Dear Colleagues,

The 2006 Association for Research in Vision and Ophthalmology (ARVO) annual meeting is around the corner. When you travel to Ft. Lauderdale, Fla., this year you may wish to focus on several landmark studies. These add to our knowledge and may potentially change our practices relevant to the prevention of serious ocular infections and the optimal use of both anti-infectives and anti-inflammatory medications for enhancing our surgical outcomes.

This pamphlet briefly describes some of the studies that will be featured at this scientific meeting.

See you there,

Kerry Solomon, M.D.
Associate Professor of Ophthalmology
Storm Eye Institute
Medical University of South Carolina

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**Teaming Ketorolac With Multifocal IOL Improves Outcomes**

By Eric Donnenfeld, M.D. and Kerry Solomon, M.D.

Intraocular lens surgeons in search of an edge to improve patients’ outcomes may benefit from adding a topical NSAID to their routine. Our recent research found the pre-op and post-op use of ketorolac tromethamine 0.4% (Acular LS, Allergan, Irvine, Calif.) significantly improved visual outcomes in patients bilaterally implanted with the ReSTOR multifocal IOL.

**The study**

The study, accepted for presentation at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), in Fort Lauderdale, Fla., sought to evaluate the effect of a topical non-steroidal anti-inflammatory drug (NSAID) on quality of vision and macular thickening with a multifocal IOL. We already know that patients treated with NSAIDs have less CME, less pain, and shorter surgical times, but we wanted to understand the effect of Acular LS on visual acuity, contrast sensitivity, and foveal thickness.

The multicenter, randomized, masked prospective clinical trial evaluated the effect of ketorolac tromethamine 0.4% (four times a day for three days pre-op and three weeks post-op) versus placebo on the quality of vision in 50 patients bilaterally implanted with the ReSTOR multifocal IOL (Alcon, Fort Worth, Texas).

Uncorrected visual acuity, best-corrected visual acuity, and mesopic and photopic contrast sensitivity under high contrast and low contrast illumination had statistically significant improvement with ketorolac versus patients who received a placebo.

We were surprised that the impact of the NSAID was even greater than we expected. The findings highlight that patients who have multifocal IOLs have stressed visual systems, and even minimal CME causes a more significant reduction in the quality of vision than it would in the average patient.

The study also highlights that ophthalmology’s definition of cystoid macular edema (CME) is very old and out dated. What was considered sub-clinical CME is probably very much medical CME. The impact is that surgeons need to more aggressively treat and prevent CME from occurring.

Cystoid macular edema’s importance will only increase as we continue to aggressively raise our outcome measurements and strive for 20/20 vision in all IOL recipients. To this end, we will need to raise the bar accordingly with our therapeutics.

The study, “The Effect of a Topical NSAID, Ketorolac Tromethamine 0.4%, on Quality of Vision with a Multifocal IOL,” was authored by Eric Donnenfeld, M.D., Kerry Solomon, M.D., and Ralph Chu, M.D.

Eric D. Donnenfeld, M.D. is a founding partner of Ophthalmic Consultants of Long Island and Connecticut, and co-chairman, Cornea at Nassau University Medical Center.

“Uncorrected visual acuity, best-corrected visual acuity, and mesopic and photopic contrast sensitivity under high contrast and low contrast illumination had statistically significant improvement with ketorolac versus patients who received a placebo.”

Eric Donnenfeld, M.D. and Kerry Solomon, M.D.
More Prostaglandin Inhibition and Penetration with Ketorolac than Nepafenac

By: Frank A. Bucci, Jr. M.D. and L. David Waterbury Ph. D.

A comparison of two topical NSAIDs, ketorolac tromethamine 0.4% (Acular LS, Allergan, Irvine, Calif.) and nepafenac 0.1% (Nevanac, Alcon, Fort Worth, Texas), demonstrates that ketorolac likely inhibits PGE2 to a greater extent than nepafenac.

