want to go a little longer and be more intense on the high-risk patients.

The research evidence does not clearly identify whether drug delivery shortly pre-op or several days pre-op is better. However, as the patients become higher risk, I tend to have a slightly longer and more intense course of antibiotic and anti-inflammatory drops.

Routine patients that never had a problem generally start to receive the drug in the operating room prior to surgery because it is easier on the patient.

Post-op routine for cataract patients

The major change in recent years from previous antibiotic experience is the peri-operative and short post-op course of the drugs. We now limit antibiotic use because the risk of endophthalmitis drops within a week when the wound seals. It is the long-term, low-dose use of these drugs that leads to resistant organisms.

Our approach is to administer antibiotics and anti-inflammatory drops (steroid and NSAID) at the end of the case. My nurses administer them again in the recovery area before the patient goes home.

I have patients use the antibiotic drops three times a day for one week. Other surgeons have them take the antibiotic for as few as five days.

However, the anti-inflammatory drug is required for longer use. Evidence suggests the blood aqueous barrier breakdown that occurs after cataract surgery persists for four to eight weeks. Because the average breakdown lasts about six weeks, we should treat with anti-inflammatory drops for one to two months in routine cases. This will prevent any rebound of inflammation or other secondary issues.

We need to have patients use the anti-inflammatory drops a bit longer than some surgeons think is necessary because often the eyes are quiet and comfortable by two to three weeks after surgery, but there is still some risk for cystoid macular edema up to six weeks post-op.

For example, for at-risk patients pre-op dosing is recommended for one week and post-op dosing is recommended for four weeks to several months (Figure 2).

The dosing regimen I use is driven by the Nevanac, which is a TID drop, a three-times daily drop. I use Vigamox, Nevanac, and a topical steroid, which seems more than adequate, as these drugs have demonstrated efficacy in contributing to good surgical outcomes.

Find the dosage for the drug

The final piece of which physicians should be aware is adding NSAID drug to their regimen. Most patients recover without complications when surgeons only use an antibiotic and a steroid. However, there are indications that over 10% of patients will develop a very mild macular edema without an NSAID. That’s a risk that NSAIDs can eliminate.

We have pretty minimally invasive cataract surgery today, and people work really hard at their surgical technique, but probably the one thing that could have the greatest impact on their outcomes would be to add an NSAID to their regimen.

The incidence of very mild macular edema without an NSAID, even in a good surgeon’s hands, is about 12%, and adding an NSAID takes it down to less than 1%, so you get a huge reduction in one of the most common sight-threatening complications of cataract surgery just by adding an NSAID and using it properly.

Proper dosing of antibiotics, NSAIDs, and steroids plays a very important role in preventing complications such as infection or CME.

Minimizing these complications with effective agents and proper therapeutic dosing regimens will improve our surgical outcomes.

References

Safely and effectively controlling inflammation

By Robert Cionni, M.D.

Non-steroidal, anti-inflammatory drugs have added a critical component of inflammation control to cataract surgery, but physicians should look for relative strengths and weaknesses.

One of the advantages of nepafenac 0.1% is its unique formulation as a prodrug or precursor to an active drug. Not all NSAIDS are prodrugs. Only NEVANAC™ suspension is the first and only produrg NSAIDS. Prodrugs are often used to allow the potent form of a drug to reach target tissues in higher concentrations and with less risk of side effects. Prodrugs typically do not convert to their active form until they reach ocular tissue.

One of the newer NSAIDS, nepafenac 0.1% (Nevanac suspension, Alcon, Fort Worth, Texas), is converted by intraocular hydroxases within the eye’s uveal tissues, retina and choroid, to its active form, amfenac. This active form is a powerful cyclooxygenase pathway inhibitor.

