Endophthalmitis After Cataract Surgery

Experts in the field respond to the recent press release from the ESCRS.

BY RICHARD B. PACKARD, FRCS, FRCOPHTH; RANDALL J. OLSON, MD; STEVE ARSHINOFF, MD, FRCSC; FRANCIS S. MAH, MD; TERRENCE P. O’BRIEN, MD; AND SAMUEL MASKET, MD

In a press release on March 13, 2006, the ESCRS announced that the results of its multicenter, prospective, randomized endophthalmitis study showed that intracameral cefuroxime significantly lowered the rate of infectious endophthalmitis. The society deemed the information sufficiently important to alert the global ophthalmic community in advance of the published study. Without details of the study’s design and a commercially available intracameral antibiotic, however, ophthalmic surgeons have been left to wonder how to proceed. Cataract & Refractive Surgery Today asked several experts for their opinions on the impact and practical implications of this landmark study.

—David F. Chang, MD, Co-Chief Medical Editor

RICHARD B. PACKARD, FRCS, FRCOPHTH

The issue of appropriate prophylaxis to minimize the risk of endophthalmitis after cataract surgery has long vexed ophthalmic surgeons. Most reports on series of patients have either been retrospective or had insufficient numbers to provide genuinely statistically sound data. The ESCRS has just closed its very large prospective study early, because one arm showed a fivefold advantage in terms of the reduced incidence of endophthalmitis. The difference in that arm was the use of intracameral cefuroxime at the end of the operation, a technique that Montan et al.1,2 described in their groundbreaking reports from Sweden. We now have to assess the effect that this information will have on clinical practice for all ophthalmologists who perform cataract surgery.

In King Edward VII Hospital in Windsor, United Kingdom, at the beginning of 2004, my colleagues and I had a cluster of nine cases of endophthalmitis after cataract surgery in 3 months. We reviewed our practices extensively and tried to isolate the cause. Despite looking at the type and site of the incision, the use or not of a topical gel, the subconjunctival injection, etc, we failed to find a single reason for the outbreak. We found no pattern.

Among the changes we instituted was the routine use of intracameral cefuroxime, as prepared by the scrub nurse, for each patient. Since that time, we have performed more than 5,000 cases. Our first incident of endophthalmitis was reported 2 weeks ago. It was culture negative, and the anterior segment cleared in 2 days with some residual vitreous haze, which is dissipating. I would endorse the findings of the ESCRS’ study, because, although the rate of endophthalmitis may be higher than previously reported, the difference between the study arms is striking and statistically valid.

RANDALL J. OLSON, MD

Any prospective, randomized clinical trial in association with a treatment for endophthalmitis is a major event. That the ESCRS’ trial showed more than a fourfold difference in the rates of endophthalmitis between the use of a topical antibiotic and intraocular cefuroxime is not a result to be taken lightly. I predict that this report will usher in an era when surgeons more frequently use intraocular antibiotics.

Should all ophthalmologists be using cefuroxime intraocularly today, and is not doing so a break from the standard of care, with all of its scary legal ramifications? I do not think so because even the cefuroxime group had an incidence of endophthalmitis of 1:1,370, which is a similar or even higher rate than that of many contemporary surgeons who use topical antibiotics. What is more surprising is the 1:300 incidence of endophthalmitis for the study’s control group. Although such a high rate may have been common in the early days of topical antibiotics and an unsutured...
clear corneal incision, it is unusual for any recent study on the subject of which I am aware. My colleagues and I examined 27 cases of endophthalmitis in a multivariate analysis and found that starting the antibiotic on the day after surgery increased the incidence of endophthalmitis by a factor of 13.7 (P=.005) compared with antibiotics on the day of surgery. I would therefore expect an investigation like that of the ESCRS to show such a difference if the study group received frequent topical drops right after and on the day of surgery versus on the next day.

Unfortunately, the protocol had the control group start topical antibiotics on the day after surgery. I am not sure that comparing the use of an intraocular antibiotic and a topical drop started on the first postoperative day is the same as comparing the former with antibiotic drops administered on the operative day and the first postoperative day. Furthermore, using an antibiotic that penetrates well into the eye, such as a fourth-generation fluoroquinolone, has kept the incidence of endophthalmitis at the John A. Moran Eye Center in Salt Lake City as low as or better than that of the cefuroxime group in the ESCRS’ study.

