Progress in Understanding Prophylaxis for Endophthalmitis

Data offer better insight into the relevance of aqueous humor antibiotic levels.

BY SUSANNE GARDNER, PharmD

Recent publications have helped to clarify the role of topical antibiotics in the prophylaxis of endophthalmitis after cataract surgery. Administering topical antibiotic drops, in addition to standard povidone-iodine antisepsis, has become a standard of care in these prophylactic regimens. The need to cleanse the ocular surface and reduce or eliminate surface microflora was emphasized in studies that showed these surface microorganisms were often identical to strains isolated in endophthalmitis cases. Using genetic analysis, investigators found that organisms recovered from the vitreous were genetically identical to isolates from patients' own eyelids, conjunctiva, or nose.[1] These findings support the need for surgeons to pay close attention to external surfaces of the eye as potential sources of contamination in prophylactic regimens. However, the development of newer antibiotic agents, that offered better corneal penetration and a broader spectrum of action raised interest in the ability of these agents to also provide protection within the eye, in the anterior segment.

STERILIZATION OF THE OCULAR SURFACE

Newer antibiotics, such as the fluoroquinolones, offer advantages over older classes of antibiotics, such as aminoglycosides, by virtue of the former's broader spectrum of action and relatively low tissue toxicity. Investigators were eager to test the ability of these new agents to eliminate bacteria, not only from the ocular surface prior to surgery, but also perioperatively by examining penetration to inner ocular structures, particularly the aqueous humor. By culturing external ocular surfaces, and measuring aqueous humor penetration, a number of studies have examined the value of adding fourth-generation fluoroquinolone drops to povidone-iodine in varying topical drop regimens.

Despite increasing doses, He and associates found that no further reduction of conjunctival flora was achieved with a 3-day versus 1-day q.i.d. dosing regimen of moxifloxacin drops.[2] Another study found similar results using gatifloxacin drops, where q.i.d. dosing for 3 days preoperatively, along with povidone-iodine, showed no advantages over povidone-iodine preparation alone.[3] In fact, a 4% to 8% positive conjunctival culture rate remained. Bucci and associates reported that, when both of these fluoroquinolone drops were administered more intensively just prior to surgery (one drop every 10 minutes, for four doses) in addition to a 2-day regimen, the study group receiving more intensive treatment surprisingly showed the higher rate of aqueous humor contamination. Furthermore, complete eradication of bacteria from the conjunctiva or eyelids was not achieved.[4] For historical perspective, irrigating solutions have also not guaranteed sterility. After use of an irrigating solution with the combination of vancomycin plus gentamicin, a 5% anterior chamber contamination rate remained.[5]

The fact that external flora persist as potential contaminants, despite preoperative antisepsis, is alarming, particularly considering the potential for inflow of extraocular fluid after wound hydrosealing and sutureless corneal incisions, as shown by Herretes and associates.[6]

TABLE 1. MEAN AQUEOUS HUMOR FLUOROQUINOLONE LEVELS (µG/ML) AFTER TOPICAL DROPS

Moxifloxacin	Gatifloxacin	Levofloxacin		Besifloxacin	
0.5%	0.3%	0.5%	1.5%	0.6%	
1.61 ±0.68				0.032 ±0.01	Yoshida 2010
		4.430 (2.56-7.46)			Sundelin 2009
		1.619			Bucci 2004
	0.052 ±0.143		0.976 ±2.215		Holland 2007
1.31	0.63				Solomon 2005
1.18 ±1.121	0.48 ±0.34				Kim 2005
1.74					Katz 2005
	1.26				Price 2005
2.28					Hariprasad 2005
1.86 ±1.06	0.94 ±0.72				McCulley 2006
2.16	0.82				Ong-Tone 2007
0.9	0.3				Holland 2008

SAMPLING OF AQUEOUS HUMOR

Studies over recent decades revealed that aqueous humor samples taken at the time of surgery showed persisting rates of bacterial contamination in at least 2% to 40% of cases, despite the use of prophylactic measures that included povidone-iodine.[7-9] Therefore, there is valid interest in our ability to deliver effective antibiotic levels to the anterior chamber, the surgical site during cataract surgery. Topically applied preoperative drops remain a primary focus for delivering these agents, although direct intracameral injection is shown to be clinically effective and superior to drops, as discussed later.