Where it is applied to the cornea and conjunctiva, nepafenac is a more gentle NSAID. Its properties allow for patient comfort and quick, safe and effective penetration into the cornea. Once in the eye, enzymes convert nepafenac into the active NSAID, amfenac. This prodrug activation allows the levels of amfenac to increase in the iris and ciliary body and reach its peak concentrations at the retina and choroid. This high level of activation allows the drugs high efficacy in controlling inflammation both anteriorly and posteriorly. The high posterior concentrations may help to decrease the risk of post-op CME.

Figure 3: Nevanac suspension delivers superior prostaglandin inhibition. NSAIDs reduce the development of inflammation through their specific ability to inhibit prostaglandins. Administration of nepafenac 0.1% suspension leads to significant suppression of PGE2 synthesis in the posterior segment.
Nepafenac 0.1%, or Nevanac, is a unique NSAID, as it is the only prodrug NSAID available. Its conversion to amfenac in the target tissues makes it an ideal option to prevent postcataract CME.

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References
5 Data on file at Alcon Labs, Ft. Worth, Texas.

Identifying the key criteria of antibiotic prophylaxis

By Edward J. Holland M.D.

A wide variety of antibiotic options are available to surgeons, but key differences can have tremendous impact in reducing patients’ risk of infections.

Surgeons can greatly improve their chances of a successful surgical outcome if they keep in mind three key criteria in selecting antibiotics: potency, penetration, and safety. A good balance of these aspects—especially potency and penetration—provides the best patient protection.

An antibiotic that is highly potent and effective at killing infections at low concentrations would lose much of its efficacy if it was unable to penetrate the tissue. Conversely, a medication that penetrates extremely well but lacks potency also would not be very functional.

Clinicians are best served by an effective combination of penetration and potency.

Although researchers are frequently asked whether potency or penetration is more important, the only clear answer is the most effective approach is to combine these factors.

Measuring potency

Identifying an antibiotic’s strength in penetration and potency is important, but surgeons should be aware that...
potency definitions vary. The most common assessment of an antibiotic’s potency, the minimum inhibitory concentration (MIC), traces whether organism growth has been stopped. However, the definition still allows viable organisms to remain. This most common term may not be the most important. Another standard, minimum bactericidal concentration (MBC), tracks whether 99.9% of the organism is killed (MBC is approximately 4x the MIC). The final measurement, mutant prevention concentration (MPC), gauges whether the organism was killed with mutations prevented (MPC is approximately 8x the MIC).

Drugs with the lowest potency numbers in MIC, MBC or MPC are among the most potent. With post-op infections being potentially sight threatening, it is ideal to exceed these levels with the antibiotic concentrations in the target tissues (Figure 4).

Penetration tracking
Antibiotic tissue penetration plays a key role in protecting against infection.

This issue arises when examining the research on various antibiotics; some may have good potency statistics in vitro, but we fail to identify the in vivo performance of the antibiotic. The latter will tell ophthalmologists what levels of the drug our patients actually will get in the cornea, the anterior chamber, and the vitreous. My research administering fluoroquinolones to a cornea transplant model prior to corneal transplant and then examining the antibiotic levels in the cornea showed moxifloxacin (VIGAMOX®, Alcon, Fort Worth, Texas) had three times the concentration of gatifloxacin (ZYMAR®, Allergan, Irvine, Calif.) (Figure 5).

Similar research at Wilmer Eye Institute, Baltimore on aqueous concentrations of antibiotics applied a series of drops pre-op and measured aqueous concentration at the time of cataract surgery. Those researchers identified the same three-fold greater penetration of moxifloxacin. Protection can be defined by overlaying these concentrations with the MICs for potential pathogens (Figure 6).