Methods
The single center, randomized, double-masked study looked at 82 patients who received either ketorolac 0.4% or nepafenac 0.1% three times daily for two days pre-op and four drops in the hour prior to cataract surgery. Aqueous samples (.15cc) were collected with a 30-gauge needle attached to a TB syringe. Following collection, aqueous samples were stored at -60° C prior to analysis. Aqueous humor was diluted 1:10 in buffer and then assayed in duplicate for PGE2 by using a competitive enzyme immunoassay using a monoclonal antibody.

Results
The analysis of 82 patients (n=42 ketorolac and n=40 nepafenac) showed that prostaglandin levels in ketorolac-treated eyes were significantly more likely to be below the level of detection (<100 pg/ml) than in nepafenac-treated eyes. The study found that 26 of 42 (64%) of ketorolac-treated eyes had prostaglandins below the level of detection compared with seven of 40 (17.5%) nepafenac eyes. The mean PGE2 value in the ketorolac-treated eyes was 159.5 + 114.6 pg/ml and 322.3 pg/ml + 197.8 pg/ml in the nepafenac-treated eyes (p=.001).

Discussion
These findings run counter to the claims that Nevanac has greater penetration into the aqueous and posterior segments of the eye. In separate testing of additional samples, Dr. Bucci also evaluated the actual penetration of both NSAIDs into the anterior chamber. We found that three times as much Acular LS was detected in the aqueous compared to amfenac, which is the active metabolite of nepafenac.

Assays were performed to detect both nepafenac and amfenac. The sum total of nepafenac and amfenac was still 40% less than the amount of ketorolac detected in the aqueous. These penetration findings, which reflect the absorption of both NSAIDs, are consistent with the findings related to prostaglandin inhibition. Inhibiting prostaglandins is critical following cataract surgery because PGE2 is a mediator of cystoid macular edema.

This study represents (to the best of the authors' knowledge) the first direct comparison of Nevanac and Acular LS in a clinical trial. These findings are noteworthy because for cataract surgeons NSAIDs provide benefits beyond just preventing postop CME, including decreasing intraoperative miosis, accelerating resolution of post-operative inflammation, and decreasing postoperative discomfort. There is also a growing realization that sub-clinical swelling frequently occurs in the weeks after cataract surgery, which delays the recovery of full visual potential and increases the probability that the patient may experience “full blown CME.”

It should also be noted that NSAIDs provide optimal surgical outcomes for cataract surgeons when used in conjunction with topical steroids. It has been shown frequently that there is a synergistic effect when topical non-steroidal and topical steroids are used together following cataract surgery.

As mentioned above, NSAIDs can effectively inhibit any discomfort associated with refractive surgeries (e.g., RK, AK, PRK, and LASIK), which are performed on the ocular surface. Non-steroidal such as Acular and Voltaren have almost a 15-year track record of effectively controlling postoperative discomfort and pain following various refractive surgeries performed on the ocular surface. There have been some recent reports of delayed epithelial healing and sub-epithelial scarring in PRK patients using Nevanac post-operatively.

In summary, these findings have clearly demonstrated superior prostaglandin inhibition and superior ocular absorption of Acular LS in comparison to Nevanac and its metabolite amfenac. These findings continue to support Dr. Bucci’s current regimen of Pred Forte and Acular LS following phacoemulsification.

Frank A. Bucci, Jr. M.D., and L. David Waterbury, Ph.D.

The study, “PGE2 Inhibition of Two Topical NSAIDs in Cataract Patients,” was authored by Frank A. Bucci, M.D. and L. David Waterbury, Ph.D.

Frank A. Bucci, Jr. M.D., founded the Bucci Cataract and Laser Vision Institute in Wilkes-Barre, PA.

L. David Waterbury, Ph.D., is a pharmacology consultant based in San Carlos, CA.

“We found that three times as much Acular LS was detected in the aqueous compared to amfenac, which is the active metabolite of nepafenac.”

