CONTINUING MEDICAL EDUCATION CME

RETHINKING OCULAR ANTIINFECTIVES

PART 2

Evolution of Fluoroquinolones: What Has Been Gained with Each New Molecule?

PRACTICE PERSPECTIVE

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PHARMACOLOGY PERSPECTIVE

Susanne Gardner, PharmD

This enduring material will discuss how ocular fluoroquinolones have evolved, as well as how these molecular changes have affected the bacteria-killing capabilities of these drugs.

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STATEMENT OF NEED

Antibiotics are widely used in ophthalmology, both to treat infection and for peri- and postoperative surgical prophylaxis. The antiinfectives most widely used in the ophthalmic practice are topical fluoroquinolones, of which there are now six different agents that are commercially available in the U.S. Developed over many years, there are significant differences between the topical fluoroquinolones, leading to questions about which agents are most appropriate for use in which clinical situations. FDA labeling cannot be used as a guide since all of the agents save one are indicated for the treatment of bacterial conjunctivitis, and the remaining agent is indicated for bacterial keratitis. None is indicated for surgical prophylaxis, although all are or have been widely used for that purpose.

Numerous factors, including molecular structure, pharmacodynamics, and pharmacokinetics, determine the efficacy of ocular antibiotics and their utility in different clinical applications.[1-6] Particularly important is the fact that most ocular antibiotics are delivered topically, which means that some of the standard metrics of efficacy, which were developed for systemic drugs, don't apply to the ocular situation. (For example, the terms "susceptible" and "resistant," which are based on achievable *serum* concentrations, have little meaning when vastly higher drug concentrations can be achieved on the surface of the eye via topical dosing.)

Recent work has challenged conventional thinking about the meaning and determinants of antibiotic potency in the ocular situation. In addition, the presence of new topical fluoroquinolone formulations with properties different from other drugs in the class, changes the options available to physicians. By being made aware of these findings, ophthalmologists will be better able to evaluate new medications and select optimal antibiotic agents, especially for surgical prophylaxis.

Rethinking Ocular Antiinfectives will educate readers about the various factors that determine the efficacy of *ocular* antibiotics. This discussion will include an overview of how ocular antiinfectives have evolved, and it will offer new thinking about drug penetration into ocular tissues and spaces as it relates to antibiotic efficacy. Novel antiinfectives will also be described, as will the impact of the growing prevalence of fluoroquinolone-resistant ocular flora. Ophthalmologists will be able to apply this information immediately as they seek out the best options for preventing and managing ocular infection.

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TARGET AUDIENCE

This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES

Upon completion of this unit the reader will be able to:

1. List three factors that promote antibiotic resistance.
2. Describe the ways in which specific changes to molecular structure have increased the potency of succeeding generations of fluoroquinolones.
3. List three strategies for combating bacterial resistance.

FACULTY AND DISCLOSURE STATEMENTS

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This activity is supported by an educational grant from Bausch + Lomb, Inc.

PHARMACOLOGY PERSPECTIVE

Evolution of Fluoroquinolones: What Has Been Gained with Each New Molecule?

▶ Susanne Gardner, PharmD

Modern fluoroquinolones may be the most frequently used class of antibiotics in the treatment or prevention of infections in and around the eye. Fluoroquinolones offer the advantages of broad-spectrum activity, and have more Gram-positive, Gram-negative, anaerobe, and atypical coverage than perhaps any other single class of antibiotics in clinical use today. However, emerging trends in recent years show a fairly rapid development of bacterial resistance to these antibiotics, which represents particular challenges for the management of important bacterial infections at various sites in the eye.[1,2]

"GENERATIONS" OF FLUOROQUINOLONES

Fluoroquinolones in ophthalmology are often referred to as "first" through "fourth generation" agents. However, some overlap occurs, particularly between third and fourth generation agents, as we have come to know them, in the basic two bacterial enzymes that are targeted (DNA gyrase and topoisomerase IV). Therefore, this generational classification may not be based on clear chemical differences, or clear differences in activity, but may be related to the time periods and uses during which these agents were introduced to market. Therefore, the classification of these agents according to any specific "generation" may differ somewhat with various resources in the literature.