In vivo potency after tissue penetration is a better measure of antibiotic efficacy than speed of kill in vitro. The latter removes all of the factors that determine how the antibiotic performs in human tissue. These studies disregard the reality of penetration of the antibiotic through human tissue. For these reasons in vivo potency and penetration studies will always have more real-world relevance than in vitro speed-of-kill research. The aqueous humor concentrations achieved in the Wilmer Eye study were tested against a Staph aureus ocular isolate by Terry O’Brien, M.D., and colleagues using disk-diffusion analysis. The moxifloxacin achieved a 24-mm zone of inhibition, and gatifloxacin had no zone of inhibition. This surrogate model accounts for tissue penetration and potency at the potential site of infection, thus defining protection (Figure 7).

Safety assessment
In addition to potency and penetration, a solid evaluation of antibiotics for surgical prophylaxis should assess whether the drug is non-toxic. Efforts to prevent the use of non-toxic medication should look for epithelial problems or endothelial problems.

As a class of drugs, the fluoroquinolones have proven to be very safe and nontoxic. My experience with all fourth-generation fluoroquinolones and non-toxic. Generally, they found that eyes treated with Vigamox healed faster and had smaller defects than those treated with Zymar.

Rabbit model studies that created epithelial defects and tracked healing when the two antibiotics are used found similar results. Clinical trials looking at healing after PRK also identified similar healing. Both fluoroquinolones are safe and non-toxic.

* Trademarks are the property of their respective owners.

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1 A comparison of ocular penetration and microbiological efficacy of fourth generation fluoroquinolones in cataract surgery patients. Terrance P. O’Brien, David W. Stroman CMIG 2006
NSAIDs: Critical ally in the fight against CME

By Samuel Masket, M.D.

Emerging evidence has highlighted the potential gains from the regular use of NSAIDs in both cataract and refractive surgery. Some literature evidence has indicated that the incidence of cystoid macular edema (CME) is significantly reduced when NSAIDs are added to the post-op topical regimen. In one study, a group of patients with uncomplicated cataract surgery had a 12% incidence of angiographic CME, but a parallel group of patients treated with an NSAID added to their steroid had no incidence of CME.

Due to such findings we see NSAIDs as a protective measure against CME. The drugs’ importance increases in light of the refractive surgery patient’s expectation of surgical success. These patients anticipate not only an excellent outcome but also one that is instant and virtually pain free.

However, with refractive lens procedures the potential complication rate is significantly higher than it was with extracapsular laser procedures. This combination of factors makes it even more important that we do everything we can to reduce the chance of statistically unlikely risks of conditions like CME.

I have used the combination of steroids and non-steroidal agents topically in the post-op period for a number of years. The routine has enabled my edema rate among average patients who lack high-risk conditions to hover near zero.

The synergy of NSAIDS and steroids seems to make sense in light of what we know about the inflammatory cascade of chemical mediators following tissue damage. The cascade of inflammatory mediators emanate from any type of trauma to cells and cell membranes and the cyclooxygenase pathway. The NSAID acts to efficiently inhibit the pathway. Its approach is very similar to ADVIL® (Wyeth, Richmond, Va.) and ibuprofen, which are COX-1 inhibitors. Similarly, the other arm of the pathway, the lypoxygenase, is inhibited by steroid agents.

These and other treatments are still based on the long-held belief that reduction of prostaglandin formation leads to pain reduction and a cut in the potential for cystoid macular edema. Inflammatory mediators—the prostaglandin-like agents and the other inflammatory chemicals—are released as a result of surgical trauma, permeate and activate in the back of the eye, and affect the capillaries in the macular region. This allows the capillaries to leak fluid, which is where the process causes CME.

Target-specific efficacy
NEVANAC™ (Alcon, Ft. Worth, Texas), or nepafenac 0.1%, activates at the target sites of inflammation converting to its active form, amfenac. This unique prodrug activation takes place in the cornea, more so in the iris ciliary body, but to the highest extent in the retina and choroid. This activation in the retina is especially important in the prevention of CME (Figure 8).

May control miotic tendencies
Non-steroidal drugs also appear to have a role in the pre-op period. Significant evidence has shown the drugs—administered pre-op—can control the tendency of the pupil to constrict during operative procedures. Many of us have used non-steroidal agents not only post-op but also in the immediate pre-op period to maintain a widely dilated pupil during surgery.