Frank A. Bucci, Jr. M.D., and L. David Waterbury, Ph.D.
Ketorolac vs. Nepafenac Study: Toxicity Delays Epithelial Healing in Nepafenac-Treated Eyes

By William Trattler, M.D.

In a double masked comparison of ketorolac tromethamine 0.4% (Acular LS, Allergan, Irvine, Calif.) and nepafenac sodium 0.1% (Nevanac, Alcon, Fort Worth, Texas) on post-op healing rates and pain control in Epi-LASIK surgery, nepafenac therapy resulted in delayed healing compared with ketorolac in the first seven patients. Ketorolac also provided greater relief of patient pain and foreign body sensation following surface ablation than did nepafenac.

While the epithelial delays with Nevanac were surprising, the results did confirm some previous anecdotal reports.

The study

The prospective, randomized, double-masked, paired-eye comparison was planned for 60 eyes of 30 patients undergoing flapless Epi-LASIK. They were randomized to receive ketorolac in one eye and nepafenac in the other. Drops were instilled immediately following the surgical procedure prior to bandage contact lens placement, and patients continued to instill the masked drops three times daily for five days.

Study follow-up visits were conducted at day one and day five post-op. Patients with delayed epithelial healing were seen daily until the epithelial defects had closed. Patients were also phoned to report their level of pain at five hours post-op and on days two, three, and four. Outcome measures included post-op pain levels (including the need for additional rescue medications), rates of healing, and adverse events.

Results

Preliminary results showed that four of seven (57%) eyes treated with Nepafenac experienced significant delays in epithelial healing ranging from two to seven days. In contrast, there were no delays in epithelial healing in the seven eyes treated with ketorolac.

The mean time to epithelial healing in eyes treated with ketorolac 0.4% was 5.7 days, compared to 7.9 days in eyes treated with Nepafenac. Due to the significant delays in epithelial healing, the study was halted.

Patients consistently reported more discomfort — pain, foreign body sensation, burning, and photophobia — in eyes treated with nepafenac as compared to the eyes treated with ketorolac. On day one, the average pain score (scale of 0 to 10, with 10 being the worst pain of their life) was 0.5 with ketorolac and 1.42 with nepafenac (p = 0.042). Scores for burning, foreign body sensation and photophobia all favored ketorolac although these scores were not statistically significant.

By the second day post-op, the mean pain score was 1.42 with nepafenac and 0.83 with ketorolac, and the mean burning score 1.38 with nepafenac and 0.63 with ketorolac (p = 0.066). Similarly, the mean foreign body sensation and photophobia scores favored ketorolac, although these scores were not statistically significant.

These findings build on incredible progress in recent years in our ability to increase patient comfort after surface ablation. The drugs that were the subjects of this study represent the latest efforts to continue advances in pain and discomfort avoidance, so a first-time clinical comparison is critical to understand the relative benefits of both the standard non-steroidal that is approved by the Food and Drug Administration for pain after refractive surgery, and the newest non-steroidal drops.

Because this study was limited by the toxicity issue, additional research is required to more clearly address whether differences exist in the drugs' pain control and patient comfort levels. Future reports will also collect and analyze toxicity and delayed healing reports from surgeons nationwide.

The study "Double Masked Comparison of Ketorolac Tromethamine 0.4% versus Nepafenac Sodium 0.1% for Postoperative Healing Rates and Pain Control in Eyes Undergoing Flapless Epi-LASIK" was authored by Margaret McDonald, M.D., and William Trattler, M.D.

Disclosures: This research project was supported with an educational grant from Allergan. Dr. Trattler has received honoraria from Alcon, Allergan, and Ista pharmaceuticals over the last year.

William Trattler, M.D. is the Cornea Specialist at the Center For Excellence In Eye Care in Miami, Fla. Dr. Trattler is a volunteer assistant professor at Bascom Palmer Eye Institute.

5 days after Epi-LASIK, the Nevanac-treated eye (left) displays an epithelial defect compared to no defect in the Acular LS-treated eye (right).
Gatifloxacin Plus BAK Versus Gatifloxacin or Moxifloxacin Alone Against MRSA

By Joseph M. Blondeau, Ph.D.

