Acute Endophthalmitis in Eyes Treated Prophylactically with Gatifloxacin and Moxifloxacin

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• PURPOSE: To study the use of prophylactic fourth-generation fluoroquinolone antibiotics, gatifloxacin and moxifloxacin, and bacterial sensitivity in cases of acute postoperative endophthalmitis following cataract surgery.

• DESIGN: Retrospective, consecutive, observational case series.

• METHODS: Forty-two eyes of 42 patients with acute endophthalmitis occurring within six weeks after cataract surgery were identified. All patients were seen in a referral vitreoretinal practice over a two-year time interval. The number of patients using prophylactic gatifloxacin or moxifloxacin and results of bacterial culture and sensitivity to all fluoroquinolone antibiotics were recorded.

• RESULTS: Thirty-one of 42 eyes (74%) were treated with perioperative gatifloxacin or moxifloxacin and 24 eyes (57%) were continuously taking one of these antibiotics at the time of diagnosis. Nineteen eyes (45%) had a positive bacterial culture. The most frequent organism isolated was coagulase-negative *Staphylococcus*. Sensitivities were performed for 14 gram-positive organisms, and sensitivities to ciprofloxacin (50%), ofloxacin (44%), levofloxacin (46%), gatifloxacin (38%), and moxifloxacin (38%) were noted. Five organisms were resistant to gatifloxacin and moxifloxacin with a minimum inhibitory concentration of 8 μg/ml. All gram-positive organisms were sensitive to vancomycin. Median visual acuity improved from hand motions to 20/40 at last follow-up.

• CONCLUSION: Acute endophthalmitis can develop after cataract surgery despite the prophylactic use of fourth-generation fluoroquinolone antibiotics. Gram-positive organisms causing acute endophthalmitis are frequently resistant to all fluoroquinolones, including a significant number of cases resistant to gatifloxacin and moxifloxacin. (Am J Ophthalmol 2006;142:721–725. © 2006 by Elsevier Inc. All rights reserved.)

ENDOPHTHALMITIS IS AN UNCOMMON, BUT SERIOUS, consequence after intraocular surgery and can lead to severe visual loss. Recent studies have suggested that the incidence after cataract extraction has increased over the last decade.[1] Fluoroquinolones are a class of broad-spectrum, bactericidal antibiotics that cover many gram-positive, gram-negative, and anaerobic organisms. They are commonly used to treat ocular infections and are widely used as prophylactic agents before and following intraocular surgery to prevent endophthalmitis.

Second- and third-generation fluoroquinolone antibiotics, such as ciprofloxacin, ofloxacin, and levofloxacin, have excellent gram-negative coverage, but they are less potent against gram-positive organisms, notably *Staphylococcus* and *Streptococcus* isolates. Recently, two fourth-generation antibiotics, gatifloxacin and moxifloxacin, have been developed. Both are available for topical ophthalmic use: 0.3% gatifloxacin (Zymar®; Allergan, Inc, Irvine, California, USA) and 0.5% moxifloxacin (Vigamox®; Alcon Laboratories, Inc, Fort Worth, Texas, USA). In recent studies by Mather and associates[2] and Kowalski and associates,[3] gatifloxacin and moxifloxacin were shown to have increased activity against both fluoroquinolone sensitive and fluoroquinolone resistant gram-positive organisms.

Antibiotic resistance is a clinically significant issue. Increasing resistance of *Staphylococcus aureus* (*S. aureus*) and other gram-positive organisms to ciprofloxacin and ofloxacin has been noted in several studies.[4–6] Levofloxacin does not appear to have more activity against these resistant organisms.[7,8] Recent reports have shown that a relatively high level of in vitro resistance to fourth-generation fluoroquinolone antibiotics may exist in methicillin-resistant *Staphylococcus aureus* (MRSA) ocular surface isolates[9] and in archived MRSA isolates (Shah MK, ARVO Meeting 2004, Abstract). The purpose of this study was to examine the prophylactic use of fourth-generation fluoro-

Accepted for publication May 25, 2006.

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0002-9394/06/$32.00
doi:10.1016/j.ajo.2006.05.044

quinolones and bacterial sensitivity to gatifloxacin, moxifloxacin, and earlier generation fluoroquinolone antibiotics in cases of acute endophthalmitis.