Some surgeons have found benefits from administering NSAIDs up to 48 hours before surgery. When NSAIDs are pre-loaded in routine cases two days prior to surgery they may better combat both miosis and post-op inflammation, and CME. Cases at a high risk to develop CME may benefit from dosing as far as one week pre-op.

NSAIDs can fight pain
Another aspect of the non-steroidal drugs is their well-known analgesic effect. The drugs are commonly employed in surface ablation laser refractive surgery to control pain. Even in cataract patients, NSAIDs can help reduce the potential for discomfort in the early post-op period.

The various benefits of NSAIDs are realized most clearly through their specific dosing. The pharmacologic dose for Nevanac is three times a day.

Typically, I have patients use Nevanac three times a day for four weeks after surgery in routine cases. Then the NSAID and steroid prescriptions are reduced to twice a day for four more weeks. I keep patients on a topical steroid and non-steroidal agent for eight weeks post-op.

It is becoming increasingly clear that NSAID therapy post cataract surgery plays an important role in ensuring good surgical outcomes, especially in light of the growing importance of refractive IOLs.

References

Figure 8: Target-specific efficacy
Nepafenac 0.1% activates at the target sites of inflammation converting to its active form, amfenac. This unique prodrug activation takes place in the cornea, more so in the iris ciliary body, but to the highest extent in the retina and choroid.

Novel ProDrug Structure

- **Optimizes Activation**
  - Upon ocular dosing, nepafenac metabolizes to its active form

- **Target-Specific Efficacy**
  - Nepafenac is converted into amfenac for optimal efficacy
  - Retina/choroid > iris ciliary body > cornea

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Cataract Prophylaxis: Proper NSAID and Anti-Infective Regimen Is Critical to Patient Success

By Richard L. Lindstrom, M.D.

The key surgical prophylaxis paradigm shift in recent years for long-practicing ophthalmologists is the growing evidence for pre-op use of both antibiotic and anti-inflammatory drops. The second shift is the realization we should discontinue antibiotics more quickly and ensure use of anti-inflammatories for the full course of therapy. These changes are key for limiting post-cataract inflammation and infection, while they prevent the development of antibiotic resistance in patients.

In the pre-op period a fourth-generation fluoroquinolone such as VIGAMOX® (moxifloxacin 0.5% solution, Alcon, Fort Worth, Texas), a non-steroidal anti-inflammatory such as NEVANAC™ suspension (1% Cyclopentolate HCl, Alcon), an antibiotic, steroid, non-steroidal, so actually they get loaded up with five different drops. Our pre-op routine is three doses of drops starting 30 to 60 minutes before surgery.

Some surgeons prefer to start the drops 24 hours pre-op, while others start the drops three days pre-op. There are select indications where anti-inflammatory drug dosing should begin a week pre-op, including high-risk cases for inflammation and secondary macular edema (Figure 1). Such patients include those with a long-term history of chronic uveitis and diabetes mellitus and patients with pigmentary retinopathy and macular edema, and those who developed macular edema in the first eye after cataract surgery.

With high-risk patients such as those who are immunocompromised or prone to infection, I might start the antibiotic three days pre-op rather than just on the table.

In my routine cases, I load the entire drop regimen in the eye in the operating room, but the high-risk cases you may start, three to seven days pre-op. There is not yet a consensus, but you may...

There are two basic ways to approach the pre-op loading. One approach provides the drops within the three- to four dose dilating regimen in the surgical induction area. I add Neosynephrine 10% (Bayer AG, Leverkusen, Germany), CYCLOGYL® Solution (1% Cyclopentolate HCl, Alcon), an antibiotic, steroid, non-steroidal, so actually they get loaded up with five different drops. Our pre-op routine is three doses of drops starting 30 to 60 minutes before surgery.

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