To measure the aqueous humor penetration of antibiotics after the instillation of topical drops, researchers use a familiar study model. Drops are given in various regimens preoperatively, and prior to the surgical incision, aqueous humor is sampled and assayed for antibiotic concentration. A great many preoperative dosing regimens have been tested in this manner, from intermittent dosing for several days preoperatively to frequently pulsed drops just before and after surgery. Results show that some drug penetration does indeed occur and that an increase in measured levels is possible by manipulating the frequency of drop administration. Table 1 displays some reported aqueous humor levels of fluoroquinolones after topical drop instillation. In these studies, inherent differences were present such as dosing regimen, drop concentration, drug lipophilicity/penetration characteristics, or presence of benzalkonium chloride, yet levels did not exceed the range of 1 to 4 µg/mL.

ASSESSING THE DATA

Several factors should be borne in mind when evaluating these reported levels of aqueous humor antibiotic concentrations. First, the levels of aqueous humor reported are means from patient study groups. A closer look at the standard deviations, when they are reported, demonstrates a huge interpatient variability. This naturally follows the very large interpatient variability that occurs to the tears after drop instillation. Table 1 displays some of these ranges, where standard deviations higher than 50% are commonplace. Since these mean concentrations are already low, the likelihood that a percentage of patients will experience even lower levels, due to the large variability, makes this form of dose delivery very imprecise.

In terms of the actual levels reported, what can eye care practitioners expect regarding the potential for bacterial killing in the aqueous humor? Reported aqueous humor antibiotic levels were regarded as sufficient if they exceeded the minimum inhibitory concentrations (MICs) of some bacterial strains. An assumption followed that these levels were adequate and would be clinically effective in eradicating bacteria

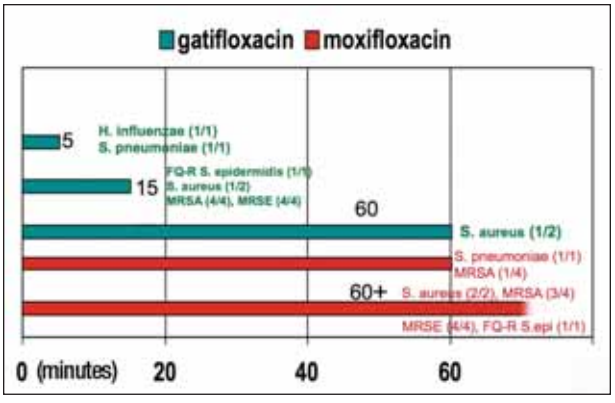

Figure 1. Time required for bacterial killing after exposure to full-strength gatifloxacin 0.3% and moxifloxacin 0.5% drops.[10] Abbreviation: FQ-R, fluoroquinolone-resistant.

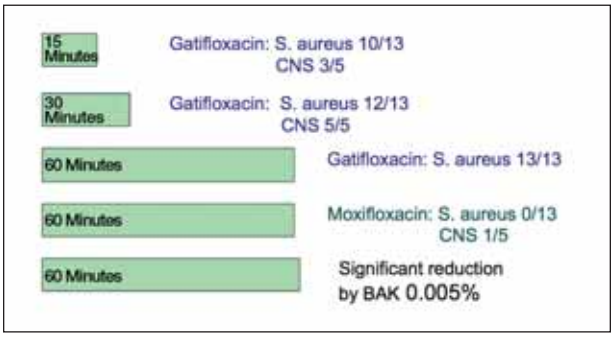

Figure 2. Time required to eradicate strains of staphylococci by full-strength gatifloxacin 0.3% drops, moxifloxacin 0.5% drops, and benzalkonium chloride 0.005%.[11] Abbreviations: CNS, coagulase-negative *Staphylococcus*; FQ, fluoroquinolone; BAK, benzalkonium chloride.

	Endophthalmitis rate (%)
Group C (pulsed drops)	0.247 (total) 0.173 (proven)
Group A Control	0.345 (total) 0.247 (proven)

Figure 3. Rates of postoperative endophthalmitis in two study groups of the ESCRS study on prophylaxis of endophthalmitis.[12] Percentage rates are total and proven of intent to treat populations.

that gain entry into the eye. However, the MIC is a definition of bacterial susceptibility or resistance generated by laboratory standards that involve incubation times near 24 hours. Therefore, any measured level must be correlated to the amount of time that microbes and antibiotic are in contact to assess the potential for bacterial eradication.

In real-life situations, these reported aqueous humor levels are not only relatively low but are also short-lived because of the approximately 2-hour aqueous turnover rate. Assuming a half-life in aqueous humor of 1 to 2 hours, a peak drug level of 1 mg/mL, for example, would become 0.5 µg/mL in 1 to 2 hours; then 0.25 µg/mL in 2 to 3 hours; then 0.125 µg/mL in 3 to 4 hours; 0.06 µg/mL in 4 to 5 hours, and so forth. Therefore, achieving a peak aqueous humor concentration of 0.5 µg/mL cannot be construed as an effective MIC if that antibiotic level in the aqueous humor is not sustained for a necessary period of time.