EARLY QUINOLONE ANTIBIOTICS

Nalidixic acid, patented in 1962, was the first "quinolone" antibiotic, found as a by-product in the production of the antimalarial agent, chloroquine (Figure 1).[5] Nalidixic acid was used primarily against Gram-negative microorganisms as a urinary tract antiseptic, reflected in its commercial name, NegGram®. Oral absorption was very poor, with peak serum concentrations of <0.5 µg/mL, but urinary concentrations were high. With more clinical experience, however, some important systemic side effects were noted, including photosensitivity that would also be associated with generations of fluoroquinolones to come. It is interesting to note that with this early compound, resistance was defined as MIC >100 µg/mL, an MIC much higher than we associate with effective MICs of the modern fluoroquinolones used today.

THE EARLY FLUOROQUINOLONES

In the late 1960s, a piperazine ring was added to the C-7 position on the basic quinolone molecule. This addition was thought to confer better bacterial cell wall penetration, and activity was improved against *Pseudomonas aeruginosa* and some Gram-positive bacteria. In the early 1970s, a fluorine atom was added at the C-6 position. With this addition, the term "fluoroquinolone" was coined, and better activity was conferred against Gram-positive microbes.[3-5]

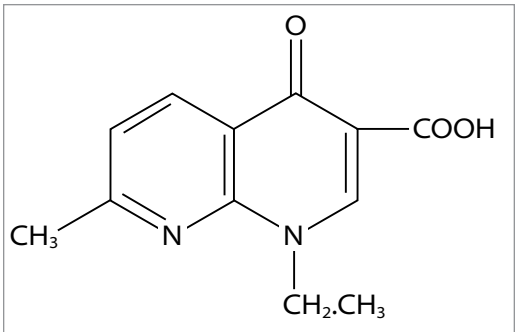

FIGURE 1. The first "quinolone" antibiotic, nalidixic acid.

Norfloxacin was the first fluoroquinolone introduced that is familiar to ophthalmology. It incorporated both these additions at the C-6 and C-7 positions (Figure 2). Considered a "first generation" fluoroquinolone, it showed better activity against Gram-positive bacteria with lower MICs and increased bacterial DNA gyrase inhibition. However, activity against staphylococci and streptococci was marginal, and this antibiotic lacked activity against anaerobes, *Chlamydia trachomatis*, mycoplasma, and mycobacteria. High serum levels of the drug were still difficult to achieve after systemic administration.[3-5]

Ciprofloxacin and ofloxacin are familiar examples of the "second generation" fluoroquinolones. Ofloxacin was introduced as an ophthalmic in 1996, and ciprofloxacin in 1998. These agents

were more useful for treating systemic infections outside the urinary or gastrointestinal tracts, having better oral bioavailability and better broad-spectrum activity. Ciprofloxacin was the first fluoroquinolone available for intravenous use. It added a cyclopropyl side-chain to the N-1 position, resulting in increased potency. Thus, it became more useful systemically against mycobacteria, mycoplasma, legionella, and added more Gram-positive and Gram-negative bacteria to its spectrum of action. However, ciprofloxacin remained ineffective against anaerobes and had borderline activity against many streptococcal species, especially in relation to safely attainable serum levels. With increased systemic use, resistant strains were also soon identified, especially among *Staphylococcus aureus*. Adverse effects became identified, such as chondrotoxicity and drug interactions, many of which would be associated with future generations of fluoroquinolones as well.[3-7]

The ofloxacin molecule contained a tricyclic core ring, as opposed to the bicyclic core ring of ciprofloxacin and norfloxacin (Figure 3). With this bridging ring between the N-1 and C-8 positions, Gram-positive activity was increased. Ofloxacin demonstrated better systemic absorption than ciprofloxacin, had a longer half-life, higher serum levels, and was more widely applied in the treatment of systemic infections. It showed activity against many Gram-negative microbes but was not more active against *P. aeruginosa* than was ciprofloxacin; it was active against chlamydia, legionella, mycoplasma, many mycobacteria, and so found more applicability for systemic infections as well.[3-5]

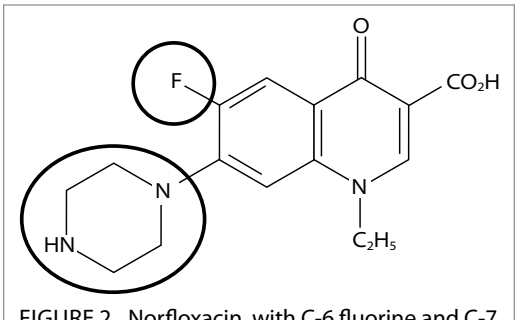

FIGURE 2. Norfloxacin, with C-6 fluorine and C-7 piperazine ring.