METHODS

WE PERFORMED A RETROSPECTIVE CHART REVIEW OF consecutive cases of acute postoperative endophthalmitis (ICD-9 360.01) seen in a referral vitreoretinal practice in Long Island, New York. Approval for this study was obtained from the Institutional Review Board at our medical center. A computerized database was used to identify patients during a two-year time interval between September 1, 2003, and August 31, 2005. The sole inclusion criterion was a new hypopyon uveitis or severe anterior uveitis with vitritis (without hypopyon) occurring within six weeks of cataract surgery. The presence of ocular pain was regarded as supportive evidence, but was not required for diagnosis. Cases were excluded if endophthalmitis was chronic (diagnosed six weeks or longer after surgery), related to trauma, endogenous, or developed after an intraocular surgery or procedure other than cataract extraction.

Patients were treated according to the recommendations of the Endophthalmitis Vitrectomy Study.[10] Vitreous taps were performed in the office under sterile conditions and specimens were sent to an outside laboratory for Gram stain and culture testing. If a vitreous specimen was unable to be obtained, an anterior chamber specimen was obtained and sent for microbiologic testing. Immediate pars plana vitrectomy was recommended for any patient with light perception vision. All patients received an intravitreal injection of vancomycin (1 mg) and either ceftazidime (2.25 mg) or amikacin (400 μg). All patients were reexamined the following day, and then periodically thereafter, depending on their clinical progress. Patients were returned to their referring ophthalmologist when their examination was stable.

The following data were recorded from the medical record: patient age; gender; time from cataract surgery to diagnosis; type and duration of prophylactic topical antibiotic therapy; visual acuity; method of initial endophthalmitis treatment; duration of follow-up; and results of intraocular culture. The referring doctor was contacted in all cases to determine when and which type of prophylactic antibiotic was begun and the most recent visual acuity.

Specimens were sent to one of two laboratories, depending on geographic location. Antibiotic sensitivities were performed by one or more of the following tests: Kirby-Bauer disk diffusion, Vitek automated bacteriology system (bioMérieux, Marcy l'Etoile, France), or E-test strip (AB Biodisk, Solna, Sweden). Sensitivities to gatifloxacin and moxifloxacin were only tested using E-test strips and this method was available in only one of the laboratories during the time of this study.

TABLE 1. Type of Perioperative Antibiotic Used in 42 Eyes With Acute Endophthalmitis

Antibiotic	Number of Patients
Gatifloxacin	24
Moxifloxacin	7
Ofloxacin	7
Tobramycin	2
Polymyxin B/neomycin*	1
None	1

*Patient started on gatifloxacin 3 days before surgery, then used Polymyxin B/neomycin postoperatively.

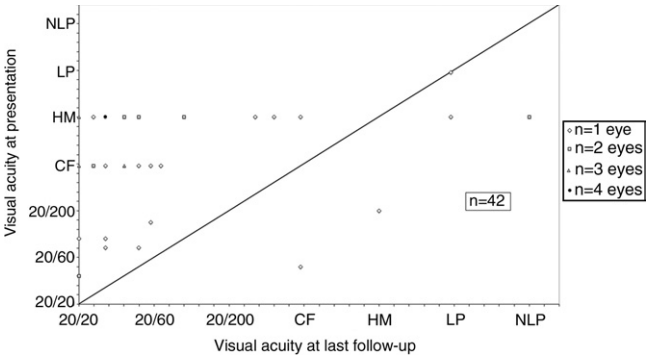

FIGURE. Change in visual acuity after treatment in eyes with acute endophthalmitis.

RESULTS

FORTY-TWO EYES OF 42 PATIENTS MET ALL INCLUSION criteria and comprise this study. The median age was 75 years (range, 49 to 93 years). Twenty-four of the patients (57%) were female. The median time from surgery to presentation was 6.5 days (range, 1 to 32 days). The type of perioperative antibiotic is summarized in Table 1. Thirty-one eyes (74%) received fourth-generation fluoroquinolones, either gatifloxacin (n = 24) or moxifloxacin (n = 7). Thirty-five eyes (83%) started antibiotic therapy two or three days before cataract surgery. Six eyes (14%) began antibiotic therapy only after surgery, and one patient did not take any antibiotic medication. At time of presentation, 32 eyes (76%) had been taking prophylactic antibiotic drops continuously since surgery (24 eyes [57%] using gatifloxacin or moxifloxacin continuously). Ten eyes were not on antibiotics at time of diagnosis.