The future is exciting in that the ESCRS’ study definitively shows the importance of antibiotics for preventing endophthalmitis. Due to increasing gram-positive resistance to cephalosporin antibiotics such as cefuroxime, supplementing intracameral fourth-generation fluoroquinolones with frequent topical drops or even an antibiotic-soaked collagen shield is probably the next step for preventing this devastating complication. Regardless, solid studies should demonstrate that surgeons are indeed improving endophthalmitis prophylaxis before they make any changes to the standard of care.

Ophthalmologists who start antibiotics on the day after surgery, however, may find the practice more difficult to defend based on the results of our study and that of the ESCRS. On the other hand, no study to date has proven that comparing the use of an intraocular antibiotic and a topical drop started on the first postoperative day is the same as comparing the former with antibiotic drops administered on the operative day and the first postoperative day. Furthermore, using an antibiotic that penetrates well into the eye, such as a fourth-generation fluoroquinolone, has kept the incidence of endophthalmitis at the John A. Moran Eye Center in Salt Lake City as low as or better than that of the cefuroxime group in the ESCRS’ study.

ERIC D. DONNENFELD, MD

Cataract surgery is one of the most common operations in the US, with approximately 3 million procedures performed annually. Modern cataract surgery is a safe and minimally invasive procedure that produces excellent outcomes. Although it is associated with an extremely low incidence of endophthalmitis, the considerable annual surgical volume still produces approximately 4,000 cases of potentially devastating endophthalmitis each year.

The use of intracameral antibiotics at the time of cataract surgery has been a common practice for more than a decade. It makes sense to place the antibiotic into the target tissue of the anterior chamber, a practice that can eradicate or partially treat the potential bacterial inoculum that occurs at the time of surgery and reduce the risk of infection. The first report of successful antibiotic prophylaxis by injection into the anterior chamber was published in the 1970s. Additionally, a number of retrospective studies have suggested that intracameral antibiotics can significantly reduce the risk of infection. Twenty years later, two large series of cataract patients and the usage of infusion fluid containing gentamicin and vancomycin were associated with no cases of endophthalmitis.

The ESCRS’ study of intracameral cefuroxime is the latest and by far the most important study to document the significance of intracameral antibiotics in preventing endophthalmitis, because it is the first controlled, double-masked, multicenter study to look at this issue. The next step is a thorough analysis of the data.

An important question that emerges, however, regards exactly what the best antibiotic to use intracameral is.

INTRACAMERAL CEFUROXIME

By Richard B. Packard, FRCS, FRCOphth

At the end of surgery, 0.93mg of cefuroxime in 0.1mL sterile water for injection is injected into the anterior chamber.

To reconstitute the cefuroxime, my scrub nurse adds 2.5mL of water for injection to 250mg of the drug to yield 93mg/mL or 9.3mg/0.1mL. She takes 0.1mL of this solution and adds 0.9mL of water for injection to get 0.93mg in 0.1mL. She then discards 0.9mL to leave 0.1mL in a syringe. I inject 0.1mL of the solution into the anterior chamber, preferably the capsular bag, with a 1-mL syringe and a Rycroft cannula. Zinacef is cefuroxime for parenteral use and is manufactured in a sterile crystalline form by Glaxosmithkline (Brentford, United Kingdom).

In a case of suspected allergy to penicillin, the consensus is still to administer cefuroxime intracamerally.

This regimen is based upon the concentration reported by Montan et al.1

Editor’s note: Although the Prince Charles Eye Unit has been using sterile water to mix cefuroxime without apparent problems, the original methodology published by Montan et al describes the use of 0.9% saline to dissolve and mix cefuroxime.—David F. Chang, MD

intracameral gatifloxacin is formulated by diluting intravenous gatifloxacin (Tequin; Bristol-Myers Squibb Company, New York, NY), which is available as 200mg in 20mL, with 180mL of balanced salt solution (9:1 balanced salt solution/gatifloxacin, which results in 200mg of gatifloxacin in 200mL or 1mg/mL). This solution is filtered under sterile conditions using a 0.2-µm filter. A sterile, 26-gauge irrigating cannula is attached to a sterile tuberculin syringe, and the surgeon injects 0.1mL, which contains 100µg of gatifloxacin, through the paracentesis incision into the center of the anterior chamber. At my practice, we mix the solution daily and use it for a full day’s surgery.

