VITREOUS PENETRATION OF ORALLY ADMINISTERED GATIFLOXACIN IN HUMANS

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ABSTRACT

Purpose: To investigate the penetration of gatifloxacin, a novel extended-spectrum fluoroquinolone antibiotic, into the vitreous humor after oral administration.

Methods: A prospective, nonrandomized clinical study of 20 consecutive patients scheduled for pars plana vitrectomy surgery between September 2001 and February 2002 at the Cullen Eye Institute, Houston, Texas. Aqueous, vitreous, and serum samples were obtained and analyzed from 20 patients after oral administration of two 400-mg gatifloxacin tablets taken 12 hours apart before surgery. Assays were performed using high-performance liquid chromatography.

Results: Mean gatifloxacin concentrations in serum (n=19), vitreous (n=19), and aqueous (n=10) were 4.98 ± 1.14 µg/mL, 1.35 ± 0.36 µg/mL, and 1.09 ± 0.57 µg/mL, respectively. Mean sampling times after oral administration of the second gatifloxacin tablet for serum, vitreous, and aqueous were 2.99 ± 0.73 hours, 3.79 ± 0.81 hours, and 3.71 ± 0.87 hours, respectively. The percentages of serum gatifloxacin concentration achieved in the vitreous and aqueous were 27.13% and 21.85%, respectively. Mean inhibitory vitreous and aqueous MIC_{90} levels were achieved against a wide spectrum of pathogens, including *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Propionibacterium acnes*, *Haemophilus influenzae*, *Escherichia coli*, *Bacillus cereus*, *Neisseria gonorrhoeae*, *Proteus mirabilis*, and other organisms.

Conclusions: Gatifloxacin is a novel fourth-generation fluoroquinolone antibiotic that has MIC_{90} levels significantly lower than those of other fluoroquinolone agents. Furthermore, it penetrates well into the vitreous cavity in the noninflamed eye. Potential uses for oral gatifloxacin may include prophylaxis against endophthalmitis in open-globe injuries, surgical prophylaxis against postoperative endophthalmitis, and adjunctive therapy for the current management of bacterial endophthalmitis.

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INTRODUCTION

Bacterial endophthalmitis is one of the most serious complications of intraocular surgery and open-globe injuries. The microbiologic spectrum of infecting organisms in postoperative endophthalmitis was investigated in the Endophthalmitis Vitrectomy Study (EVS). The EVS represents the largest number of postoperative endophthalmitis cases from which bacteriologic data were prospectively obtained. The vast majority (94.2%) of confirmed growth isolates were gram-positive pathogens, most commonly *Staphylococcus epidermidis* and *Staphylococcus aureus.* Gram-negative pathogens, the most common being *Proteus mirabilis*, accounted for only 5.9% of confirmed growth isolates.[1] The spectrum of infecting organisms in posttraumatic endophthalmitis differs from those of postoperative endophthalmitis, with *Bacillus* species playing a more prominent role.[2]

The EVS investigated the use of intravenous amikacin and ceftazidime in conjunction with intravitreal antibiotic injection for postoperative endophthalmitis and found no improved outcomes with the use of systemic antibiotics.[3] Later studies found that amikacin and ceftazidime had very poor intravitreal penetration.[4,5] On the basis of the EVS data, the only conclusion that can be drawn regarding the use of systemic antibiotics is that amikacin and ceftazidime specifically have no role in postoperative endophthalmitis. Since the EVS, there have been major advancements in the development of antibiotics, and the potential uses of these new-generation agents in the treatment of endophthalmitis need to be revisited. Over the past 10 years, there has been mounting evidence in the literature that agents in the fluoroquinolone class of antibiotics are able to achieve effective concentrations in the vitreous after oral administration.[6-8]

