Clinical Study Update: Surgical Therapeutics

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Aqueous Penetration and Biological Activity of Moxifloxacin 0.5% and Gatifloxacin 0.3% Ophthalmic Solutions in Cataract Surgery Patients

This figure shows the median minimum bactericidal concentration (MBC) for gatifloxacin (ZYMAR®) and moxifloxacin (VIGAMOX® solution, Alcon, Fort Worth, Texas) against a variety of gram-positive and gram-negative organisms compared to the mean aqueous concentration levels achieved by the two fluoroquinolones in a study completed by researchers at the Wilmer Eye Institute, Johns Hopkins Bayview Medical Center, Baltimore.1

A lower concentration of moxifloxacin is needed to kill the relevant bacteria when compared to gatifloxacin, and moxifloxacin achieves higher drug levels than does gatifloxacin in the aqueous humor. These data are clinically significant as they are representative of real-life cataract surgery with human tissue concentrations for anti-infectives and potential infectious pathogens.

Physician Perspective:
Moxifloxacin shown to have greater potency and better penetration

Minimum bactericidal concentration (MBC) levels are similar to minimum inhibitory concentrations (MIC) in terms of measurement but vary slightly in what they measure. MIC levels determine how much of a particular antibiotic is necessary to inhibit the growth of specific bacteria; MBC levels determine how much of the antibiotic is necessary to kill the bacteria outright. Typically, the MBC is four to five times that of the MIC (i.e., more drug is necessary to kill than inhibit).

“MBC is a more powerful measurement,” said Stephen S. Lane, M.D., adjunct professor of ophthalmology, University of Minnesota, St. Paul. “These data have important implications with regard to postop endophthalmitis. As surgeons, we don’t want to just prevent bacteria from growing after cataract surgery; we want to kill what is there.”

Clinically, this study shows the two antibiotics tested at a dosing schedule typically seen in a clinical setting, Dr. Lane said. Most patients are dosed three to four times on the day of surgery with an antibiotic before undergoing cataract surgery, he said.

“Both fluoroquinolones have low MBC values, and they are similar with respect to common organisms,” he said. “But the green bar overlay shows that with moxifloxacin (VIGAMOX® solution, Alcon, Fort Worth, Texas) the amount inside the eye is more than enough to kill all the organisms. Gatifloxacin (ZYMAR®) doesn’t cover three of the organisms.”

The results of the study indicate that “if they’re dosed in the same amounts and dosed equally, moxifloxacin penetrates into the aqueous humor better and is therefore more available to kill bacteria than gatifloxacin,” Dr. Lane said.

The study confirms that both fluoroquinolones have good kill rates and remain effective, but “the higher penetration of moxifloxacin leads me to use it preferentially over gatifloxacin because, as this study shows, it gets into the eye better,” Dr. Lane said. “I just want to use an antibiotic that is effective against the most common organisms and gets to the potential site of these organisms in the highest concentration possible. In this way, I feel I provide the best prophylaxis for my patients.”

References

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This NSAID study evaluated the aqueous humor concentrations of commercially available NEVANAC® suspension (nepafenac 0.1%, Alcon, Fort Worth, Texas), ACULAR® LS (ketorolac 0.4%), and XIBROM® (bromfenac 0.09%) following topical administration. There were 75 patients randomized to receive one drop of the drug at 30, 60, 120, 180, or 240 minutes before surgery; aqueous humor samples were collected at the time of paracentesis.

The key finding of this study was that one drop of NEVANAC® suspension provided better bioavailability and duration in the aqueous chamber across all time points tested.

The Physician Perspective:

**NEVANAC® suspension shows greater ocular bioavailability than other NSAIDs**

Previous studies have compared the intraocular concentrations of nonsteroidal anti-inflammatory drugs (NSAIDs) to various administration schedules, but this is the first study to compare the aqueous concentrations after a single drop and over multiple time periods, said Michael B. Raizman, M.D., Ophthalmic Consultants of Boston, Massachusetts. The single-drop dosing is representative of a “real-world” setting, whereas other studies were not necessarily designed to mimic clinical settings and tended to use unrealistic pulse dosing, he said.

“We compared the NSAIDs in a uniform manner over an extended period of time, with tight time intervals,” Dr. Raizman said. The large study was both randomized and investigator masked, and all investigators were careful to take samples at multiple time points within several minutes of the designated time point, he added.