By Eric D. Donnenfeld, MD

The most broad-spectrum antibiotics currently available are fourth-generation fluoroquinolones, which come as gatifloxacin 0.3% solution preserved with benzalkonium chloride and moxifloxacin 0.5% self-preserved eye drops. My last 1,000 intraocular cases received prophylactic intracameral moxifloxacin 100.0µg/0.1mL (1:5 dilution of moxifloxacin with balanced salt solution prepared in a sterile fashion in the OR). I have encountered no infections or untoward side effects. The eyes have been quiet postoperatively, with minimal inflammation. I intend to use this prophylactic regimen for all my intraocular cases. After the ESCRs’ report, I believe that using nothing intracamerally may soon leave surgeons open to legal liability if an infection occurs.

At present, further study to determine the optimal drug and dosage for intracameral usage is needed. I would be reluctant to recommend that everyone adopt intracameral prophylaxis in the absence of a detailed analysis of the ESCRs’ study and further clarification of the safety of our apparent drugs of choice. At the same time, surgeons must balance the seemingly low risk of intracameral prophylaxis (due to currently unknown potential toxicity, possible diluting errors, and erroneous mixing with sterile water rather than balanced salt solution) with the current alternative of accepting a low but significant rate of continued loss of eyes to endophthalmitis when it appears that we can effectively prevent this complication. Additional study of the issue is urgently needed.

Francis S. Mah, MD

The press release from the ESCRs caused shock waves throughout the ophthalmic community because, on first blush, it seems that the major complication of intraocular surgery could be drastically reduced by completely chang-
ing the standard of care to administering intracameral cefuroxime at the end of surgery. Although the results of the study seem dramatic, we should step back and examine whether they make sense in terms of our current knowledge of medications, pharmacokinetics, and pharmacodynamics. In other words, maybe these results are not the end but rather a critical piece of the puzzle that will help lead us to a better way of preventing the devastating complication of postoperative endophthalmitis.

The ESCRS’ original prospective protocol called for four groups: (1) intracameral cefuroxime and postoperative levofloxacin; (2) pre- and postoperative levofloxacin only; (3) a combination of intracameral cefuroxime and pre-/postoperative levofloxacin; and (4) neither a preoperative antibiotic nor intracameral cefuroxime, only postoperative levofloxacin. It is important to note that all patients received preoperative povidone-iodine, the only method by consensus to reduce endophthalmitis.

Supposedly, the study was stopped prematurely due to a lack of funding. The organizers combined groups, seemingly arbitrarily, to examine intracameral cefuroxime versus no intracameral cefuroxime. They could just as easily have examined preoperative levofloxacin versus no preoperative levofloxacin, since there were four groups, not two. In other words, the study is not as statistically clean as it looks; there are possible confounders due to the mixing and matching of subsets that were not initially grouped together. The overall rate of endophthalmitis seems high, and it will be interesting to read the peer-reviewed publication to see if we can identify other reasons for the seemingly elevated rate of endophthalmitis.

Regarding the medications used, many ophthalmologists already realize the benefits of the topical fourth-generation fluoroquinolones moxifloxacin and gatifloxacin, including an improved spectrum of coverage, delayed antibiotic resistance, and better tissue penetration. Would these agents perform better than topical levofloxacin in the prevention of endophthalmitis? Although it seems logically so, we cannot answer that question.

Even though using cefuroxime as the intracameral test drug seems to have been of benefit, it may not have been the best choice, either. Cefuroxime is a second-generation beta-lactam, which provides just average coverage of both gram-positive and gram-negative bacteria. Furthermore, and of more concern, is the fact that the drug has a high rate of resistance; in fact, it would not cover any methicillin-resistant \textit{Staphylococcus aureus}.