Visual acuity data are summarized in the Figure. Forty-one of the 42 eyes initially had hand motions or better vision; one patient had light perception vision. All patients underwent immediate tap and injection of intravitreal antibiotics. For the one patient with light perception vision, immediate pars plana vitrectomy was recommended, but the patient and family refused due to health

TABLE 2. Results of Bacterial Culture and Antibiotic Sensitivities With MIC in Eyes With Endophthalmitis (n = 15 Eyes)

		Vanco		CIP		OFX		LEV		GAT		MOX	
Source	Culture Result		MIC		MIC		MIC		MIC		MIC		MIC
Vit	CNS	S	2	S	≤0.5	S	≤0.5	S	≤0.12	S	≤0.5	S	≤0.5
Vit	CNS	S	2	R	≥8	R	≥8	R	≥8	R	8	R	8
Vit	MRSA	S	≤0.5	R	≥4	—		R	≥8	—		—	
Vit	CNS	S	*	S	*	—		S	*	—		—	
Vit	CNS	S	2	R	≥4	R	*	R	*	R	8	R	8
Vit	CNS	S	2	S	≤0.5	—		S	≤1	—		—	
AC	MRSA	S	*	—		—		—		—		—	
Wound	*Staphylococcus aureus*	S	≤1	R	≥8	R	≥8	R	≥8	R	8	R	8
Vit	CNS	S	2	S	≤0.5	S	≤0.5	S	≤0.12	—		—	
Vit	CNS	S	2	R	≥4	—		R	≥8	—		—	
Vit	*Enterobacter cloacae*	—		S	≤0.5	—		S	≤1	—		—	
Vit	CNS	S	2	S	≤0.5	R	*	R	*	R	8	R	8
AC	*Streptococcus sanguis*	S	*	—		S	*	S	*	S	≤0.5	S	≤0.5
Vit	MRSA	S	2	R	≥4	R	*	R	*	R	8	R	8
AC	CNS	S	≤1	S	≤0.5	S	≤0.5	S	≤0.12	S	≤0.5	S	≤0.5

Vanco = vancomycin; CIP = ciprofloxacin; OFX = ofloxacin; LEV = levofloxacin; GAT = gatifloxacin; MOX = moxifloxacin; MIC = minimum inhibitory concentration; vit = vitreous; AC = anterior chamber; CNS = coagulase negative *Staphylococcus*; MRSA = methacillin-resistant *Staphylococcus aureus*; S = sensitive; R = resistent; — = not performed; CLST = clinical and laboratory standards institute.

*Kirby Bauer testing (CLSI protocols used).

reasons. Thirty-one eyes (74%) had a successful vitreous tap. In 11 eyes, a vitreous specimen could not be obtained and an anterior chamber tap was performed. Patients were followed for a median of 27.9 weeks (range, 2.9 to 105.0 weeks). Patients were returned to their referring ophthalmologist if their examination was stable and there was no evidence of persistent infection.

Overall, 19 of the 42 eyes (45%) had a positive culture. Fourteen of the 31 eyes (45%) undergoing an initial vitreous tap had a positive culture. Four eyes had a positive anterior chamber culture, and one eye had a positive culture from a corneal wound abscess. Twenty organisms were identified—19 gram-positive organisms: coagulase-negative *Staphylococcus* (CNS) (n = 12), MRSA (n = 3), *S. aureus* (n = 1), *Streptococcus sanguis* (n = 1), *Propionibacterium acnes* (n = 1), and *Bacillus* species (n = 1), and one gram-negative organism: *Enterobacter cloacae* (n = 1). One eye had a mixed CNS and *P. acnes* infection.

Sensitivities were able to be performed for 15 eyes (Table 2). In four cases, the laboratory did not perform further testing. Not all cases were tested for all antibiotics and depended on the laboratory testing method. The one gram-negative organism isolated (*Enterobacter*) was sensitive to both of the fluoroquinolone antibiotics tested (ciprofloxacin and levofloxacin). All 14 gram-positive organisms (100%) were sensitive to vancomycin. Regarding fluoroquinolone antibiotics, sensitivities to ciprofloxacin (6/12 organisms; 50%), ofloxacin (4/9; 44%), levofloxacin (6/13; 46%), gatifloxacin (3/8; 38%), and moxifloxacin (3/8; 38%) were noted. Five organisms were resistant to gatifloxacin and moxifloxacin with a minimum inhibitory concentration (MIC) of 8 μg/ml.

DISCUSSION

THIS STUDY DEMONSTRATES THAT ACUTE ENDOPHthalmitis can develop in eyes treated prophylactically with newer fourth-generation fluoroquinolone antibiotics, including eyes started on antibiotics for several days before surgery. These results also show that *S. aureus* and CNS isolates in endophthalmitis cases may be resistant to gatifloxacin and moxifloxacin. This study confirms previous reports of bacterial resistance to earlier generation fluoroquinolones in ocular specimens.[4–8] Resistance to vancomycin was not noted in gram-positive organisms.