Nepafenac had an “excellent ocular bioavailability and high concentrations in the aqueous humor,” Dr. Raizman said. Of the three NSAIDs, nepafenac was the highest at 30 minutes and remained at the highest concentration throughout the study.

“Looking specifically at amfenac, its aqueous concentration was low at 30 minutes, as it was for bromfenac and ketorolac, but amfenac was high at one hour and remained high during the remaining time points,” he said, adding that “nepafenac acts as a reservoir for continued amfenac formation over time.”

This study showed that the concentrations of both nepafenac and amfenac were “higher than suggested in other studies of different designs,” Dr. Raizman said. As the only prodrug NSAID, the study demonstrates that the two agents, amfenac and nepafenac, work in concert, and NEVANAC® suspension showed the highest concentration.

Dr. Raizman added that all the NSAIDs in this study “appear to reach the aqueous humor. The findings of high concentrations of nepafenac and amfenac, however, corroborate the clinical data demonstrating reduction in pain and inflammation after cataract surgery.”

**References**

Human Corneal Concentrations of Moxifloxacin and Gatifloxacin in a Penetrating Keratoplasty Model

This novel study analyzed corneas from 48 patients undergoing penetrating keratoplasty. The controlled, randomized, open-label, multidose study compared the corneal penetration levels of VIGAMOX® solution (moxifloxacin, Alcon, Fort Worth, Texas) and ZYMAR* (gatifloxacin). Study eyes received two drops of either antibiotic five minutes apart, with the last dose at 0.25, 0.5, one, or two hours before corneal samples were assayed for moxifloxacin and gatifloxacin concentrations.

As the graph shows, the mean peak epithelial level of moxifloxacin was about sevenfold higher than gatifloxacin; the mean peak stromal level of moxifloxacin was about threefold higher than gatifloxacin mean peak stromal level; and the mean peak endothelial level of moxifloxacin was about tenfold higher than gatifloxacin. This indicates moxifloxacin provides enhanced penetration that should contribute to superior activity against common ocular pathogens associated with endophthalmitis and keratitis.

Physician Perspective:

**VIGAMOX® solution shown to have greater human corneal concentration than ZYMAR**

The first human study to examine corneal penetration of fourth-generation fluoroquinolones found that moxifloxacin (VIGAMOX® solution, Fort Worth, Texas) had higher corneal concentrations than gatifloxacin (ZYMAR®).

“This study provides encouraging information on the corneal penetration of fourth-generation fluoroquinolones on two levels: peak concentration levels as well as the time required to reach these peak concentrations,” said Terry Kim, M.D., associate professor of ophthalmology, Duke University Eye Center, Durham, N.C. “The peak stromal concentration was 48.5 µg/g for moxifloxacin (and 15.7 µg/g for gatifloxacin), which represents levels high enough to surpass the reported minimum inhibitory concentrations (MICs) for many of the microorganisms causing infectious keratitis, especially after LASIK surgery. In addition, these peak concentrations were shown to occur within 15 minutes after dosing. This information becomes clinically relevant in preventing potential microbial contamination that can occur during flap creation/lifting and stromal ablation, as high levels of antibiotic will be present in the corneal stroma very soon after dosing.

Because these high antibiotic levels are being maintained in the cornea with regular dosing after refractive surgery, the risk of developing infectious keratitis after LASIK is probably reduced, he said.

“Before this study, we had no human data to support the delivery of sufficient antibiotic concentrations to the target tissue,” he said. “With this information, I now feel comfortable prophylactically dosing a refractive surgery patient with two to three drops of a topical fluoroquinolone like moxifloxacin five minutes apart within half an hour before surgery, as opposed to two or three days pre-operatively, to achieve high levels in the human cornea.”

The results of this study provide assurance that our fourth-generation fluoroquinolones have the capability of reaching therapeutic concentrations in human corneal tissue to prevent potential infection and treat infectious keratitis. They also have the potential to favorably impact the routine prophylactic antibiotic dosing regimens of both cataract and refractive surgeons, Dr. Kim said. Further, the study results clearly favor moxifloxacin, as it demonstrates higher levels throughout the corneal tissue versus gatifloxacin. Dr. Kim opts for moxifloxacin for prophylaxis or treatment of infection because of its potency and penetration profile.