Regarding the pharmacokinetics of antibiotics in the anterior chamber, it is generally less than 2 hours. This figure makes sense because the turnover of aqueous humor in the anterior chamber is 1% per minute. Therefore, after 100 minutes, all of the aqueous has been replaced. An elegant study looked at intracameral vancomycin and gentamicin—far superior antibiotics in terms of spectrum of activity.\cite{10} Vancomycin is a time-dependent killer, like cefuroxime, whereas gentamicin has both time- and concentration-dependent killing characteristics. In the study, when \textit{Staphylococcus epidermidis} and \textit{S. aureus} were incubated with both vancomycin and gentamicin for 2 hours, there was no killing of bacteria. Possibly, a better antibiotic to utilize, if a cleaner study of larger magnitude were performed, would be a concentration-dependent killing antibiotic such as a fluoroquinolone. My laboratory and others have been able to show the complete eradication of bacteria within 1 hour of exposure to fluoroquinolones.\cite{11}

Before all 2.5 million cataract patients per year receive intracameral cefuroxime, the potential short- and long-term issues of intracameral antibiotics need to be examined. Who knows if these drugs are associated with diseases such as
The methods aimed at preventing postoperative pseudophakic endophthalmitis are controversial. Moreover, prophylaxis is not treatment, and often the two may be confused in the minds of physicians geared toward the treatment of infection. I commend our colleagues from the ESCRS for undertaking an ambitious, multicenter, multinational study in an attempt to provide evidence-based data comparing topical antibiotics and intracameral cefuroxime in patients undergoing cataract surgery.

The investigators reported postoperative endophthalmitis in the intracameral cefuroxime group (0.07%) and a surprisingly high rate in the control group (0.34%). The findings suggest a highly favorable reduction with intracameral cefuroxime compared with topical antibiotics. The incidence of this complication reported in other European studies varies (0.05% to 0.20%).

US cataract surgeons should take note of the ESCRS’ study without overly extrapolating the findings to the prevailing situation in this country’s ambulatory surgery centers. The ESCRS’ study involved levofloxacin in the topical arm rather than the advanced-generation 8-methoxy fluoroquinolone compounds most commonly used in the US that have a greater antibacterial potency and superior aqueous penetration.

Although intracameral injection is indeed a direct delivery route that may be rational for prevention, problems with dilutional errors and toxicity need to be considered, as evidenced by the recent epidemic of TASS. Moreover, the pharmacodynamics of intracameral medications needs careful study, because the turnover rate of the aqueous humor is accelerated after phacoemulsification.

Cases of postoperative endophthalmitis after the use of intracameral cefuroxime is mostly due to a high rate of resistance to this drug among the ocular isolates causing endophthalmitis. Other limitations of cefuroxime include extemporaneous compounding, short-term stability, and hypersensitivity. The ESCRS’ study may therefore hint at the right concept (intracameral delivery) without using the most advantageous agent. The study’s results suggest that the optimal antibiotic regimen and route of delivery for the prevention of endophthalmitis in cataract surgery require further study.

**SAMUEL MASKET, MD**

Endophthalmitis remains a serious concern for both patients and physicians. Furthermore, its management represents a significant economic burden in direct and indirect healthcare costs. Given its relative rarity and the many variables in surgical styles, etc, the condition’s prophylaxis has been difficult to study.

As one strategy for preventing postsurgical infection, ophthalmic surgeons have often employed intracameral antibiotics, but the evidence that this practice is beneficial has been largely derived from anecdotal case series and/or...
from survey data. Although recent studies have confirmed a potential anti-infective benefit, the investigations were not controlled. The routine use of intracameral antibiotics has therefore been somewhat controversial, because numerous questions about its use remain.

Many surgeons have been concerned that errors in diluting antibiotics for intraocular instillation could harm more eyes than would possibly be saved from infection. Other questions include:

- Which agent(s) is best?
- What is the appropriate dosage?
- What are the potential toxicities?
- Is it best to infuse antibiotic(s) with balanced salt solution, to add a bolus of antibiotic at the close of surgery, or to do both?

Although the answers to some of the questions are a matter of pharmacodynamics, others have not been well studied. Now, with the release of preliminary data from the collaborative, randomized, prospective investigation by the ESCRs, there is seemingly bona fide evidence of the prophylactic benefit of intracameral antibiotics, at least with respect to cefuroxime, a second-generation cephalosporin.

The ESCRs’ investigation provided an answer to an important question, but, as to be expected, it generated new queries. Only one topical antibiotic, a third-generation fluoroquinolone (levofloxacin), was investigated, and it was found to offer no statistical benefit against infection when employed in the manner of the ESCRs’ study protocol. Would the fourth-generation topical agents (moxifloxacin and gatifloxacin) used more commonly in the US have proven more effective?