Ophthalmologists have a strong ally in the fight against methicillin-resistant Staph. aureus (MRSA) based on recent in vitro efficacy findings for gatifloxacin with benzalkonium chloride (BAK).

The study
As part of an evaluation of antimicrobial efficacy of gatifloxacin with and without BAK and unpreserved moxifloxacin against MRSA, 67 clinical isolates of MRSA were evaluated. The study of MRSA clinical isolates, scheduled to be presented at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Fort Lauderdale, Fla., found the combination of gatifloxacin and BAK provided MIC (minimum inhibitory concentration) values that were approximately 2- to 500-fold better than the MIC values provided by gatifloxacin or moxifloxacin alone.

In light of the appearance of increasingly resistant pathogens in eye diseases, the findings have clinical relevance for ophthalmologists because commercial gatifloxacin ophthalmic solution (Zymar, Allergan, Irvine, Calif.) is preserved with 0.005% BAK, while commercial moxifloxacin (Vigamox, Alcon, Fort Worth, Texas) is unpreserved.

The study used MIC testing by microbroth dilution in accordance with the recommended CLSI procedure. Approximately 105 colony forming units per milliliter (CFU/ml) of clinical isolates of MRSA (collected through the Department of Clinical Microbiology, Royal University Hospital, Saskatoon, Canada) were added to Mueller-Hinton broth containing two-fold concentration increments of the drugs.

We added 2.5 microliters of a 10% solution of BAK along with gatifloxacin to the first well of the plate to give a BAK concentration of 0.125% and then serially diluted it with the drug after an organism was added to each well. Plates were incubated for 18 hours in ambient air, and the lowest concentration showing no growth was recorded as the MIC.

In a series of separate experiments, the growth of 30 MRSA isolates was tested in appropriate media containing two-fold concentration increments of gatifloxacin. Each well was adjusted to contain 0.005% BAK—the percentage in Zymar.

Results
The study results showed that the combination of gatifloxacin and BAK was more efficacious in vitro than either fluoroquinolone without BAK. MIC values ranged from ≤0.008 micrograms/ml to 0.125 micrograms/ml for gatifloxacin plus BAK, from 0.063 micrograms/ml to ≥8 micrograms/ml with unpreserved gatifloxacin, and from ≤0.016 micrograms/ml to 16.0 microgram/ml with moxifloxacin. These values for unpreserved gatifloxacin and moxifloxacin are consistent with MIC values previously reported from our laboratory on clinical isolates of MRSA (Metzler et al, International Journal of Antimicrobial Agents, 2004;24:161-167).

Thirty independent MRSA isolates failed to grow in the presence of 0.005% BAK with concentrations of gatifloxacin ranging from 0.016 micrograms/mL to 2 micrograms/mL. Viable MRSA were recovered from only five of 48 wells.

Some of our previous research found the addition of BAK to gatifloxacin reduced the MICs of these ocular pathogens to values that were lower than the MICs of both gatifloxacin and moxifloxacin alone. When we started to test resistant strains in the presence of gatifloxacin and moxifloxacin, with or without BAK, we noticed that the MICs in the presence of BAK were reduced, regardless of whether the organism was susceptible or resistant to the parent drug.

According to our searches, this is a fairly new area of investigation for us and in the peer-reviewed literature. Although BAK has been around for many years and some of the antimicrobial properties of BAK have been known, its application in this study appears to be breaking new ground.

The study, “Antimicrobial Efficacy of Gatifloxacin with and without Benzalkonium Chloride Compared with Moxifloxacin Against Methicillin-Resistant Staphylococcus Aureus” was authored by Joseph M. Blondeau, Ph.D. and Shantelle Borsos, BsC.