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Gatifloxacin is a fourth-generation, 8-methoxy fluoroquinolone with a spectrum of activity encompassing gram-positive and gram-negative pathogens, including *S epidermidis*, *S aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Escherichia coli*, *Bacillus cereus*, *Neisseria gonorrhoeae*, and *P mirabilis*. Additionally, gatifloxacin has excellent activity against atypical pathogens, such as *Mycoplasma*, *Legionella*, and *Chlamydia* species, as well as the anaerobic organism *Propionibacterium acnes*.[9,10] Gatifloxacin has 96% oral bioavailability and can be administered without regard to food, reaching peak plasma concentrations 1 to 2 hours after oral dosing. Serum protein binding of gatifloxacin is only 20% and is widely distributed throughout the body into many body tissues and fluids. The new fluoroquinolones, such as gatifloxacin, grepafloxacin, moxifloxacin, and trovafloxacin, represent advances in the evolution of this antibiotic class. The more favorable pharmacokinetic properties of the previously mentioned agents are due to alterations of the original fluoroquinolone moiety. For example, gatifloxacin and moxifloxacin possess an 8-methoxy side chain, which may be responsible for the enhanced activity against gram-positive, atypical pathogens and anaerobes while retaining potencies and broad-spectrum coverage against gram-negative organisms comparable to older-generation fluoroquinolones.[10]

We chose to study the intravitreal penetration of orally administered gatifloxacin in humans for two reasons. First, older-generation fluoroquinolones, such as ofloxacin, ciprofloxacin, and levofloxacin, have been shown to achieve effective levels in the vitreous after oral administration in the noninflamed eye.[6-8] Second, the MIC_{90} values of gatifloxacin against the pathogens most commonly responsible for postoperative, posttraumatic, and bleb-associated endophthalmitis were generally lower than those of the other fluoroquinolone antibiotics we surveyed (Table I).[9,10]

TABLE I: IN VITRO SUSCEPTIBILITIES OF GATIFLOXACIN, LEVOFLOXACIN, OFLOXACIN, AND CIPROFLOXACIN SHOWING MINIMUM INHIBITORY CONCENTRATIONS AT WHICH 90% OF ISOLATES ARE INHIBITED (µg/mL)[8-10]

ORGANISMS	GATIFLOXACIN	LEVOFLOXACIN	OFLOXACIN	CIPROFLOXACIN
Maximum vitreous penetration	1.35 ± 0.36 µg/mL	2.39 ± 0.70 µg/mL	0.43 ± 0.47 µg/mL	0.56 ± 0.16 µg/mL
Gram-positive				
*Staphylococcus epidermidis**†‡	0.25	0.50	0.50-0.83	0.38
Staphylococcus aureus (MSSA) *†	0.13	0.25	0.25-2.00	0.80
*Streptococcus pneumoniae**†‡	0.50	2.00	2.00-4.00	3.13
Streptococcus pyogenes	0.50	1.00	1.00-4.00	0.78
Bacillus cereus ||	0.25	----	----	----
*Enterococcus faecalis**	2.00	2.00	2.00-8.00	1.56
Gram-negative				
Proteus mirabilis†	0.25	0.25	0.12-0.39	0.27
Pseudomonas aeruginosa	32.0	32.0	----	0.78
Haemophilus influenzae‡	0.016	0.06	0.03-0.10	0.014
Escherichia coli	0.008	0.03	0.12-0.39	0.08
Klebsiella pneumonia	0.13	0.13	0.12-0.19	0.30
Neisseria gonorrhea	0.016	0.016	0.06	0.004
Anaerobic				
Bacteroides fragilis	1.00	2.00	4.0-12.5	----
Propionibacterium acnes§	0.50	0.75	1.50	----

MSSA, methicillin-sensitive *S aureus*.
*Responsible for more than 2% of postoperative endophthlamitis.[1]
†Associated with endophthalmitis resulting from ocular trauma.[2]
‡Most common causative organisms in bleb-associated endophthalmitis.[14]
§Most common causative organisms in chronic postoperative endophthalmitis.[12]
|| On file, Briston-Myers Squibb Co (SENTRY Global Antimicrobial Surveillance System 1997-2000).
¶Data not available.

