INTRACAMERAL PROPHYLAXIS IN CATARACT SURGERY

Selecting an agent.

BY STEVE ARSHINOFF, MD, FRCSC

Since the publication of the European Society of Cataract & Refractive Surgeons (ESCRS) Study Group's report, intracameral (IC) antibiotic prophylaxis against endophthalmitis has been standard in most European countries.[1] Canadian ophthalmologists, straddling European and US medical practices, adopted IC antibiotics with reluctance. US surgeons looked at their own low rates of postoperative infection, and they wondered why the rest of the world published higher rates without IC prophylaxis and then added IC antibiotics to bring the rates down to what Americans thought were typical of the US experience with topical antibiotics alone.[2-4]

As time went on and more studies were published, however, it became apparent that, no matter what the baseline rate of infection was in each study, the introduction of IC antibiotics decreased it by about 80%, as the ESCRS study had reported. The table lists numerous small and large studies using IC cephalosporins, all of which support this statement. The aggregate number of eyes treated exceeds 1 million, an aggregate sample size probably exceeding anything previously reported in ophthalmology and giving the data great weight in our deliberations over the issue.

Once we surgeons acknowledge the evidence that IC antibiotics decrease the postoperative infection rates significantly after cataract surgery, our next task is to identify the best antibiotic. The ESCRS study, which analyzed only IC cefuroxime, never addressed this issue. Other antibiotics may be better or worse. For us to decide on the "best" IC prophylaxis for our patients, we desperately need comparative data on whatever antibiotics are available to us.

CANDIDATES

A survey of available antibiotics shows that our armamentarium is shallow in bench strength. We are looking for a broad-spectrum antibiotic. Although 95% of postoperative intraocular infections have always been reported to be gram-positive, with *Staphylococcus epidermidis* the most common, gram-negative infections tend to be devastating to the eye.

A very small safety margin in ocular tissues makes aminoglycosides—long-standing favorites in medicine—poor candidates for prophylactic use. Only five agents are reasonable candidates for IC prophylaxis: the complex glycopeptide vancomycin; two cephalosporins, cefazolin and cefuroxime; and the fourth-generation fluoroquinolones gatifloxacin and moxifloxacin. Within the cephalosporin class, cefuroxime has a broader spectrum than cefazolin. Because cefazolin has no particular comparative advantage, cefuroxime has become the favorite. Among the fourth-generation fluoroquinolones, gatifloxacin has been shown to cause dysglycemia when administered systemically, so the systemic product was withdrawn from global markets. The topical preparation of this drug, Zymar (Allergan), contains benzalkonium chloride, making it undesirable for intraocular injection. Moxifloxacin is easily available in a self-preserved and appropriately concentrated nonpreserved solution for our needs as Vigamox (Alcon), so it is the logical choice in this class. We are therefore left with three agents from which to choose: vancomycin, cefuroxime, and the Vigamox preparation of moxifloxacin.

ATTRIBUTES TO COMPARE

To compare the three available agents, we must consider five microbiological and pharmacological attributes.

No. 1. Activity

Bactericidal antibiotics exhibit either time- or dose-dependent activity. Bacteriostatic agents are not desirable for our intended use, because their duration of action is limited in the anterior chamber (AC) by aqueous turnover. Both vancomycin and cefuroxime inhibit bacterial cell wall synthesis and exhibit time-dependent effects. Montan et al have shown that the concentration of an antibiotic in the AC drops by 50% every half-hour, making time-dependent kinetics relatively undesirable for IC prophylaxis.[5] Alternatively, moxifloxacin operates through inhibition of DNA gyrase and topoisomerase, and the agent demonstrates dose-dependent kinetics. Research has shown this drug to be considerably more effective in killing *Staphylococcus aureus* in culture than cefuroxime at dosing levels achieved in IC injections into the AC.[2,6]

TABLE. PUBLISHED STUDIES OF INTRACAMERAL PROPHYLAXIS WITH CEPHALOSPORINS[a]