The rates of infection in the ESCRs’ investigation were alarmingly high; only the group receiving the intracameral cefuroxime displayed a rate of infection that approached those reported in the accepted literature. Greater attention to the incision’s construction and closure is clearly warranted. Is cefuroxime the appropriate agent for intracameral use in the US? Are the offending microbes in this country similar or dissimilar to those in Europe? Would it be more appropriate to consider intraocular doses of fourth-generation fluoroquinolones or other agents?

All in ophthalmology are indebted to the ESCRs for conducting this important investigation. Now, the results must be carefully evaluated, and new investigations, where appropriate, should begin. Heretofore, the FDA has been reluctant to consider new drug applications for prophylactic intraocular antibiotics. We can hope that the evidence from the ESCRs, if accepted as valid, will make the agency more prone to consider such products. Given the chance to produce unit doses of antibiotics, the ophthalmic pharmaceutical industry may be able to provide surgeons with commercially available single doses in order to prevent errors in diluting antibiotics.

At present, surgeons should compare their own rates of infection with those reported by the ESCRs. Should the surgeon’s experience be favorable, perhaps no change in prophylaxis is needed. If the surgeon’s rates are high, however, then careful attention to all aspects of infection’s prevention is warranted, including the use of intracameral antibiotics.

All recommendations for antibiotic prophylaxis in cataract surgery are currently off label.

Steve Arshinoff, MD, FRCS, is in private group practice at York Finch Eye Associates in Toronto, and he is a lecturer at the University of Toronto. Dr. Arshinoff is a consultant for Alcon Laboratories, Inc., and Advanced Medical Optics, Inc., but he states that he receives no commercial benefit from any antibiotic-related work or recommendations. Dr. Arshinoff may be reached at (416) 745-6969; saaeyes@direct.com.

Eric D. Donnenfeld, MD, is a partner in Ophthalmic Consultants of Long Island and Connecticut, and he is Co-Chairman of Corneal and External Disease at the Manhattan Eye, Ear, and Throat Hospital in New York. He is a consultant for Allergan, Inc., Alcon Laboratories, Inc., and Bausch & Lomb. Dr. Donnenfeld may be reached at (516) 766-2519; eddoph@aol.com.

Francis S. Mah, MD, is Assistant Professor for the Department of Ophthalmology and Medical Director for The Charles T. Campbell Ophthalmic Microbiology Laboratory at the University of Pittsburgh School of Medicine. He is a consultant for and has received research grants from Alcon Laboratories, Inc.; Allergan, Inc.; Ista Pharmaceuticals, Inc.; Insite Vision Incorporated; Polymedix Inc.; and Mpex Pharmaceuticals, Inc. Dr. Mah may be reached at (412) 647-2259; mahfs@upmc.edu.

Samuel Masket, MD, is in private practice in Century City and is Clinical Professor of Ophthalmology at the UCLA Geffen School of Medicine, Jules Stein Eye Institute, Los Angeles. Dr. Masket is also the President of the ASCRS. He is a consultant to Alcon Laboratories, Inc. Dr. Masket may be reached at (310) 229-1220; sammasket@aol.com.

Terrence P. O’Brien, MD, is Professor of Ophthalmology and Charlotte Breyer Rodgers Distinguished Chair in Ophthalmology at the Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, in Palm Beach, Florida. He is a nonsalaried consultant for Alcon Laboratories, Inc., Allergan, Inc., Bausch & Lomb, and Santen, Inc. Dr. O’Brien
may be reached at (561) 515-1544; tobrien@med.miami.edu.

Randall J. Olson, MD, is the John A. Moran Presidential Professor, Chair of Ophthalmology, and Director of the John A. Moran Eye Center at University of Utah Health Sciences in Salt Lake City. He is a consultant to Allergan, Inc. Dr. Olson may be reached at (801) 585-6622 or (801) 581-8703; randall.olson@hsc.utah.edu.

Richard B. Packard, FRCS, FRCOphth, is Clinical Director of the Prince Charles Eye Unit at King Edward VII Hospital in Windsor, United Kingdom. He acknowledged no financial interest in the material mentioned herein. Mr. Packard may be reached at +44 20 7580 1074; eyequack@vossnet.co.uk.