METHODS

The study was carried out with the approval of the institutional review board of Baylor College of Medicine. Twenty adult patients (age range, 39-82 years; mean age ±SD, 64.4 ± 12.2 years) who underwent elective pars plana vitrectomy surgery between September 2001 and February 2002 at the Cullen Eye Institute were included in the study. Exclusion criteria included the following: known sensitivity to fluoroquinolones, renal disease (creatinine, >1.8 mg/dL), use of any other antibiotic in the preceding 3 weeks, pregnancy or currently breast-feeding, current use of a class IA or III antiarrhythmic agent, fresh vitreous hemorrhage as indication for vitrectomy (<1 month old), and active endophthalmitis.

Indications for operation in the 20 patients were as follows (Table II): epiretinal membrane (11 patients), macular hole (5), retinal detachment (2), nonclearing vitreous hemorrhage (1), and tractional retinal detachment secondary to proliferative diabetic retinopathy (1).

After informed consent was obtained, patients were asked to take two 400-mg gatifloxacin tablets orally 12 hours apart before surgery. Prospectively completed data forms were designed to include medical history, collection times of various samples, and concentrations of gatifloxacin in serum, aqueous, and vitreous. Patients were asked to record on each of the two gatifloxacin blister packs the exact time of oral administration. These packs were returned on the day of surgery. Aqueous, vitreous, and serum samples were obtained before infusion of any intravenous or intraocular irrigating solution in order to obtain pure samples. Approximately 8 to 10 mL of venous blood was collected less than 1 hour prior to surgery in the preoperative holding area. In the operative suite, approximately 0.1 mL of aqueous fluid was aspirated with a 30-gauge needle attached to a syringe through a paracentesis site in those patients in whom it was felt safe to do so (ie, pseudophakic patients or phakic patients with deep anterior chambers). Within 10 minutes, 0.2 to 0.3 mL of vitreous fluid was obtained by using a vitreous cutting device attached to a syringe via a short length of tubing.

Aqueous and vitreous samples were immediately frozen at -20ºC. The blood sample was centrifuged, and the serum collected from this was frozen as well. These samples were shipped with dry ice in appropriate packaging material to the Hartford Hospital Laboratory, Hartford, Connecticut. Gatifloxacin concentrations were determined in each of the samples by using a previously described high-performance liquid chromatography technique.[11] Serum, aqueous, and vitreous gatifloxacin concentrations were compared to already established in vitro MIC_{90} data.[9,10] Student's *t* test was performed to determine if any significant differences existed between various subsets of patients, including diabetic versus nondiabetic patients and phakic status.

TABLE II: SERUM, AQUEOUS, AND VITREOUS LEVELS (µG/ML) OF GATIFLOXACIN AFTER SECOND ORAL DOSE

PATIENT NO.	AGE	HOURS FROM SECOND DOSE TO VITREOUS	INDICATION FOR SURGERY	DIABETIC	SERUM (µg/mL)	AQUEOUS (µg/mL)	VITREOUS (µg/mL)
1	70	4.67	ERM	No	5.19	*	1.27
2	77	2.20	MH	No	4.86	1.02	1.57
3	54	4.12	RD	No	4.26	0.34	1.33
4	51	3.83	MH	No	4.81	0.68	0.98
5	72	3.50	ERM	No	4.04	†	0.62
6	78	5.25	ERM	No	7.18	†	1.70
7	68	4.67	ERM	Yes	5.77	†	1.38
8	82	3.50	ERM	No	4.76	1.12	1.23
9	81	3.42	ERM	No	5.72	1.34	1.14
10	73	3.25	MH	No	6.70	2.39	2.05
11	39	5.75	ERM	No	2.93	0.932	0.95
12	55	3.25	ERM	No	5.49	1.518	1.75
13	44	3.50	NCVH	No	3.65	0.834	1.45
14	63	3.75	ERM	No	2.85	0.701	0.83
15	67	3.50	TRD	Yes	5.35	*	1.15
16‡	72	3.00	ERM	No	4.67	†	*
17	66	3.17	RD	No	4.60	†	1.46
18	67	3.67	MH	No	4.61	†	1.44
19	61	3.50	MH	No	6.15	†	1.60
20	55	3.50	ERM	No	5.65	†	1.76

ERM, epiretinal membrane; MH, macular hole; NCVH, nonclearing vitreous hemorrhage; RD, retinal detachment; TRD, tractional retinal detachment.
*Insufficient sample volume.
†Sample not taken because of risk of compromising surgical procedure.
‡Patient data not included in study.