Study	IC Antibiotic	Years	N	POE: No IC	POE: IC	Rate	*P* Value
Garat et al[1] Barcelona, Spain	Cefazolin 2.5 mg/0.1 mL	2004-2007	18,603	1/240	1/2,130	0.047%	< .001
Romero et al[2] Reus, Spain	Cefazolin 1 mg/0.1 mL	2001-2004	7,268	1/160	1/1,809	0.055%	< .001
Garcia-Saenz[3] Madrid, Spain	Cefuroxime 1 mg/0.1 mL	1999-2008	13,652	1/169	1/2,352	0.043%	< .001
Montan et al[4] Sweden	Cefuroxime 1 mg/0.1 mL	1990-1999	66,200	1/383	1/1,600	0.06%	< .001
Wejde et al[5] Swedish NCR	Cefuroxime 1 mg/0.1 mL	1999-2001	188,151	1/454	1/1,887	0.053%	< .001
Lundström et al[6] Swedish NCR	Cefuroxime 1 mg/0.1 mL	2002-2004	225,471	1/290	1/2,231	0.045%	< .001
Friling et al[7] Swedish NCR	Cefuroxime 1 mg/0.1 mL	2005-2010	464,996	1/255	1/3,756	0.027%	< .001
ESCRS Study Group[8]	Cefuroxime 1 mg/0.1 mL	2003-2006	16,603	1/357	1/1,621	0.07%	< .001
Shorstein et al[9] Kaiser, California	Cefuroxime 1 mg/0.1 mL	2007-2011	16,264	1/310	1/3,125	0.032%	< .001
Arshinoff and Bastianelli[10] ISBCS	Cefuroxime 1 mg/0.1 mL	2010-2011	69,720	1/1,987	1/9,175	0.011%	< .01
Sum	Weight averaged	1990-2011	1,086,928	1/412	1/3,242	0.031%	< .001

Abbreviations: IC, intracameral; POE, postoperative endophthalmitis; NCR, National Cataract Register; ESCRS, European Society of Cataract & Refractive Surgeons; ISBCS, immediate sequential bilateral cataract surgery.
aTen studies, ranging from very small to extremely large, all demonstrate approximately an 80% reduction in the POE rate when IC cephalosporin prophylaxis is used, as does the weight-averaged sum of the data. Dates refer to surgery dates.

1. Garat M, Moser CL, Martin-Baranera M, et al. Prophylactic intracameral cefazolin after cataract surgery: endophthalmitis risk reduction and safety results in a 6-year study. *J Cataract Refract Surg*. 2009;35:637-642
2. Romero P, Mendez I, Salvat M, et al. Intracameral cefazolin as prophylaxis against endophthalmitis in cataract surgery. *J Cataract Refract Surg*. 2006;32:438-441.
3. Montan PG, Wejde G, Koranyi G, Rylander M. Prophylactic intracameral cefuroxime. *J Cataract Refract Surg*. 2002;28:977-981, 982-987.
4. Wejde G, Montan P, Lundstrom M, et al. Endophthalmitis following cataract surgery in Sweden: national prospective survey 1999-2001. *Acta Ophthalmol Scand*. 2005;83:7-10.
5. Lundström M, Wejde G, Stenevi U, et al. Endophthalmitis after cataract surgery: a nationwide prospective study evaluating incidence in relation to incision type and location. *Ophthalmology*. 2007;114:886-870.
6. ESCRS Endophthalmitis Study Group. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33:978-988.
7. García-Sáenz MC, Arias-Puente A, Rodríguez-Caravaca G, Bañuelos JB. Effectiveness of intracameral cefuroxime in preventing endophthalmitis after cataract surgery: ten year comparative study. *J Cataract Refract Surg*. 2010;36:203-207.
8. Friling E, Lundström M, Stenevi U, Montan P. Six-year incidence of endophthalmitis after cataract surgery: Swedish national study. *J Cataract Refract Surg*. 2013;39:15-21.
9. Shorstein NH, Winthrop KL, Herrinton LJ. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *J Cataract Refract Surg*. 2013;39:8-14.
10. Arshinoff SA, Bastianelli PA. Incidence of postoperative endophthalmitis after immediate sequential bilateral cataract surgery. *J Cataract Refract Surg*. 2011;37:2105-2114.

No. 2. Scope

All three antibiotic candidates for IC use raise potential concerns about their scope of bacterial coverage. Vancomycin is ineffective against gram-negative bacteria. Cefuroxime is ineffective against methicillin-resistant *S aureus* and coagulase-negative staphylococci as well as gram-negatives. Moxifloxacin, perhaps because of its extremely common and general usage, is encountering progressive resistance from *S epidermidis* and other bacteria. This reported assessment of resistance, however, is based upon levels of the antibiotic attained in serum with systemic administration and not on intraocular levels attained with IC use.