Joseph Blondeau, Ph.D., is a clinical microbiologist and head of clinical microbiology at Royal University Hospital and the Saskatoon Health Region in Saskatoon, Saskatchewan, Canada.
The addition of benzalkonium chloride (BAK) to gatifloxacin appears to have a synergistic effect against one of the most common types of infections faced by ophthalmologists.

Gatifloxacin 0.3% ophthalmic solution with 0.005% BAK (Zymar, Allergan, Irvine, Calif.) showed greater efficacy against gram-positive species than did moxifloxacin 0.5% ophthalmic solution (Vigamox, Alcon, Fort Worth, Texas). This superior potency was demonstrated for both Zymar and for gatifloxacin powder plus 0.005% BAK, which suggests that gatifloxacin and BAK work synergistically to lower MICs.

The study
Our study, scheduled to be presented at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), in Fort Lauderdale, Fla., examined efficacy of different formulations of antibiotics against some of the most common causes of ocular infections: Staph. epidermidis, Staph. aureus (methicillin sensitive and methicillin resistant), Strep. pneumoniae, and Strep. viridans.

We determined the minimal inhibitory concentrations (MICs) against these species for the ophthalmic formulations of fourth-generation fluoroquinolones gatifloxacin 0.3% ophthalmic solution (Zymar), and moxifloxacin 0.5% ophthalmic solution (Vigamox) as well as MICs for solutions prepared from injectable powder forms of gatifloxacin and moxifloxacin. We also investigated the effect of BAK on MIC values because gatifloxacin 0.3% ophthalmic solution is preserved with 0.005% BAK.

We analyzed ocular isolates of each species and determined MICs by micro dilution methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. BAK was 0.005% when present. Eighteen-hour cultures of the test strains were diluted to approximately 105 CFU/mL for inoculation. Assays were incubated overnight at 37° C and growth determined both spectrophotometrically and by plating MIC test wells onto blood agar.

Results
Among gatifloxacin powder, moxifloxacin powder, and Vigamox, MICs for Staph. epidermidis ranged from 0.24-0.98 micrograms/mL, MICs for methicillin-sensitive Staph. aureus ranged from 0.06-0.24 micrograms/mL, MICs for methicillin-resistant Staph. aureus ranged from 1.95-15.6 micrograms/mL, MICs for Strep. pneumoniae ranged from 0.01-0.49 micrograms/mL, and MICs for Strep. viridans ranged from 0.12-0.49 micrograms/mL.

MICs for Zymar, which contains BAK, and gatifloxacin powder supplemented with BAK were < 0.03 micrograms/mL for all strains tested. For all but two strains examined, the MIC for gatifloxacin 0.3% ophthalmic solution plus BAK was 2- 260-fold less than for Vigamox. The addition of BAK to gatifloxacin powder resulted in a similar improvement in MIC values.

We saw that the Zymar formulation much more effectively inhibits and kills these organisms than does Vigamox. In addition, when we looked at gatifloxacin and moxifloxacin powders, the efficacy was about the same. When BAK was added to gatifloxacin powder, the inhibition and the killing was a lot greater than the moxifloxacin by itself.

These results were logical based on BAK’s composition, but the extent to which the minimum inhibitory concentrations were lowered was surprising to us. We reported less than .03 micrograms/mL, but subsequent results have continued to move much lower. More recent findings have determined that it is 100-fold lower than in the research planned for presentation. It was surprising how low the MIC went and just how effective it was.

The research was conducted at the Department of Ophthalmology, University of Oklahoma Health Sciences Center, Molecular Pathogenesis of Eye Infections Research Center, Dean A. McGee Eye Institute, Oklahoma City, Okla.

The study, “Efficacy of Fourth-generation Fluoroquinolones Against Gram-positive Species Commonly Involved in Ocular Infections,” was authored by Michelle C. Callegan, Ph.D.

Michelle Callegan, Ph.D., is associate professor in the Departments of Ophthalmology, Microbiology & Immunology, and Oklahoma Center for Neuroscience.
Gatifloxacin Effectively Prevents Endophthalmitis

By Luis E. Fernández de Castro, M.D.