**References**


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A Double-Masked Study of Nepafenac 0.1% and Ketorolac 0.4% for Pain and Epithelial Healing Following PRK

This study compared the epithelial wound healing effects of nepafenac 0.1% (NEVANAC® suspension, Alcon, Fort Worth, Texas) and ketorolac 0.4% (ACULAR® LS) on 40 patients (80 eyes) who underwent photorefractive keratectomy (PRK). Each patient received one drop three times per day, on top of the contact lens, for three days. Patients graded pain, burning, irritation, comfort, and photophobia at days one, three, four, five, and seven. The final results showed no significant difference in epithelial healing and a slight advantage for NEVANAC® suspension in terms of pain control. Nepafenac also showed greater tolerability with more comfort, less irritation, and less burning and stinging following PRK than ACULAR® LS.

This slide shows the results in epithelial healing. All patients had an equal initial defect size due to the 8.5-mm well in preparation for the PRK procedure. The difference in healing time between the treatment groups was negligible.

Physician Perspective:
Epithelial healing shown to be equivalent among NSAIDs

Daniel S. Durrie, M.D.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) after photorefractive keratectomy (PRK) has often been mentioned as a means of reducing post-op pain. This study compared two topical ocular NSAIDs, NEVANAC® suspension (nepafenac 0.1%, Alcon, Fort Worth, Texas) and ACULAR® LS (ketorolac 0.4%).

“This study showed that it is beneficial to use an NSAID in patients undergoing PRK on days one, two, and three post-op,” said Daniel S. Durrie, M.D., professor of ophthalmology, University of Kansas Medical Center, Overland Park. “In this study, NEVANAC® suspension was a little better at controlling pain. There was no difference in the re-epithelialization rate between the two,” so NEVANAC® suspension is a good choice for PRK.

Although the use of nepafenac in PRK is off label, Dr. Durrie said this generation of NSAIDs is much different from its predecessors. Dr. Durrie has used both ACULAR® LS and NEVANAC® suspension to treat his refractive patients. When NEVANAC® suspension was first approved, he used it most on re-treatments but started using it in regular clinic once he got scientific evidence from a wound healing standpoint.

“Twenty years ago we had problems with NSAIDs in cataract surgery, but the modern drugs seem to be very safe and effective,” he said. “Over the last year, I’ve used NEVANAC® suspension in 500 cases in my clinic, and I have not seen any wound healing problems because of NEVANAC® suspension.”

References
1. Donnenfeld ED, Durrie DS, Holland EJ, Raizman MB. A Double-Masked Study of Nepafenac 0.1% and Ketorolac 0.4% for Pain and Epithelial Healing Following PRK. Accepted for presentation to the American Academy of Ophthalmology, November 11-14, 2006, Las Vegas, NV

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Evaluation of the Safety of Prophylactic Intracameral VIGAMOX® Solution in Cataract Surgery Patients

This study was designed to determine the safety of intracameral moxifloxacin 0.5% (VIGAMOX® solution, Alcon, Fort Worth, Texas) in 65 eyes undergoing cataract surgery. The average patient age was 69.5. Patients received an intracameral injection of 0.1 mL VIGAMOX® solution 0.5% through a 27-gauge cannula at the end of the case.

This slide shows that the mean decrease in endothelial cell density pre-op compared to endothelial cell density post-op is 70, which was not statistically significant. Further, anterior chamber cell and flare were seen only at day one post-op. Intracameral VIGAMOX® solution 0.5% appears to be non-toxic in terms of visual rehabilitation, anterior chamber cell/flare, and endothelial cell density.1

Physician Perspective:

Intracameral VIGAMOX® solution shown to be safe after cataract surgery

Intracameral antibiotic use during cataract surgery has been at the forefront of the subspecialty recently, with the recent large European study on endophthalmitis showing patients dosed with an intracameral antibiotic had lower rates of endophthalmitis than those who did not, said Francis Mah, M.D., assistant professor of ophthalmology, University of Pittsburgh School of Medicine, Pennsylvania.