No. 3. Allergy

Allergic responses are much more common to cephalosporins than to vancomycin or moxifloxacin.

Figure 1. Aprokam, prediluted cefuroxime for IC injection, is marked for single use but is not available in the United States.

Figure 2. 4 Quin PFS 0.5 mL, 0.5% isotonic moxifloxacin in a single-use prefilled syringe, is supplied with a disposable 27-gauge hockey-stick cannula. It is also unavailable in this country.

No. 4. Preparation

Single-use preparations of IC antibiotics are not available to US surgeons, and the dilution of the available systemic preparations is particularly complex for both vancomycin and cefuroxime, requiring the use of Millipore filters. Moxifloxacin has been used at either full strength from the Vigamox bottle or in very simple dilution formulas (as will be discussed) not requiring Millipore filtration, because the drug is supplied in solution. Only the Vigamox brand of moxifloxacin has been demonstrated to be safe for IC use. Other preparations such as Moxeza (Alcon) have been shown to be unsafe.

For single use, an anhydrous preparation of 50 mg cefuroxime (Aprokam; Thea Laboratories; not FDA approved), when reconstituted with 5 mL saline, contains 1 mg/0.1 mL—the commonly used concentration for IC injection of the standard dose of 0.1 mL. It is safely prediluted but not really a single-use preparation, unless 96% of the reconstituted solution is simply discarded (Figure 1). With respect to moxifloxacin, 4 Quin PFS (Entod Pharmaceuticals; not FDA approved) is a single-use preparation containing 0.5 or 1 mL of 0.5% in a prefilled syringe (Figure 2). It is to be hoped that these prediluted single-use preparations will be made available to US surgeons in the near future.

No. 5. Infection

Finally, we must consider what happens in the event that our IC prophylaxis is unsuccessful. If an infection occurs after we use IC moxifloxacin, it will likely be moxifloxacin-resistant *Staphylococcus*, which is usually very sensitive to the typical endophthalmitis protocol of vancomycin and ceftazidime. (Moxifloxacin acts by a completely different mechanism than vancomycin and ceftazidime, reducing the risk of cross-resistance.) In contrast, infections that occur with IC cefuroxime are often destructive, resistant bacteria such as *Enterobacter*. (Cefuroxime acts by a mechanism similar to that of ceftazidime and vancomycin, making cross-resistance more likely.)

Generally, it is better for us to perform prophylaxis with an agent completely unrelated to the agents we currently use as a last resort to treat endophthalmitis than routinely to use one of those agents for prophylaxis (vancomycin) or a closely related agent (cefuroxime).

RESEARCH

In 2013, a Cochrane Review of the prevention of acute endophthalmitis after cataract surgery was published.[7] The investigators searched the literature up to October 25, 2012. Of the 492 reports on postoperative endophthalmitis prophylaxis that they reviewed, only four met the authors' rigid criteria. These studies involved 100,876 patients.

Two of the accepted reports were published in 1979 and 1986 by Norval Christy and colleagues.[8,9] These researchers reviewed their experience with intracapsular cataract surgery in cataract camps in Northern Pakistan for which they used 500,000 units of benzyl penicillin via subconjunctival or retrobulbar injection for prophylaxis. The Cochrane Review also included the ESCRS study and a 2003 study by Sobaci et al.[10] The latter reviewed their experience using vancomycin and gentamicin in the bag of irrigating balanced salt solution while performing phacoemulsification on 644 eyes. (This study reported no significant findings.)

The conclusions of the Cochrane Review—in the authors' attempt to relate to modern phaco surgery—were therefore based almost entirely on the ESCRS study and their reading of other articles that were excluded from the Cochrane Review. The conclusions favored IC antibiotics and single-use commercial preparations. The review's authors suggested a randomized controlled trial of IC moxifloxacin versus IC cefuroxime.

MY CONCLUSION

For the reasons set forth in this article, I have chosen to use moxifloxacin routinely for IC prophylaxis for cataract and other surgical cases—more than 7,000 eyes as of December 1, 2014. It is desirable that the AC concentration

INTRACAMERAL MOXIFLOXACIN PREPARATION AND USE

SUPPLIED

Alcon: Vigamox (moxifloxacin [Bayer]) 0.5% eye drops = 500 µg/0.1 mL

GOAL

150 µg/0.1 mL (dilution: 3 parts Vigamox + 7 parts BSS [Alcon])
To get 150 µg/0.1 mL, simply dilute eye drops to 30% concentration of supplied Vigamox.

