ENDOPHTHALMITIS PROPHYLAXIS

The quest for an ocular injectable antibiotic product continues in the United States.

BY SUSANNE GARDNER, PharmD

With increasing age and diversity of the patient pool and rising bacterial resistance in ocular isolates, refreshed interest in the prophylaxis of endophthalmitis via an intracameral (IC) antibiotic injection is welcome, and, perhaps, inevitable. In lieu of an update to the article written by the late Peter Barry, FRCS, in *CRST Europe*'s September 2008 issue,[1] below I address why it is crucial that an ocular antibiotic injectable product be commercially available in the United States.

Results of the European Society of Cataract and Refractive Surgeons (ESCRS) landmark endophthalmitis prophylaxis study, published in 2007,[2] were embraced in Europe but greeted with much skepticism in the United States. Critics cited factors that remain the substance of debates, editorials, additional observational studies, and publications to this day. Nevertheless, an IC cefuroxime injection received approval from the European Medicines Agency in 2012 (Aprokam; cefuroxime 50 mg, Théa Pharmaceuticals). Since that approval, hundreds of thousands more patients have been treated with this prophylaxis regimen, generating a body of literature that describes clinically meaningful reductions in postoperative endophthalmitis (POE) after instituting IC cefuroxime or other antibiotic injection at the close of cataract surgery. These reports have confirmed the benefits of the IC antibiotic injection, and a key time-trend study demonstrated this benefit in a US setting as well.[3]

CONFOUNDING VARIABLES

An initial critique levied against the ESCRS study suggested that no effect could be attributed to an antibiotic regimen alone, given the large number of confounding variables inherent in cataract surgery and the thousands of patients who would be required to separate these variables.[4] It seems the multiplicity of studies now showing reduced POE after IC antibiotic would mitigate against this argument, as more variables could hardly be imagined than are reflected in reports now emanating from every corner of the globe. One notable exception may be the Far East, where microbes reflect different sensitivity patterns than in the West, and where patient colonization patterns and surgical environment also likely differ.

To repeat such studies in a randomized, controlled, prospective, masked fashion may not be feasible for many reasons. A close look at the ESCRS methodology (the only prospective, randomized, partially masked study performed to date) reveals degrees of rigor and standardization, with inclusion of a control group, that are unlikely to be reproduced or improved upon elsewhere at this time. At the least, operating room sterility standards at each site were carefully addressed, sites were routinely monitored, and antibiotic drops were packaged in masked fashion and assigned to numbered kits for randomization in prospective fashion, all within a protocol that took 1 year to write and comprised 200 pages. These efforts began more than 15 years ago, and too much has transpired in the interim to repeat these basics, in my opinion.

FUTURE STUDY DESIGN FACTORS

Today, debate regarding cataract surgery prophylaxis continues over several clinical options (see *Cataract Surgery Prophylaxis: Debating the Clinical Options*). Each pharmacologic option reflects distinct pharmacokinetic/pharmacodynamic profiles of antimicrobial action that fully underlie the efficacy, or lack thereof, of each regimen within the eye, yet few laboratory studies are published that adequately explore this underlying fundamental science. Such preliminary studies would appear to be a logical next step before clinicians subject thousands more patients to cart-before-the-horse explorations, not to mention the enormous costs that would be involved in such full-scale, protocol-driven, randomized, masked studies.

With US surgeons already claiming low POE rates, how many patients would be required to show statistical significance with multiple study arms, especially when a true control group is no longer advisable at this stage? If study entrance criteria exclude high-risk patients, the differences would be even more difficult to detect. If high-risk patients are included, how will they be evenly distributed in prospective randomized fashion between study arms, as many risk factors such as posterior capsular rupture, lengthy surgery, complications, and surgeon factors are unlikely to be assessed at randomization time? If these factors cannot be properly randomized, then the arms could potentially be imbalanced.

ENDOPHTHALMITIS PROPHYLAXIS: DEBATING THE CLINICAL OPTIONS

Which is better, IC or topical drops?

Which antibiotic drops?

What regimen of antibiotic drops?

What about no antibiotics at all?

What about so-called *dropless* cataract surgery?

What about surgical technique itself?