RESULTS

Mean gatifloxacin concentrations in serum (n=19), vitreous (n=19), and aqueous (n=10) were 4.98 ± 1.14 µg/mL, 1.35 ± 0.36 µg/mL, and 1.09 ± 0.57 µg/mL, respectively. Mean sampling times after oral administration of the second gatifloxacin tablet for serum, vitreous, and aqueous were 2.99 ± 0.73 hours, 3.79 ± 0.81 hours, and 3.71 ± 0.87 hours, respectively. The percentages of serum gatifloxacin concentration achieved in the vitreous and aqueous were 27.13% and 21.85%, respectively (Table II).

Patient 16 was removed from the study because no aqueous specimen was collected and there was an insufficient vitreous sample volume to perform HPLC. Although a serum gatifloxacin concentration was determined on this patient, it was not felt that this added any value to the purpose of the study, and therefore this patient's data was removed from any data analysis.

Two of the 19 patients were diabetic. The mean gatifloxacin concentrations in the serum and vitreous for these two patients were 5.56 ± 0.30 µg/mL and 1.26 ± 0.16 µg/mL, respectively (Table II). These levels were not significantly different from those of the 17 nondiabetic patients, whose serum and vitreous concentrations were 4.91 ± 1.19 µg/mL and 1.36 ± 0.37 µg/mL, respectively (*P*=.46 and *P*=.73, respectively).

Eight of the 19 patients were phakic. The mean gatifloxacin concentrations in the serum, vitreous, and aqueous for these eight patients were 4.83 ± 0.87 µg/mL, 1.24 ± 0.32 µg/mL, and 0.62 ± 0.25 µg/mL, respectively. These levels were not significantly different from that of the one aphakic and 10 pseudophakic patients whose serum, vitreous, and aqueous concentrations were 5.08 ± 1.34 µg/mL, 1.43 ± 0.38 µg/mL, and 1.29 ± 0.55 µg/mL, respectively. (*P*=.65, *P*=.28, and *P*=.09, respectively).

No serious adverse reactions were attributed to the antibiotic agent. One patient complained of mild gastrointestinal discomfort. Another patient (patient 7) vomited 30 minutes after taking the second gatifloxacin dose. The concentrations of gatifloxacin in serum and vitreous in this patient were 5.77 µg/mL and 1.38 µg/mL, respectively (Table II). These values were above the mean of the rest of the group.

DISCUSSION

Endophthalmitis is one of the most serious complications of intraocular procedures or open-globe trauma. Systemic antibiotics have had an uncertain role in the prophylaxis or management of endophthalmitis as the EVS was unable to demonstrate any benefit with the use of intravenous antibiotics in postoperative infection.[3] Over the past 10 years, several studies have indicated that fluoroquinolone antibiotics achieve significant concentrations in the vitreous after oral administration.[6-8] Unfortunately, many of the older-generation fluoroquinolones achieved intravitreal levels that barely reached the MIC_{90} against the pathogens most commonly responsible for postoperative, posttraumatic, and bleb-associated endophthalmitis. If one is to consider the use of a systemic antibiotic for the prophylaxis of, or as an adjunct in the management of, endophthalmitis, one must find a systemic antibiotic with the highest possible intravitreal penetration as well as the lowest MIC_{90} for the organisms of concern. We believe that gatifloxacin may represent a major advance in this regard.

