival and emergence of mutant strains. As with the prior two definitions, the lower the number, the more potent the antibiotic. Fluoroquinolone MPCs are typically eight to 10 times the MIC. (Figure 1)

The definitions above outline the importance of reaching sufficiently high concentrations in the relevant tissues. For ophthalmologists, the greater the concentration, the greater the protection against post-operative infection. Older-generation fluoroquinolones often have reached and exceeded their MICs and, at times, even MBCs and MPCs in the ocular surface and into the cornea, but were ineffective doing so in the anterior chamber.

With the fourth-generation fluoroquinolones now available, can these new agents achieve therapeutic...
levels in the aqueous humor with topical dosing at routine frequencies administered just prior to modern cataract surgery performed under topical anesthesia with phacoemulsification and foldable IOL implantation through a clear corneal incision approach?

A comparison of penetration levels

In order to answer this question, our investigation team at The Wilmer Eye Institute, Baltimore, including Dianne Kim, M.D., Walter Stark, M.D., and I decided to launch a prospective, double-masked, parallel group study in patients undergoing routine cataract surgery at Johns Hopkins Hospital, with dosing that is typically the same as found in surgical centers around the country.

This was a comparative study that assessed the achievable concentrations of the commercial preparations of Vigamox (moxifloxacin 0.5% non-preserved, Alcon, Fort Worth, Texas) and Zymar†, (gatifloxacin 0.3% preserved with benzalkonium chloride 0.005%, Allergan, Irvine, Calif.).

Specimens of aqueous humor were obtained at the time of the initiation of the incision, and these specimens were then analyzed in a standardized assay for determination of drug concentration. Our study results disclosed that the achievable concentrations for Vigamox in the aqueous humor were nearly four-fold greater than for Zymar dosed at the identical frequency. (Figure 2)

While the differences in concentration in the commercial preparations of 0.3% versus 0.5% would make one suspect that the Vigamox would attain a slightly higher degree of concentration in the aqueous humor, we did not expect to see a four-fold difference. This indicates that there may be greater intrinsic solubility with Vigamox than with Zymar, accounting for this improved pharmacokinetic observation of achievable drug concentration.

I see this as a clinically relevant difference and one that is encouraging because the achieved levels of moxifloxacin not only exceeded the minimal inhibitory concentration (MIC) of the most commonly found susceptible bacteria, but also exceeded the minimal bacterial concentrations (MBC), and the mutant prevention concentrations (MPC). Similarly high, potentially protective concentrations were not achieved with identical dosing in eyes administered Zymar.

Additionally, moxifloxacin was the only fourth-generation fluoroquinolone to achieve its MICs even against fluoroquinolone-resistant staphylococcus aureus.

This is the first time that a topically applied fluoroquinolone has been capable of achieving such results. I think that this is good news not only for cataract surgeons, but also for the biosphere at large in that as responsible users of antimicrobial agents, ophthalmologists hopefully are not contributing to the alarming increase in resistance by achieving levels of moxifloxacin that exceed the mutant prevention concentration.

Topical dosing of Vigamox prior to cataract surgery achieves levels that kill the most likely bacteria gaining entry into the aqueous humor and, simultaneously, prevents surviving bacteria from undergoing mutation to become resistant. These results show, for the first time, the capability of providing superior protection with moxifloxacin by virtue of the extraordinarily favorable pharmacodynamic profile.

Overall, I see the results of our study as demonstrating a clinically relevant difference in terms of penetration into the aqueous humor between Vigamox and Zymar that provides cataract surgeons with valuable information in terms of trying to prevent infection in their patients undergoing clear corneal cataract surgery.
The new fourth-generation antibiotics have potential to be ideal for ophthalmic procedures. In clinical studies they have proven to be very effective, safe, non-toxic, and well tolerated. While these are certainly safe and effective proven qualities for most ophthalmic procedures, I wanted to ensure the same held true for LASIK. Therefore, I joined my colleagues to undertake a study on this.

With elective procedures such as LASIK, we need to meet even higher standards when selecting an antibiotic for prophylactic use. If we’re using an antibiotic that in any way causes patients discomfort or blurred vision, it may make them unhappy with their experiences, and they may dissuade others from undergoing the same procedure. Also, we must remember that while infection rates, fortunately, are extremely low with LASIK, they must remain so in order to remain a viable elective procedure.

