The Implications of the ESCRS Study

Before changing their protocol, cataract surgeons must examine the study and its implications.

BY DEEPINDER K. DHALIWAL, MD

The ESCRS study of the prophylaxis of postoperative endophthalmitis after cataract surgery[1] created quite a stir among ophthalmologists. Finally, there was a prospective, randomized, placebo-controlled study demonstrating a benefit of intracameral antibiotics in preventing endophthalmitis. Specifically, the report showed that an intracameral injection of cefuroxime at the end of cataract surgery lowered the risk of endophthalmitis by a factor of five. This landmark study evaluated nearly 14,000 patients from 24 centers in nine European countries. Additional risk factors for endophthalmitis gleaned from the study included clear corneal wounds and silicone IOLs.[2]

Before we surgeons all instruct our surgical nurses to take 750 mg of cefuroxime powder and dilute it to a concentration of 1 mg/0.1 mL of balanced salt solution for our next cataract cases, we need to examine the study closely and understand its implications.

TOPICAL ANTIBIOTICS

Fourth-Generation Fluoroquinolones

The subjects of the ESCRS study were not treated with what we consider the standard of care in the US for surgical prophylaxis, fourth-generation fluoroquinolones, both pre- and postoperatively. Although all patients received preoperative povidone-iodine and postoperative levofloxacin (a third-generation fluoroquinolone), only two of the four groups received preoperative levofloxacin. It has been demonstrated in several studies that the fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, have an improved spectrum of coverage, higher potency, delayed antibiotic resistance, and better tissue penetration (especially moxifloxacin) when compared with second- and third-generation fluoroquinolones.[3]

An animal study conducted at the University of Pittsburgh[4] showed that topical moxifloxacin could *prevent* postoperative endophthalmitis in eyes that had been inoculated with *Staphylococcus aureus*. The eyes that did not receive topical moxifloxacin all developed endophthalmitis due to the number of organisms inoculated in the eye. None of the eyes that received topical moxifloxacin before and after inoculation developed endophthalmitis. This striking study illustrated just how powerful topical antibiotics can be in the prevention of endophthalmitis. It showed that a topical agent can penetrate the eye at a high enough concentration to reach therapeutic, bacteriocidal levels. It is unknown what the ESCRS study's results would have been had all patients received pre- and postoperative moxifloxacin or gatifloxacin.

Safety

The greatest advantage of topical antibiotic prophylaxis over intracameral antibiotics is safety. There is no concern of dilutional error, toxic anterior segment syndrome, endothelial toxicity, or the introduction of potentially contaminated substances into the anterior chamber. Antibiotics for intracameral use must be mixed correctly 2,700 times to reduce severe visual loss from endophthalmitis in one patient while avoiding toxic ocular effects in noninfected patients.[5] When mixed in the appropriate concentration, cefuroxime has not demonstrated any toxicity to the corneal endothelium or retina.[6] The pH of the solution is 7.42, and the osmolality is 311 mOsm/kg, well within the suitable range for humans.[5] Also, another study has shown no increased incidence of cystoid macular edema in patients who received intracameral cefuroxime.[7]

An additional issue in regard to an antibiotic's safety is a patient's potential hypersensitivity to the drug. Someone who is allergic to a topical agent will typically have contact dermatitis or conjunctivitis but will not develop an anaphylactic reaction. Patients with hypersensitivity to an intracameral agent, such as cefuroxime, can actually develop systemic anaphylaxis with associated morbidity and possible mortality, as reported by Villada et al.[8] They

described a patient with a history of allergy to oral ampicillin who received 1 mg of cefuroxime intracamerally (the same concentration as used in the ESCRS study) at the conclusion of an uncomplicated phaco case. Five minutes later, the patient developed problems breathing and went into hypovolemic shock due to the anaphylactic reaction. Fortunately, the anesthesiologist was present in the recovery room and quickly administered intravenous methylprednisolone, ephedrine, 3 L of Ringer's lactate solution, and antihistamines. The patient recovered from this life-threatening allergic reaction in half an hour but was admitted to the hospital for observation. Referring to this case, Liu et al[9] stated, "conceptually speaking, intracameral antibiotic administration in a patient with a history of antibiotic allergy is highly akin to the direct intravenous route of administration in terms of bioavailability, particularly in the face of a disrupted blood-aqueous barrier during phacoemulsification."