BACTERIAL KILLING RATES IN AQUEOUS HUMOR

Two recent studies assessed bacterial killing after the shorter time frames more akin to topical drop dosing in the eye (Figures 1 and 2). Callegan and associates used the full-strength commercially available moxifloxacin and gatifloxacin drop concentrations and evaluated bacterial killing over 5 to 60 minutes.[10] Hyon and associates performed a similar study that also looked at benzalkonium chloride independently.[11] Both studies showed that, even at concentrations of 3,000 and 5,000 µg/mL (the equivalent of the 0.3%- and 0.5%-drop concentrations), poor bacterial eradication was accomplished over shorter periods of time, and resistant organisms often persisted beyond the study period. Worth remembering is that the approximately 1- to 4-µg/mL fluoroquinolone concentrations found in aqueous humor after the administration of topical drops are approximately 1,000 times lower than the concentrations used in these studies. Therefore, the likelihood of effecting bacterial kill at these infinitesimally smaller concentrations, short-lived as they are in the aqueous humor, is somewhat remote.

An additional precaution in relating MICs to effective prophylaxis in aqueous humor is being aware of current MICs that accurately reflect the MICs (and MIC_{90}) of isolates taken from clinical cases of endophthalmitis and not from arbitrarily chosen "library" strains. Trends in actual endophthalmitis isolates reflect the true challenges for prophylactic regimens. When study discussions select only bacterial strains with low MICs, or strains with known high susceptibility, then conclusions can be skewed and may be a disservice to the daily needs of the clinician.

A final but important factor is that the aqueous humor antibiotic levels (Table 1) described after preoperative doses are expelled with the surgical incision, so even these low levels are no longer present during the operative and perioperative period. If meaningful antibiotic levels are expected to be present after the surgical procedure (that is, immediately after surgery and during the next week or 2 when patients self-administer drops), then the potential of topical drop regimens to achieve effective levels during these time periods should be viewed separately. Postoperative drop regimens are usually less vigorous than the preoperative regimens tested and are accompanied by the drawbacks of patients' self-administration and compliance.

Certainly, the anterior chamber may be capable of clearing a small inoculum of bacteria. However, as bacterial strains grow increasingly resistant, as the spectrum of bacteria identified in endophthalmitis isolates changes, and as the population of cataract patients

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CLINICAL EVIDENCE

Only one study has offered a prospective analysis of clinical outcomes after the use of topical drops for the prophylaxis of postoperative endophthalmitis. The ESCRS multicenter study of more than 16,000 patients allows comparison of outcomes among four treatment groups, including a control group and patients receiving frequently applied topical fluoroquinolone drops (levofloxacin 0.5%)—as well as patients receiving an intracameral injection of cefuroxime 1 mg.[12] The study group receiving the pulsed-dosing regimen of a topical fluoroquinolone did not achieve a statistically significant reduction in postoperative endophthalmitis rates compared with controls, although somewhat lower absolute rates were seen (Figure 3). While statistical powers were aimed primarily at evaluating the effects of the intracameral injection, the effect of topical drops, as applied in this study, versus controls could be observed in a subgroup of about 4,000 patients each. Here, the lack of statistical difference is of clinical interest and highlights the need to better define where and how topical antibiotics may best exert their effects. In contrast, the intracameral injection unequivocally reduced endophthalmitis rates by approximately fivefold.

An independent study reproduced the identical fluoroquinolone dosing regimen used in the ESCRS study. Investigators measured aqueous humor antibiotic levels over a 90-minute postdose period in pooled patient groups.[13] This dosing regimen produced the highest reported levels of fluoroquinolone in aqueous humor reported to date (4.4 µg/mL, Table 1); the regimen consisted of two preoperative drops (one each at 60 and 30 minutes preoperatively) plus three pulsed drops (one every 5 minutes at the end of surgery). The pulsed drops also served to replace levels lost at the beginning of surgery. In contrast to topical drops, the intracameral injection (1 mg or 1,000 µg cefuroxime in this case) is capable of delivering a much higher dose instantaneously to the aqueous humor, since drops must first diffuse through several corneal layers.

CONCLUSION

Recent evidence, taken together from reported antibiotic levels in the aqueous humor, studies that examined bacterial killing with high antibiotic concentrations over shorter periods of time, and clinical findings from a large multicenter trial, suggest we should take a closer look at expected antimicrobial effects in the aqueous humor after topical drop administration. Because these reported levels are consistently low, future investigations may benefit from closer scrutiny of antibiotic actions on the ocular surface, as compared with internal sites such as the aqueous humor, for the prophylaxis of postoperative endophthalmitis. ■

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