When you perform an elective procedure, it’s imperative that you have an antibiotic that has a very broad spectrum and is especially effective in battling common, opportunistic bacteria. This means you need a drug that has good coverage of both gram-positive and gram-negative pathogens, and has at least some coverage on atypical mycobacterium that have been found in as many as 50% of cases. Also, you want antibiotics that are least likely to result in drug resistance.

When you weigh all of these factors, the fourth-generation fluoroquinolones really shine. These drugs have a broad spectrum, they offer some effect against the atypical mycobacterium and, because of their method of action, they’re less likely to develop resistance.

We already have concerns about resistance with the third-generation (Figure 1). Fourth-generation fluoroquinolones have two modes of action. To get around those would mean that the bacteria would have to undergo at least two separate mutation cycles.

Studying safety
I don’t believe even practitioners understand how well tolerated these fourth-generation drugs are in the LASIK population. All of the previous research done was performed either in animals, in the laboratory, or in cataract patients.

The LASIK patient provides a unique challenge because of the microkeratome cut which creates a space for potential microorganism sequestration and proliferation deep within the stroma.

I felt that it was important to launch a small but significant randomized, prospective, masked study that targeted this unique LASIK population, and to see if there were any differences between the two fourth-generation agents, Vigamox and Zymar. The single-center study, which included 60 eyes in 30 patients, was a contralateral one — we instilled Vigamox in one eye and Zymar in the other. While we didn’t do a direct comparison to any third-generation or other antibiotics, we did have quite a bit of clinical history from which to draw.

We wanted to determine if there was a difference in how well each drug was tolerated and if there was anything out-of-the ordinary in the healing profile from what we’d previously seen in clinical trials with Tobradex® (Alcon) or Quixin® (Santen, Napa, Calif.).

We evaluated criteria such as slit lamp findings, conjunctival injection, corneal staining, corneal edema, comfort of one eye versus the other, grittiness, dryness, scratchiness, pain, and any other difference between their eyes that was significant at any level. In evaluating these factors, we found no significant differences between Vigamox and Zymar — both were extremely safe in this population. Also, we found no significant differences compared to our experience with third-generation agents.

I believe that these findings are a real boon for refractive surgeons. These results have bolstered my confidence in how these fourth-generation agents will perform in my LASIK patients. I would, of course, welcome further studies.

Currently, my personal preference is to use Vigamox which has a more neutral PH balance than Zymar. I also like the fact that Vigamox is a self-preserved antibiotic, free of the toxic BAK preservative which has been known to harm epithelial cells.

I continue to feel very comfortable using Vigamox not only for my LASIK patients, but also for cases of CK and burgeoning refractive lensectomy cases. We are in the process of doing studies for surface ablation to see if we have similar results.
A special report… The latest science on ophthalmic fluoroquinolones

"My overall conclusion from our own extensive work is that we don’t find that these fourth-generation fluoroquinolones appear to effect any wound healing in the PRK models."

Richard W. Yee, M.D.

Richard W. Yee, M.D. is the Joe M. Green endowed chair of the department of ophthalmology and visual science at the University of Texas Health Science Center at Houston, and director of the laser vision correction center at the Hermann Eye Center.

A look at fourth-generation wound healing effects in PRK patients

By Richard W. Yee, M.D.

PRK, which was fading from the refractive scene as recently as two years ago, is again on the rise thanks to practitioners trying to circumvent LASIK complications and minimize HOA induction caused by flaps.

I see more and more physicians in the area in which I live advertising that they offer a safer laser vision correction from “flapless LASIK.”

While there are numerous advantages to PRK, we must also be more cognizant about wound healing with the procedure.

With two new, fourth-generation agents available, we wanted to know if either of the two had less of a toxic effect than other. This seemed especially important since Vigamox does not contain the BAK preservative found in Zymar.

We independently decided to launch an initial investigation spurred on by concerns that if either of these drugs delayed wound healing they might cause scarring or haze development which would diminish acuity, cause regression, and induce additional higher order aberrations.

This initial study involved an in vitro tissue culture model that used a human epithelial immortalized cell line. We took 160 tissue culture wells and laced the wells with epithelial cells. Then we exposed them to undiluted Vigamox and Zymar for five minutes and 15 minutes.

In looking at the relative differences of the antibiotic comparisons, we found that Vigamox was less toxic than Zymar. This was consistent with what we might have assumed to have occurred since Vigamox does not include the BAK preservative.

We then went to the next step, studying the wound healing effects of Vigamox, Zymar, and Quixin, in 32 white leghorn chickens.