The rate of any hypersensitivity to a cephalosporin such as cefuroxime is reported to be 1% to 3%.[10] The rate of anaphylaxis with cephalosporins is reported to be 0.1% to 0.0001%.[11] With approximately 2.5 million cataract surgeries performed each year in the US, as many as 2,500 patients per year could potentially develop anaphylaxis if every case were performed according to the ESCRS study guidelines and each patient received intracameral cefuroxime. Montan and colleagues[6] continue to use cefuroxime on a wide-scale basis in Sweden by pretreating patients with a history of anaphylaxis to this antibiotic with oral antihistamines. In the ESCRS study, patients were excluded if they were allergic to penicillins and cephalosporins. What if the patient has not been exposed to enough antibiotics, however, to realize a hypersensitivity exists?

Compliance

Topical antibiotic prophylaxis depends on patients' compliance in order to be effective. Intracameral antibiotics have the advantage of being placed into the anterior segment at the conclusion of surgery. Moreover, these agents are effective if they have a sufficiently high concentration for an adequate length of time with a spectrum of activity that encompasses the organisms that enter the anterior chamber during or soon after cataract surgery.

SPECTRUM OF ACTIVITY

The decision to use cefuroxime in the ESCRS study was based on work by Montan et al,[12] who showed a statistically significant reduction in postoperative endophthalmitis in patients who had received intracameral cefuroxime in a prospective, uncontrolled, 3-year survey. Cefuroxime is a second-generation cephalosporin with fair antibiotic coverage against gram-positive organisms and some gram-negative organisms. It has a time-dependent killing action, and its bacteriocidal effect is due to interference with cell wall synthesis. In terms of bacterial susceptibility, cefuroxime has good activity against most *Staphylococcus* and *Streptococcus* species, *Escherichia coli*, *Proteus* species, *Propionibacterium* species, *Klebsiella*, and *Haemophilus influenzae*. There are significant gaps in coverage, however. Cefuroxime does not cover methicillin-resistant *S. aureus* (MRSA), some *Enterococcus* strains, and *Pseudomonas*. It is important to note that patients from long-term nursing homes were not eligible to participate in the ESCRS study, because this patient population is known to have a greater risk of colonization with resistant strains of bacteria such as MRSA.

A study performed at the University of Pittsburgh showed that moxifloxacin and gatifloxacin provided higher susceptibility to *Bacillus*, *Enterococcus*, and gram-negative bacteria than cefuroxime using actual endophthalmitis isolates and equal susceptibility for *Staphylococcus* and *Streptococcus* strains. The researchers concluded that, in regard to the choice of an intracameral agent, fourth-generation fluoroquinolones might provide more broad-spectrum coverage of endophthalmitis-causing bacteria than cefuroxime.[13]

EFFICACY OF CEFUROXIME

Due to the constant turnover of aqueous, the concentration of a drug in the anterior chamber would decrease by one half in 70 minutes, although it might decrease even more rapidly due to quicker aqueous dynamics in the postoperative inflamed eye.[14] A study evaluating the pharmacokinetics of intracameral cefuroxime determined that the concentration declined by a factor of four in 1 hour.[5] Cefuroxime has a slower, time-dependent bacteriocidal action, and, therefore, a certain amount of time must pass before bacteria are killed, even if the concentration of antibiotic is very high. In contrast, agents such as the fluoroquinolones are concentration dependent.

A kinetics of kill study was performed with cefuroxime against staphylococcal ocular isolates.[15] It showed that less than one log kill was achieved in 3 hours. The researchers contrasted this result to the kinetics of kill of moxifloxacin, which showed a greater than three log kill (> 99.9%) after less than 2 hours. This difference may explain the development of endophthalmitis secondary to a cefuroxime-susceptible strain of *S. aureus* in a patient who received intracameral cefuroxime at the end of surgery.[11]

CONCLUSION

The authors of the ESCRS study on the prophylaxis of postoperative endophthalmitis after cataract surgery should be congratulated for undertaking this important task. They designed a partially masked, randomized, placebo-con-

trolled, multinational clinical study to prospectively evaluate the effect of intracameral cefuroxime and/or perioperative topical levofloxacin on postoperative endophthalmitis. Although the total study size goal was 35,000 patients, the study was halted at the end of 2005 after the recruitment of only 13,698 patients, because a clearly beneficial effect from the use of intracameral cefuroxime had been observed.

There are several factors we need to keep in mind before we change our practice patterns in 2007. First, certain groups of patients were ineligible to participate in the ESCRS study, including nursing home patients. In addition, cefuroxime is a slow, time-dependent killer that is ineffective against MRSA, *Pseudomonas*, and some *Enterococcus* species. There are several issues of safety with this agent, including reports of severe anaphylaxis. Finally, ESCRS study patients did not receive adjunctive topical fourth-generation fluoroquinolones, which have an improved spectrum of coverage, higher potency, delayed antibiotic resistance, and better tissue penetration compared with the third-generation fluoroquinolone used in the ESCRS study. ■

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