After cataract extraction, bacterial endophthalmitis is most commonly caused by *S epidermidis* (70% of EVS isolates).[1] The endophthalmitis typically presents as a moderately severe infection 5 to 7 days after surgery. Less commonly, two other forms of endophthalmitis can take place after cataract extraction. The first is a chronic, indolent endophthalmitis that presents several months after surgery and is usually caused by *P acnes*.[12] A second, less common form of postoperative endophthalmitis is an early, fulminant type usually presenting 2 to 4 days after surgery, which is caused by streptococcal or staphylococcal species, as well as gram-negative organisms (most commonly *P mirabilis*[1]). In our study, vitreous levels of gatifloxacin were 5.4 times the MIC_{90} for *S epidermidis*, 10.4 times the MIC_{90} for *S aureus*, 2.7 times the MIC90 for *P acnes*, 2.7 times the MIC_{90} for *Streptococcus* species, and 5.4 times the MIC_{90} for *P mirabilis*. Gatifloxacin was unable to achieve intravitreal levels effective against *Enterococcus* or *Pseudomonas*. Fortunately, these two organisms are only very rarely encountered in postoperative endophthalmitis.[1]

The importance of finding a good bacterial endophthalmitis prophylaxis technique for cataract surgery was emphasized in a recent study by Ciulla and associates.[13] Performing a systematic review of the literature from 1966 to 2000 to assess commonly used techniques of bacterial endophthalmitis prophylaxis for cataract surgery, they found that only preoperative povidone-iodine preparation could receive a moderate clinical recommendation (moderately important to clinical outcome). All other measures received the lowest clinical recommendation level (possibly relevant but not definitely related to clinical outcome). Furthermore, the study revealed that no prophylactic technique in the literature could receive the highest of three possible clinical recommendations (crucial to clinical outcome).[13] Unfortunately, systemic antibacterial agents were not included in this study. Given our findings, one could consider the use of oral gatifloxacin before and after surgery as prophylaxis against endophthalmitis. Ciulla and associates[13] estimate that

there are nearly 2,000 cases of endophthalmitis after cataract surgery alone annually in the United States. If all intraocular surgeries and cases of open-globe trauma were included, this number would be far greater. Therefore, the importance of finding good prophylaxis against postoperative endophthalmitis cannot be underestimated.

Conjunctival filtering bleb-associated endophthalmitis can occur any time after trabeculectomy surgery. Infection of the bleb alone, or "blebitis," can sometimes be managed with intensive topical antibiotics. The most common causative organisms in bleb-associated endophthalmitis are *S epidermidis* and *H influenzae*.[14] The level of gatifloxacin achieved in the aqueous and vitreous were about 68 and 84 times the MIC_{90} for *H influenzae*, respectively. Gatifloxacin may prove to be valuable in the management of blebitis or as an adjunct in the current management of bleb-associated endophthalmitis.

The role of systemic antibiotics in open-globe trauma deserves special attention. Posttraumatic endophthalmitis occurs in 2% to 7% of all open-globe injuries and in 7% to 13% of injuries with retained intraocular foreign bodies.[15,16] Injuries that occur in a rural setting result in up to a 30% incidence of endophthalmitis compared with 11% in a nonrural setting.[17] *Staphylococcus*, *Streptococcus*, and *Bacillus* species are the most commonly encountered organisms in posttraumatic endophthalmitis.[18] While the role and significance of intravenous antibiotics in the treatment of infection associated with open-globe trauma remain unresolved, Ariyasu and colleagues[19] studied events leading to the development of posttraumatic endophthalmitis by examining the significance of 15 factors on microbial contamination of injured eyes. Only intravenous antibiotic therapy was found to significantly reduce anterior chamber microorganisms at the time of surgical repair, supporting their prophylactic use against the development of posttraumatic endophthalmitis.

On the basis of Ariyasu's findings and the known high incidence of endophthalmitis after open-globe injuries, the prompt and routine use of systemic antibiotics for prophylaxis against infection in the setting of trauma needs to be further explored. The choice of antibiotic will be one that meets the following criteria: achieves high intravitreal concentrations well above the MIC_{90} for the specific organisms of concern, is well tolerated, and preferably is one that achieves excellent bioavailability with oral administration. Gatifloxacin fulfills these criteria. The levels achieved in the aqueous and vitreous were several times higher than the MIC_{90} levels for those organisms that are most commonly associated with posttraumatic endophthalmitis (Table I). In addition, previous studies suggest that intraocular penetration of systemic antibiotics may be higher in an eye that has sustained trauma, is infected, or is inflamed. This may be due to disruption of the blood-ocular barrier.[20,21]