After undergoing transepithelial PRK, the chickens were randomized so that each received one drop of antibiotic four times a day in one eye, and balanced salt solution in the other eye. When we compared the rates of healing among these three fluoroquinolones, we found no significant difference between the treated and the control eyes. (Figure 1)

Studies in patients

Ultimately, we went to a human model in work sponsored by Alcon and Allergan to confirm that there was no toxicity of these medications. We performed PRK in both eyes of 38 patients who were randomly assigned to receive either Vigamox or Zymar until their epithelium healed.

We deliberately opted to study patients, not eyes, to eliminate potential inaccuracies resulting from variation within patients eyes, patient error, and the possibility of a cross-over effect.

Beginning three days before surgery, each patient administered the assigned antibiotic four times a day in a masked fashion. Patients were then treated using a 9 mm chemical debridement, with 20% alcohol for 60 seconds. In this protocol no soft contact lens was used. Following the procedure the patients continued with their assigned antibiotic which they took together with Pred Forte 1%, four times a day for seven days.

Our results showed no significant difference in wound healing rates between these two fourth-generation agents. (Figure 2) At one month, we found no difference in the haze grading between the two groups, or in uncorrected visual acuity.

My overall conclusion from our own extensive work is that we don’t find that these fourth-generation fluoroquinolones appear to effect any wound healing in the PRK models. I would certainly feel comfortable using either agent after refractive surgery — without concerns about wound healing.

Figure 1: Animal models of epithelial wound healing provide relevant clinical data.

- Transepithelial PRK on 32 White leghorn chicken eyes
- Antibiotics QID until healed: moxifloxacin, gatifloxacin, levofloxacin & BAK (control)
- Wound healing rates and time to wound closure were measured via digital images
- Results: No significant difference found in treated group vs control.

Figure 2: Epithelial Wound Healing In Humans After PRK
LASEK wound healing with fourth-generation fluoroquinolones

By William Trattler, M.D.

More and more practitioners are now taking another look at their surface ablation roots, opting for new advanced LASEK procedures over LASIK. Many practitioners are realizing that with new advanced surface ablation procedures they can attain very good quality of vision while avoiding the risks of LASIK such as flap complications and keratectasia.

However, in order to maximize results with any surface ablation procedure, practitioners need to be cognizant of epithelial healing rates. Anything that slows down the healing rate may lead to corneal haze and that potentially can result in some loss of best-corrected acuity. To avoid this healing issue, it can be helpful to identify those patients who may be at particular risk for slower epithelial healing — for example, diabetic patients and those with dry eye — and take steps to forestall epithelial healing problems.

Looking for fast epithelial healing

Since maximizing epithelial healing is so important with surface laser procedures, and with the mounting popularity of the new fourth-generation agents, my colleagues and I at the Center for Excellence in Eye Care, Miami decided to embark on a study to determine if either of the fourth-generation regimens would promote quicker recovery of the epithelium.

We included in the prospective study 30 consecutive patients who were having bilateral LASEK and who agreed to be enrolled. This was a single-center, investigator-masked trial. As part of the protocol we performed preoperative Shirmer’s tests on all patients and identified patients with complaints of dry eye. Patients with dry eyes were pretreated with punctal plugs and provided lubricating drops prior to surgery.

My LASEK technique included applying dilute alcohol on an 8 mm sponge, and then placing this on the cornea to loosen the epithelium. I then made a superior-hinge LASEK flap. Using a hockey stick spatula, I slid the epithelium. Then after drying the stromal bed, the laser treatment was applied, and I smoothed it back into place. A bandage contact lens (BioMedics 55*) was placed on the eye, and this lens was kept in place until the epithelium was completely recovered (between 4-8 days).

After undergoing LASEK (Figure 1) the patients were then randomized to receive Zymar and other Allergan medications in one eye and Vigamox and those who did better with the Zymar. A good number of patients showed identical results in both eyes. The contact lens was only removed when the epithelium had re-healed and smoothed over. I found that it took an average of 5.5 days for the epithelium to heal with Vigamox, and 5.65 days to heal with Zymar. (Figure 2) With the Vigamox the range of time to healing was four to seven days and with the Zymar it was four to eight days. Our conclusion was that following LASEK the time to re-epithelialization with Vigamox and Zymar regimens is equivalent.

Overall, I think the key to achieving the best possible vision with LASEK is to work hard to encourage rapid epithelial healing. My experience with both fourth-generation agents has been very favorable.

Overall, I think the key to achieving the best possible vision with LASEK is to work hard to encourage rapid epithelial healing. My experience with both fourth-generation agents has been very favorable.

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