In a recent study, rabbit eyes treated with gatifloxacin (Zymar, Allergan, Inc., Irvine, Calif.) demonstrated significantly less inflammation, infection, and culture positive endophthalmitis compared to those of the control animals. The findings indicate further investigation is needed to fully understand the clinical implications from this prophylactic study.

The study
The study, scheduled to be presented at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), in Fort Lauderdale, Fla., is titled “Prevention of Staph. aureus Endophthalmitis with Topical Gatifloxacin in a Rabbit Prophylaxis Model.”

The study’s findings are significant because the management of post-op bacterial endophthalmitis is associated with a poor visual outcome, but the selection and role of therapeutic modalities have remained controversial. Previous studies have supported the hypothesis that the most common source of post-op endophthalmitis is the patient’s external flora. Because of this, a variety of bacterial endophthalmitis prophylaxis measures are practiced.

The study randomly placed 40 New Zealand white rabbits into Group A (20 rabbits), where they received one drop of 0.3% gatifloxacin in their right eye every 15 minutes for 45 minutes, and Group B (20 rabbits), where they received one drop of balanced salt solution in their right eye every 15 minutes for 45 minutes. The anterior chamber of each rabbit was injected with 0.025 mL saline containing 5 x 105 colony forming units of a clinical isolate of Staph. aureus (vancomycin sensitive) following this treatment regimen. After the inoculum injection the treatment regimen continued immediately post-injection, six, 12, 18, and 24 hours post-op.

A masked examiner then photographed, anesthetized, and euthanized the animals. The aqueous and vitreous humors were collected to determine the number of viable bacteria.

Results
The study demonstrated significantly fewer signs of endophthalmitis and fewer culture positive gatifloxacin eyes when compared to the control eyes. This indicates that topical prophylaxis with gatifloxacin can reach levels in the anterior chamber that can reduce bacterial numbers.

The median clinical scores for the gatifloxacin group were significantly lower than the control group (P <.05). Bacterial recovery of Staph. aureus was significantly higher in the control group in both the aqueous and vitreous humor (P <.05).

Considering that fluctuations of IOP following sutureless, clear corneal cataract surgery may allow entry of surface fluid into the anterior chamber during the initial postoperative period when the wound is not healed and that the most common route of infection is through introduction via the normal flora on the ocular surface and surrounding structures, it is important to use a fast-acting antibiotic that rapidly kills bacteria on the ocular surface.

Our previous research in this area includes treatment and prevention of mycobacterial keratitis after LASIK comparing gatifloxacin, ciprofloxacin, and amikacin. We also studied the effects in corneal wound healing of the latest generation of fluoroquinolones (gatifloxacin and moxifloxacin) and previous generation fluoroquinolones (ciprofloxacin, levofloxacin, and ofloxacin), and collagen Type IV expression in the corneal epithelium.

The study was authored by Luis E. Fernández de Castro, M.D., Helga P. Sandoval, M.D., Luanna R. Bartholomew, Ph.D., David T. Vroman, M.D., and Kerry D. Solomon, M.D. and was conducted at the Magill Research Center for Vision Correction, Medical University of South Carolina, Storm Eye Institute. Supported in part by NIH/NEI EY-014793; an unrestricted educational grant to Magill Research Center MUSC-SEI from Allergan Laboratories, Irvine, CA, USA; and an unrestricted grant to MUSC-SEI from Research to Prevent Blindness, New York, NY, USA.

Luis E. Fernández de Castro, M.D., is a research instructor at the Storm Eye Institute, Medical University of South Carolina.
Rabbit Study: BAK Significantly Enhances Gatifloxacin Against MRSA

By Francis S. Mah, M.D.

Both Zymar (0.3% gatifloxacin + 0.005% BAK) and 0.3% gatifloxacin without BAK were very effective in reducing the number of fluoroquinolone-resistant S. aureus in a recent rabbit study, but Zymar was significantly more effective than gatifloxacin without BAK.