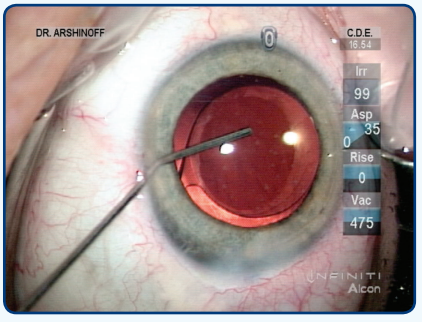
METHOD

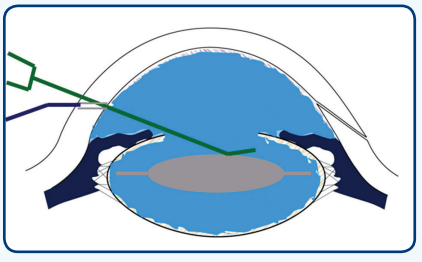
Inject 0.3 mL of Vigamox 150 µg/0.1 mL at the end of each case = 450 µg → 1.5 mg/mL in the anterior chamber.
(This is essentially an exchange of the entire anterior chamber volume with the Vigamox solution.)

TO MAKE UP 150 µG/0.1 mL VIGAMOX

1. 3 mL Vigamox is withdrawn into a 10- or 12-mL syringe with a sterile needle from a new Vigamox bottle.
2. 7 mL BSS is drawn into the same syringe from a new 15-mL BSS bottle (mixed by the turbulence of aspiration).
   - 0.5 mL is injected into a medicine cup on a surgical tray by the circulating nurse
3. The scrub nurse draws up the Vigamox solution into a tuberculin syringe to hand to the surgeon.
4. The surgeon injects approximately 0.3 mL through the sideport as the last step of surgery under the distal capsulorhexis edge (1) and then exits the eye with a final injected spurt at the incision (2), he or she making sure the anterior chamber is left pressurized. This is a planned exchange of the entire contents of the anterior chamber and is therefore very easy to do.

Note: I have performed more than 7,000 cases to date using variations of this method and have seen no toxicity.





of Vigamox exceed the MIC_{90} (minimum inhibitory concentration) of the most resistant staphylococci reported to date of 32 mg/L (usual staphylococcal sensitivity is to 0.06 mg/L) by a factor of 10 (ie, 320 mg/mL) for a sufficient period to ensure a bactericidal effect.[11] If the concentration drops by 50% every half-hour, as Montan has demonstrated (see No. 1 under Attributes to Compare),[5] we need to inject at least 320 × 4 = 1,280 mg/mL to be assured of 320 mg/mL after 1 hour. It is desirable to administer the drug in a manner that can be easily and consistently performed, leaving the eye sealed and the surgical procedure finished.

I prefer simply to replace the entire AC volume with the antibiotic solution injected through the sideport incision rather than to inject the traditional 0.1 mL. My reasons are as follows. First, an AC replacement injection does not really require measurement (but is about 0.3 mL). Second, it allows me to use the moxifloxacin solution to irrigate into the capsular bag (a sequestered space containing a foreign body) and to ensure, while exiting the AC, that the sideport incision through which it has been administered has been sealed with the injection.

In order to replace the entire AC volume with the injected solution, it is necessary to dilute the moxifloxacin such that the AC is irrigated with a solution not dissimilar to BSS (Alcon). Vigamox contains 500 µg moxifloxacin per 0.1 mL (5 g/L). I dilute it by adding 7 mL of BSS to the full content of the Vigamox bottle (3 mL) in a 12-mL syringe (see *Intracameral Moxifloxacin Preparation and Use*). Injecting

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0.1 mL directly from the Vigamox bottle yields an AC concentration of 1,660 mg/L, whereas replacing the AC volume with the solution I use and sealing the incision with it yields a final AC concentration of 1,500 mg/L. Both achieve the desired 10× bactericidal dose for the most resistant staphylococci for over 1 hour after surgery, despite progressive aqueous dilution with time. ■

Editor's note: all intracameral injections of antibiotics are off label.

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