The guidelines set forth by the EVS regarding the management of postoperative endophthalmitis should not be translated to posttraumatic endophthalmitis.[3] The incidence of endophthalmitis from open-globe trauma is many times greater than after ocular surgery. In addition, up to 42% of cases from rural areas have more than one organism cultured; often, more virulent bacteria are isolated in posttraumatic endophthalmitis than in postoperative endophthalmitis. For example, *Bacillus* infections are rare in postoperative endophthalmitis but may occur with a frequency of 20% to 46% in posttraumatic cases.[17] *Bacillus* produces severe, rapidly progressive endophthalmitis. Therefore, in the setting of open-globe trauma, rapid administration of an oral antibiotic known to penetrate into the posterior segment may help prevent ocular damage secondary to infection. On the basis of our data, it appears that oral administration of gatifloxacin may be a promising choice for prophylaxis against endophthalmitis in open-globe injuries before and after surgical intervention.

Two groups have recently studied the fourth-generation fluoroquinolones for possible use in ophthalmology. Mather and associates[22] have described the fourth-generation fluoroquinolones as "new weapons in the arsenal of ophthalmic antibiotics." They performed an in vitro study determining the differences in susceptibility patterns and potencies of second-, third-, and fourth-generation fluoroquinolones to 93 bacterial endophthalmitis isolates. They demonstrated that coagulase-negative staphylococci that were resistant to second-generation fluoroquinolones (ciprofloxacin and ofloxacin) were statistically most susceptible to the fourth-generation fluoroquinolones, specifically gatifloxacin and moxifloxacin. Additionally, *S viridans* and *S pneumoniae* were least susceptible to the older-generation fluoroquinolones. Overall, the fourth-generation fluoroquinolones retained equivalent potencies to gram-negative bacteria as compared to older-generation fluoroquinolones such as levofloxacin and ciprofloxacin while demonstrating enhanced potencies for gram-positive bacteria.

In another recent study, Garcia-Saenz and associates[23] investigated the penetration of orally administered moxifloxacin into the human aqueous humor as a potential prophylactic agent against bacterial endophthalmitis in cataract surgery. They found that moxifloxacin achieved a mean aqueous concentration of 2.33 ± 0.85 µg/mL; however, their reported MIC_{90} for *S epidermidis* was 2.00. The concentration achieved is borderline for the most common causative organism in postoperative endophthalmitis. This is not the case with gatifloxacin, as intraocular concentrations after oral administration were found to be several times higher than the MIC_{90} for *S epidermidis*. Additionally, penetration of moxifloxacin into the vitreous was not investigated; therefore, no conclusions can be made regarding its use in open-globe trauma involving the

posterior segment or its use as an adjunctive therapy for endophthalmitis management.

Overall, gatifloxacin is very well tolerated; the majority of adverse reactions are described as mild. The most common ones include nausea, vaginitis, diarrhea, headache, and dizziness. In our series, one patient complained of mild gastrointestinal discomfort and another (patient 7) vomited 30 minutes after taking the second gatifloxacin dose. The concentrations of gatifloxacin in serum and vitreous in this patient were above the mean of the rest of the group. Since gatifloxacin is eliminated primarily by renal excretion, a dosage modification is recommended for patients with a creatinine clearance of less than 40 mL/min. Gatifloxacin should be avoided in patients receiving a class IA (quinidine or procainamide) or class III (amiodarone or sotalol) antiarrhythmic agent, because gatifloxacin may have the potential to prolong the QTc interval of the electrocardiogram in some patients.

SUMMARY

Orally administered gatifloxacin achieves therapeutic aqueous and vitreous levels in the noninflamed human eye, and the activity spectrum appears to appropriately encompass the most frequently encountered bacterial species involved in the various causes of endophthalmitis. Because of its broad spectrum of coverage, low MIC_{90} levels for the organisms of concern, good tolerability, and excellent bioavailability with oral administration, gatifloxacin may represent a major advance in the prophylaxis or management of postoperative, posttraumatic, and bleb-associated bacterial endophthalmitis.