“The early report shows the key to the European study is that intracameral antibiotics seemed to provide a benefit in preventing endophthalmitis in conjunction with topical antibiotics. This was statistically better than topical antibiotics alone in cataract surgery,” he said. Simply put, the lesson seems to be more antibiotic in the anterior chamber is better for infection prevention. “In this particular study, what’s interesting is that one of the main problems with widespread adoption of intracameral antibiotics, namely extemporaneous preparations, seems to be answered—the investigators are using moxifloxacin (VIGAMOX® solution, Alcon, Fort Worth, Texas) prepared from a widely available bottle. They’re taking 0.1 mL from commercially produced VIGAMOX® solution and injecting it right into the eye, without dilutions or calculations or any extraordinary maneuvers.”

Dr. Mah said surgeons are looking for ways to reduce post-op complications. “Anything to make the whole process easier and more effective is better. It’s a better process for the patient and surgeon.”

This study marks the first time a commercially available drug has been used without modification and placed directly in the eye “without any extraordinary maneuvers,” he said. “It seems to be non-toxic in the short-term. As with any medication used in the eye, long-term data are always necessary.”

Dr. Mah is still evaluating their use in his practice but said data seem to be pointing favorably toward intracameral antibiotics. If I start, I want to use something that’s going to be easy for me and my nurses and technicians to use, [something] that won’t increase the risk of developing TASS (toxic anterior segment syndrome) or endophthalmitis above the 1:1000 that is currently accepted in the United States.”

This study—and fluoroquinolones in general—“may be better and more effective intracamerally than cefuroxime,” he said. “They have better kill kinetics than betalactans. Regardless of the concentration, it takes eight to twelve hours for cefuroxime to achieve kill rates; fluoroquinolones are concentration-dependent and have been shown to kill common endophthalmitis-causing organisms within an hour or two.”

References

This study compared nepafenac 0.1% (NEVANAC® suspension, Alcon, Fort Worth, Texas) to ketorolac 0.5% (ACULAR®) and placebo for the prevention and treatment of ocular inflammation and pain associated with cataract surgery. A total of 227 patients was enrolled in the double-masked, randomized, placebo- and active-controlled parallel group study, with each group receiving one drop three times per day for an average of 23 days.

Statistically, nepafenac resulted in a significantly higher clinical success rate (0-5 cells, no flare) at the post-op day 14 visit compared to ketorolac and placebo; nepafenac also was found to have a higher percent of pain-free patients at the post-op day three visit. Patients treated with nepafenac experienced significantly better comfort upon instillation compared to ketorolac at day seven post-op.

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Physician Perspective:

**NEVANAC® suspension effective for post-op cataract surgery inflammation and pain**

Edward J. Holland, M.D., director, cornea services, Cincinnati Eye Institute, Ohio. Despite this, Dr. Holland said surveys have shown only about a 50% rate of routine use of NSAIDs by cataract surgeons, although he noted this number is growing rapidly.

“NSAIDs play as important a role as steroids in managing inflammation,” he said. “We now know with OCT [optical coherence tomography] studies that cystoid macular edema (CME) is much higher than we initially thought. With multifocal IOLs gaining acceptance and popularity in the cataract segment, even a minimal level of CME can significantly reduce the quality of vision in those patients. This study really points to the value of the NSAID in the management of cataract patients.”

Dr. Holland said cataract surgeons not currently using NSAIDs should at least consider it. NEVANAC® suspension (nepafenac, Alcon, Fort Worth, Texas) has “an excellent record,” he said. “It’s my NSAID of choice.” It is also interesting to note that the study was powered to show a difference relative to placebo. The fact that nepafenac demonstrated a difference relative to ketorolac is impressive.

The perception of complications with using NSAIDs was relevant years ago when they were associated with corneal melts. The safety profile of ocular NSAIDs has improved significantly,” Dr. Holland said, “and the risk is extremely minimal. The value of adding nepafenac to the post-op care regimen is tremendous.”

References

1. Nardil M, Cunliffe I, Cano, J, Cochener B, Nietvold R, Wiernas T. Neurosciences-Clinica Oculistica, University of Pisa, Pisa, Italy; Ophthalmology, Birmingham Heartlands Hospital, Birmingham, United Kingdom; Ophthalmology, Hospital Municipal, Badalona, Spain; Ophthalmologie, CHU Morvan, Brest, France, R & D, Alcon Research Ltd., Fort Worth, TX. Placebo-Controlled Trial of Nepafenac 0.1% (NEVANAC®) and Ketorolac Tromethamine 0.5% (ACULAR®) for Treatment of Ocular Pain and Inflammation Following Cataract Surgery. Abstract submitted to IOVS, 2007.

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