THE MODERN FLUOROQUINOLONES: THIRD AND FOURTH GENERATION

The "third generation" of fluoroquinolones came along in the early 1990s, a time marked by a heightened awareness of pharmacokinetic parameters that describe drug behavior. These parameters included the AUC (area under the curve), the relation of the AUC to the MIC (minimum inhibitory concentration), and the AUIC (area under the inhibitory curve). These parameters became applied to descriptions of fluoroquinolone activity and were utilized as predictors of clinical response to the antibiotics.[8-10] The "third generation" agents were developed with improved pharmacokinetics in mind, and a primary emphasis remained on developing potent but safe fluoroquinolones for systemic use, particularly in the treatment of upper respiratory infections. High serum levels were an objective, along with high levels relative to the MICs of targeted organisms, and greater AUCs. These third generation fluoroquinolones did have improved antimicrobial activity, especially against some resistant strains of *Streptococcus pneumoniae*, and they showed better activity against anaerobes than did previous generations. A few were associated with serious side effects, leading to withdrawal of agents such as temafloxacin. Still, an emphasis remained on developing potent but safe fluoroquinolones for systemic administration in order to achieve high serum levels safely.

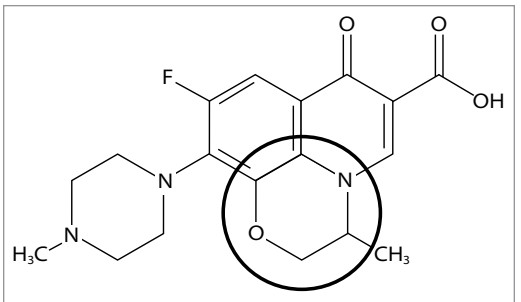

FIGURE 3. Ofloxacin, with tricylic core ring.

The most familiar to ophthalmology among the third generation fluoroquinolones is levofloxacin, the levoisomer of ofloxacin. Levofloxacin targeted both bacterial DNA gyrase and topoisomerase IV enzymes, whereas ciprofloxacin and ofloxacin had targeted primarily only DNA gyrase. While different groups of fluoroquinolones targeted both these bacterial enzymes, there are differences among individual fluoroquinolone agents in the MICs that effectively inhibit each enzyme.[11] Levofloxacin, like ofloxacin, contained a tricyclic core ring. These agents were also developed for expanded antimicrobial coverage. Again, they targeted streptococcal infections, focusing on the potential for successful treatment of respiratory infections, among others.

The "fourth generation" fluoroquinolones familiar to ophthalmology are gatifloxacin and moxifloxacin. At the C-8 position, both added a me-

thoxy group, and each had a "bulky group" at the C-7 position, although not identical in both agents. These agents were also developed with the aim of greater potency against many of the pathogens of interest in respiratory infections. Both contained a methoxy group at C-8 that improved activity against some anaerobes and atypicals. The C-8 methoxy group was associated with fewer systemic side effects than were some other substitutions at this position, but the systemic use of gatifloxacin was stopped in 2006. At the C-7 position, moxifloxacin has a "bulky group" (diazabicyclic ring) that is thought to be associated with increased lipophilicity. These fluoroquinolones were very useful in the treatment of community acquired pneumonia and showed good activity against *S. pneumoniae*.[3-5]

THE CHLORINATED FLUOROQUINOLONES

One of the newer agents introduced to market recently, besifloxacin, is related to a subgroup of fluoroquinolones that were halogenated (fluorine or chlorine) at the C-8 position, and were developed throughout the years. It is interesting to note that some of these earlier agents had a favorable antibiotic spectrum, including activity against some important resistant strains, and a lower tendency for bacterial resistance development.[12-14] However, these earlier agents were not further developed for systemic use because the high serum levels needed to treat serious systemic infections were also associated with some degree of photosensitivity, albeit limited to skin, with no specific ocular adverse effects noted.[15,16]

Clinafloxacin was one of these C-8 chlorinated agents and, compared to some fluoroquinolones, was more potent, with lower MICs against a variety of Gram-positive and Gram-negative microbes, especially against some resistant strains.[17,18] Another C-8 chlorinated fluoroquinolone of interest was sitafloxacin, a compound showing particular activity against multidrug-resistant Gram-positive pathogens in patients with systemic infections due to MRSA or VRE (vancomycin-resistant enterococci). At concentrations of 1μg/mL, sitafloxacin inhibited 90% of MRSA strains and 50% of VRE strains and showed activity against ciprofloxacin-resistant strains. It was effective in approximately 40% of patients with MRSA infections unresponsive to vancomycin. VRE was eradicated in 7 of 9 patients, with skin rash occurring in 28% of patients, although no phototoxicity was noted in ocular tissues.[19]