The study
The study, scheduled to be presented at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, Fla., found 0.005% BAK significantly enhances the antibacterial efficacy of 0.3% gatifloxacin in the Staph. aureus (MRSA) NZW rabbit keratitis model. However, 0.005% BAK demonstrated no decrease in the number of colony counts compared to the control.

The findings were based on an examination of 24 NZW rabbits inoculated intrastromally in both eyes with approximately 3000 cfu of a gatifloxacin-resistant, MRSA ocular isolate. The rabbits were randomly divided into four treatment groups, each with six rabbits.

The first group was treated with Zymar (Allergan, Irvine, Calif.), while the second group was treated with 0.005% BAK. A third group was treated with 0.3% gatifloxacin (0.3% gatifloxacin in complete vehicle but without 0.005% BAK), while a final group received saline (control).

Four hours post-inoculation, topical treatment was initiated in both eyes every 15 minutes for 5 hours, with 21 total doses administered. One hour after therapy the rabbits were euthanized, and the corneas were homogenized to determine viable bacterial counts. The colony counts from both eyes were averaged, Log10 converted, and analyzed using ANOVA.

Results
The study found that even though gatifloxacin was effective, the commercial product (Zymar) killed better. When we looked at the rabbits, there was no added toxicity due to the BAK.

We could not differentiate between them clinically. But when we took the corneas and cultured the bacteria that were left in the corneas, Zymar had killed more bacteria in our model than the gatifloxacin without the BAK.

It was quite a surprising result because we anticipated a minor difference that would take hundreds of rabbits to demonstrate. But the difference was readily apparent and statistically significant.

The study found both Zymar (2.3 ± 0.8 Log10 cfu/ml) and 0.3% gatifloxacin (3.8 ± 0.4 Log10 cfu/ml) demonstrated significantly fewer mean colony counts per cornea compared to 0.005% BAK (7.4 ± 0.2 Log10 cfu/ml) and the control (7.5 ± 0.5 Log10 cfu/ml) (p=0.000, power = 1.0).

Zymar also demonstrated significantly fewer mean colony counts per cornea compared to 0.005% BAK in the NZW rabbit keratitis model than the gatifloxacin alone. There was no difference between 0.005% BAK and control.

The study’s hypothesis was based on an understanding of BAK as a preservative, which we know will prevent the growth of most bacteria, viruses, and fungi, and adding the antibiotic to BAK would enhance the killing times, prevent the contamination in the bottles, and potentially be synergistic.

The first study we conducted on the combination studied time/kill curves in various concentrations of gatifloxacin and moxifloxacin with BAK. BAK was tested, and the fluoroquinolones were tested against three different bacteria: Staph. aureus, Staph. epidermidis, and Pseudomonas. BAK helped speed the kill of the gram-positive bacteria —Staph. aureus and Staph. epidermidis— when it was added to the fluoroquinolones (gatifloxacin or moxifloxacin). That was somewhat of a surprise.

That research led to this recent study in which we wanted to move beyond a contamination model—one that examined whether the drug would kill bacteria inside a bottle a little faster—to examine whether it produced actual clinical differences.

The study, “Benzalkonium Chloride (BAK) Significantly Enhances the Antibacterial Efficacy of Gatifloxacin in the Staphylococcus aureus NZW Rabbit Keratitis Model,” was authored by FS Mah, EG Romanowski, RP Kowalski, KA Yates, and YJ Gordon, and performed at The Charles T. Campbell Laboratory, UPMC Eye Center, Ophthalmology and Visual Science Research Center, Eye and Ear Institute, Department of Ophthalmology, UPMC, Pittsburgh, PA.

Francis S. Mah, M.D., is co-medical director of the Charles T. Campbell Ophthalmic Microbiology Laboratory, University of Pittsburgh School of Medicine.
Comparing the Efficacy of Vigamox Applications—One Hour Versus One Day

According to recent research, ophthalmologists using Vigamox for endophthalmitis prophylaxis should consider extending their pre-op doses to one to three days before the procedure.