It would seem more prudent to move the needle forward to focus on patients known to be at higher risk for POE, as these patients will benefit most from study findings. In fact, these patients might specifically be targeted in future clinical trials. In the hands of leading surgeons, surgical complications are likely to be minimized and surgical technique perfected, yet this may not reflect all study sites or circumstances around the United States. How can we identify where these pharmacologic interventions would be most useful? Additionally, how can we determine the need for an intraocular presence of antibiotic versus an external presence of antibiotic? And again, what regimen is best?

INTO THE EYE

It is now well understood that, to deliver a drug into the eye, the best method of delivery is in fact into the eye. This understanding is corroborated by the number of drug products approved in recent years, by the US FDA and other regulatory bodies, for direct intravitreal injection, including extended-release intravitreal products. This route is clearly superior to systemic drug delivery, through which adequate transfer across the blood-eye barrier is not realistic. Topical drops are subject to 100% variability in external tear film concentrations and approximately 50% variability

AT A GLANCE

- Ophthalmology in the United States is handicapped by the lack of availability of an approved ocular antibiotic IC injection.
- It should be understood that the best way to deliver antibiotics to the eye is directly into the eye.
- Although there are myriad variables in antibiotic choices and regimens for ocular surgery, nothing should block the approval of an ocular antibiotic injectable product in the United States, especially for patients at higher risk who undoubtedly stand to benefit the most.

in penetration to the aqueous humor. Therefore, if the objective is to deliver high, reliable intraocular antibiotic levels, direct injection is the best option, consistent with other body systems encumbered by unique pharmacokinetic characteristics.

Topical drops surely have a place as well, particularly as events in the immediate postoperative period that contribute to POE are not well defined, and because wound healing along with other patient factors play a role. The argument that use of fourth-generation fluoroquinolone drops would have made a significant difference over the third-generation fluoroquinolone used in the ESCRS study is a relatively weak argument; there is a lack of evidence that, at the concentrations delivered in drops, use of the newer-generation drug would have made any difference. Furthermore, the pulsed dose drop delivery used in two study arms was subsequently tested and found to deliver approximately four times higher aqueous humor antibiotic levels than ever reported previously.[5] That dosing regimen—two preoperative drops plus three pulsed drops given 5 minutes apart at the close of cataract surgery—had not been implemented before and has not been duplicated in studies since; however, even this regimen was not statistically comparable to the IC injection. Other important details of the ESCRS study may also not be fully appreciated or explored relative to the opinions and criticisms rendered.

MOVING FORWARD

Certainly, studies are needed to develop society guidelines that set standards for patient care, but the track for further official approvals of intraocular antibiotic products could follow a different course. Drug delivery and antimicrobial action are distinctly separate factors from surgical techniques, and these weigh separately on patient outcomes and prevention of ocular infection. Furthermore, patient factors are crucial variables in the broad picture. It is understood that we have a need for injectable antibiotics for the eye. It should also be understood that, in order to deliver antibiotics into the eye, we best deliver them directly into the eye. To continue to protect the ocular surface in the immediate postoperative period is an added important factor that merits ongoing exploration.

Therefore, perhaps we should not again compare antibiotic drops versus IC injection. Rather, we could move forward with the understanding that we need both types of products approved—drops as well as injection—within the specialty of ophthalmology and that further clinical studies should be aimed at providing a better understanding of each surgeon's and patient's particular needs for any given case of cataract or other ocular surgery.

Ophthalmology in the United States is unfairly handicapped by the lack of availability of an approved ocular antibiotic injection. No available injectable antibiotic of choice is packaged in the much smaller, preservative-free doses required for ocular injection. Such products are available for intrathecal use, but ophthalmology remains stranded and, faced with a huge clinical need, is forced into extemporaneous compounding and lack of access in an emergency.

Many unanswered questions regarding the time-kill profiles of antibiotics and their pharmacokinetics and pharmacodynamics within the eye can first be addressed in simple, scientific ways outside of clinical trials. Whether antibiotic drops, in the levels they deliver over time, are sufficient to kill bacteria inside the eye can easily be studied in preliminary models. Yes, there may be too many variables in ocular surgery to make broad sweeping statements about one antibiotic or one regimen, but certainly such confusion should not further block the approval of an ocular antibiotic injectable product in the United States, especially for patients at higher risk who undoubtedly stand to benefit the most. ■

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