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DISCUSSION

DR MAURICE B. LANDERS III. Endophthalmitis remains a devastating complication of intraocular surgery and ocular trauma despite recent advances in diagnosis and treatment. Two thirds of these cases of endophthalmitis are postoperative. The outcome of treatment for postoperative endophthalmitis has improved dramatically during the past two decades. Some of the factors involved in these improved outcomes include: higher incidence of endophthalmitis produced by less virulent organisms; earlier diagnosis and treatment; widespread acceptance of intravitreal antibiotic therapy; employment of vitrectomy surgery; and control of the inflammation seen in endophthalmitis

The incidence of postoperative endophthalmitis over the past 2 decades, nevertheless, has declined only a little, if at all, during that time. Thus, effective prophylaxis of postoperative endophthalmitis remains an important and elusive goal for ophthalmic surgeons.

Doctors Hariprasad, Mieler, and Holz have presented a study of the vitreous penetration of orally administered fourth-generation extended-spectrum fluoroquiolone antibiotic, gatifloxacin, (TEQUIN) in humans. In a prospective, randomized clinical study of 20 consecutive patients undergoing elective pars plana vitrectomy, the serum, aqueous, and vitreous concentration of gatifloxacin was measured after the oral administration of two 400-milligram tablets taken 12 hours apart before surgery. No serious adverse reactions were found attributable to the antibiotic agent.

The levels of gatifloxacin found in the aqueous and vitreous specimens were compared to established in vitro MIC_{90} data for a number of bacteria that may potentially cause endophthalmitis

The authors found that orally administered Gatifloxacin achieved therapeutic aqueous and vitreous levels in the non-inflamed human eye and that the antibiotic activity spectrum appears to appropriately encompass the most frequently encountered bacterial species involved in endophthalmitis. The authors found that this novel fourth-generation fluoroquiolone antibiotic penetrates well into the vitreous cavity, exceeding MIC_{90} levels of most bacteria of concern with the exception of the *Enterococcus faecalis* and pseudomonas bacteria. They conclude that oral gatifloxacin may prove useful for prophylaxis against post-operative endophthalmitis, traumatic endophthalmitis, and even as adjunctive therapy for the current treatment of bacterial endophthalmitis.

I have three questions for the authors of this excellent study: Is the rapidity of sterilization of the vitreous cavity in a case of endophthalmitis likely to be a function of the excess concentration of a bactericidal antibiotic over the MIC_{90} for a particular organism?

Is anything known about the ocular toxicity of gatifloxacin given orally over a several day course of treatment? Would the administration of oral gatifloxacin in any way compromise the beneficial, antimicrobial effects of intravitreal vancomycin and ceftazidime administered in the standard doses?

DR ERIC R. HOLZ. Question 1: Is the rate of sterilization of the vitreous a function of antibiotic concentration? The answer to that, I think, is clearly yes. Drug levels have to exceed MIC_{90} of the common pathogens in order to sterilize the anterior chamber or vitreous in endophthalmitis. Question 2, regarding the ocular toxicity of gatifloxacin: Certainly in previous studies that have been performed with oral gatifloxacin or other fourth-generation fluoroquinolones, patients receiving the drug for weeks at a time don't have any ocular toxicity that's been reported to date. Now, I must admit, we did not inject gatifloxacin into the vitreous; other fluoroquinolones injected into the vitreous have been shown to have some toxicity problems, so we have not administered this directly into the vitreous as a single injection, but we're looking, rather, at penetration after oral administration. Question 3: Could gatifloxacin compromise other antibiotic treatment? I guess the question is if you're going to put vancomycin and ceftazidime, or amikacin, into the vitreous to treat endophthalmitis, would gatifloxacin somehow compromise that treatment? I think the answer is unknown, but concurrent use should not interfere with the effectiveness of standard intravitreal antibiotics. I think gatifloxacin may be an adjunctive treatment that would not compromise the current treatment of endophthalmitis.