Fluoroquinolones are broad-spectrum antibiotics that are frequently used in infection prophylaxis before and after intraocular surgery. Although the use of perioperative antibiotics is widespread to prevent the development of endophthalmitis, only preoperative povidone-iodine treatment was supported by a recent large review of the current literature.[11] Gatifloxacin and moxifloxacin have been reported to be more effective than earlier generation fluoroquinolones in treating gram-positive organisms, the most common cause of acute endophthalmitis, and moxifloxacin may prevent experimental endophthalmitis in a rabbit model with a sensitive organism.[12] This study did not attempt to determine whether these antibiotics were able to prevent other cases of endophthalmitis, although other

endophthalmitis cases have been noted in patients using fourth-generation fluoroquinolone antibiotic prophylaxis.[13] Additionally, Miller and associates have reported a significant increase in the rate of resistance of recent and archived CNS specimens to gatifloxacin and moxifloxacin over the last 15 years.[14]

Fluoroquinolone antibiotics act by inhibiting two bacterial enzymes, DNA gyrase and topoisomerase IV. Second- and third-generation antibiotics appear to inhibit one of these enzymes, depending on whether the organism is gram-positive or gram-negative, whereas fourth-generation fluoroquinolones appear to inhibit both enzymes.[15] Theoretically, this may decrease the likelihood of bacterial resistance, because spontaneous mutations in both enzymes is unlikely. However, resistance can also develop by other methods, such as the expression of a multidrug resistant efflux pump, which actively pumps antibiotic out of the bacterial cell.[15]

Antibiotic sensitivities are determined in vitro and MIC values are calculated based on serum values. Studies in a rabbit model have suggested that in vitro antibiotic resistance may not correlate with in vivo resistance (Mah FS, ARVO Meeting 2004, abstract), primarily because topical therapy results in locally high concentration of antibiotic significantly above the achievable serum MIC. Recent studies have measured the anterior chamber concentration of moxifloxacin[16,17] and gatifloxacin[17] after preoperative topical administration. Depending on the dosing regimen, levels that exceed the MIC for some sensitive organisms were obtained. However, except for possibly every-two-hour dosing of moxifloxacin, none of these regimens exceeded the median MIC for fluoroquinolone-resistant CNS or *S. aureus*,[2,3] and none, including very frequent dosing of moxifloxacin, exceeded the MIC90 for these resistant gram-positive organisms. Most important, the true measure of an antibiotic's efficacy used as prophylaxis is prevention of in vivo infection (that is, endophthalmitis). All of the eyes in this clinical study developed clinically significant endophthalmitis with visual loss. Seventy-four percent of eyes in this study were treated with prophylactic fourth-generation fluoroquinolones and over half of eyes were taking one of these antibiotics continuously at the time of diagnosis.

This study is limited by its retrospective nature and small size. The patients involved in this study were from one geographic region in suburban New York City, which may or may not reflect antibiotic resistance patterns elsewhere. There was variability in the microbiology testing because of differences in laboratory protocols. Only one laboratory in our region (Long Island Jewish Medical Center) was able to test for fourth-generation fluoroquinolone sensitivity, because of availability of E-test strips. Many commercial laboratories do not test for sensitivity to gatifloxacin and moxifloxacin. It is important for the clinician to recognize the differences in microbiologic testing and be aware that laboratory results may not be adequate in all cases to determine whether organisms are resistant to newer antibiotic agents, such as gatifloxacin and moxifloxacin. Last, although all eyes developed sudden visual loss with severe acute inflammation, it is possible that not all eyes had microbial endophthalmitis, and that some of the milder culture-negative cases had a sterile uveitis.

Gatifloxacin and moxifloxacin may not provide increased protection over earlier generation fluoroquinolone antibiotics in the prophylaxis of acute endophthalmitis. Initiation of topical antibiotic prophylaxis for several days before cataract surgery does not appear to be protective. This study cannot determine if topical fluoroquinolone antibiotics induce resistance in organisms that later cause endophthalmitis, nor can it determine if fluoroquinolones are better or worse than other classes of antibiotics for infection prophylaxis following cataract surgery. Clinically relevant bacterial resistance to gatifloxacin and moxifloxacin exists, and additional studies are needed to study the prophylactic benefit of fourth-generation fluoroquinolone antibiotics.

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Biosketch

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