The study
The study, by Christopher Ta, M.D., compared the efficacy of a one-hour application to a one-day application of Vigamox. The findings, accepted for presentation at the 2006 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), in Fort Lauderdale, Fla., indicate a one-hour application is not effective in killing bacteria on the ocular surface.

The study included a prospective, non-randomized evaluation of 58 eyes of 29 patients scheduled to undergo intraocular surgery (cataract, glaucoma, and corneal transplant). Cultures were obtained from the palpebral conjunctival sacs in both eyes. Patients then were instructed to instill topical moxifloxacin (Vigamox, Alcon, Fort Worth, Texas) into the surgical eye four times a day, starting one day before surgery.

On the day of surgery, cultures were taken from the surgical eye, which had received Vigamox for one day prior, and the untreated fellow eye, which had not received any antibiotics. In the hour before surgery both eyes received three doses of Vigamox, given five minutes apart. At least 30 minutes following the last application of antibiotics, conjunctival cultures again were obtained from both eyes. Culture swabs were inoculated onto blood agar, chocolate agar, and Septichek culture broth, and incubated at 37°C for three, seven, and five days, respectively.

Results
The rate of positive cultures was lower in the surgical eye treated with Vigamox for one day before surgery compared to the non-surgical eye that received Vigamox only in the hour prior to surgery. The study found 38% of the cultures were positive in blood agar cultures for non-surgical eyes (one-hour dosing), and 14% were positive in the surgical eyes (1 day pre-op dosing). Similarly, 52% of one-hour-dosing eyes were positive in Septichek broth cultures, while 24% of surgical eyes were positive.

The study found that 48% of the non-surgical eyes treated with Vigamox were positive in chocolate agar cultures, and 24% of surgical eyes were positive in chocolate agar cultures.

On the day of surgery, prior to the three applications of Vigamox every five minutes, 41% of cultures for non-surgical were positive in blood agar cultures, while 24% of the surgical eyes were positive.

In baseline cultures taken from the palpebral conjunctival sacs in both eyes, 72% of the non-surgical eyes and 76% of surgical eyes were positive for blood agar cultures. Eighty-three percent of non-surgical eyes were positive for Septichek broth cultures, as were 59% of the surgical eyes. Fifty-two percent of non-surgical eyes and 48% of surgical eyes were positive for chocolate agar cultures.

“The application of topical Vigamox only in the hour prior to surgery does not appear to provide sufficient time to kill bacteria on the ocular surface,” said Dr. Ta. Kill times of Vigamox require at least one day of pre-op dosing in order to more sufficiently reduce the ocular surface bacterial flora.

According to Dr. Ta, several previous studies conducted on the effective dosing with antibiotics before cataract surgery have shown that administering topical antibiotics three days before surgery is more effective at eliminating bacteria from the ocular surface than giving it immediately before surgery. However, because many ophthalmologists frequently use antibiotics just before surgery, the current study aims to identify the effect of this on a successful dosing regimen.

This study used the standard dosing of four times a day to reflect common clinical practice and did not delve into identifying the optimum dosing frequency for these drugs. Dr. Ta emphasized that it is important to realize that the study only looked at ocular-surface bacteria, not the actual risk of endophthalmitis. Even though the study found that there are more bacteria present on the surface in the one-hour group, it does not necessarily mean there is a higher risk of infection. The ocular-surface bacteria are only a surrogate marker. There was no examination of actual rates of infection.

The study, “Prospective Comparison of 1-day vs 1-hour Pre-Operative Vigamox Prophylaxis for Intraocular Surgeries,” was authored by Christopher Ta, M.D. and conducted at the Department of Ophthalmology, Stanford University School of Medicine, Stanford, Calif.

Christopher Ta, M.D., is assistant professor, director of residency program, cornea and external diseases, department of ophthalmology, Stanford University School of Medicine, Stanford, Calif.