The FDA approved besifloxacin in 2009 as a topical ophthalmic drop only.[20] Besifloxacin is not used systemically, but is indicated for topical use in the treatment of bacterial conjunctivitis caused by susceptible isolates of a variety of bacteria. Besifloxacin ophthalmic suspension 0.6% is also formulated in a proprietary base intended to prolong the ocular surface contact time. This new agent has a chlorine atom at the C-8 position and contains a "bulky group" (amino-azepinyl) at the C-7 position. Besifloxacin has shown increased potency via lower MICs in vitro against many strains that showed relative resistance to other fluoroquinolones.[21] Because it is specialized for ophthalmic use only as an eyedrop, the serum levels previously associated with phototoxicity are not achieved with this eye drop form. In clinical trials, no phototoxicity reactions were seen and no meaningful systemic levels were achieved after normal eye drop use.[22,23] When there is no systemic use of antibiotics, such as fluoroquinolones, overall use of the antibiotic is less widespread and therefore less bacterial resistance potential is anticipated.

SUMMARY

In summary, bacterial DNA gyrase and topoisomerase IV are the two bacterial enzymes that are primary targets for recent generation fluoroquinolone antibiotics. Earlier fluoroquinolones target only one of these enzymes, but the third and fourth generation agents target both, as does the newly introduced besifloxacin. The overall pharmacologic effect of a fluoroquinolone entity depends on many factors outside of its molecular structure alone. While several modifications of the basic molecular quinolone configuration have been associated with certain clinical or antibacterial effects, it is difficult to assign with certainty any one specific pharmacologic effect to any one specific molecular modification. The interaction, or resonance, among atoms of the entire molecular structure seem to be involved in determining its ultimate clinical characteristics.

Nevertheless, all fluoroquinolones have a few chemical groups in common: a carboxylic group at position 3 and a carbonyl group at position 4, both thought to be important for binding the DNA/DNA gryase complex, for bacterial cell entry, and for interaction with elements such as magnesium, aluminum, and iron. In addition, they all have a fluorine atom at C-6, resulting in the "fluoroquinolone" name, improved activity against Gram-positive microbes, substantially lower MICs, and increased bacterial gyrase inhibition. Moreover, essentially all modern fluoroquinolones have a "bulky group" at

position C-7 that is usually an amino derivative of piperazide, piperazine, or pyrollidine. Substitutions at this position affect antimicrobial spectrum, potency, side effects, and pharmacokinetic characteristics. A good deal of variation in the "bulky group" at C-7 is permissible while still maintaining good antimicrobial activity.[5] At the C-8 position, a methoxy group, as in moxifloxacin and gatifloxacin, was aimed at systemic safety and avoidance of phototoxicity. However, historically, halogenation, such as chlorination, at C-8 has been associated with antibiotic potency that included activity against many resistant bacterial strains, with relatively low MICs, although systemic use was associated with phototoxicity. Besifloxacin is a new chlorinated fluoroquinolone with a chlorine atom at the C-8 position. It is not used systemically, and no phototoxicity was observed clinically with use of the topical drops.

FUTURE FOCUS

In looking to the future, we should acknowledge the reports of increasing bacterial resistance to the "fourth generation" fluoroquinolones as we know them. With more than 10,000 quinolone molecules being patented to date, some researchers acknowledge the limited potential of further modifications to the core molecular structure that perpetuate the same objectives of recent "generation" fluoroquinolones—namely, the safe attainment of high serum levels for the treatment of a variety of systemically manifested infections. There is renewed interest in the potential of compounds previously identified that may find applicability in the management of infections in more specialized ways.

Susanne Gardner, PharmD, is an educator, writer, researcher, and consultant to the pharmaceutical industry in the area of ocular infections and diseases. She is based in Atlanta, GA.

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PRACTICE PERSPECTIVE

Evolution of Fluoroquinolones: What Has Been Gained with Each New Molecule?

▶ Marguerite B. McDonald, MD

As cornea fellows in the 1980s, my colleagues and I would spend 1-2 hours each day at the hospital checking on patients with corneal ulcers. Because of the fear that these patients' infections might spread, they were secluded in private rooms and assigned private nurses. These patients were treated with fortified antibiotics, applied topically as often as every 15 or 30 minutes—the drops were given all day and sometimes all night as well. Corneal ulcer patients would remain in the hospital for days.

Now, even with a referral practice, I have not admitted a patient for a corneal ulcer in years. This is a testament to the many advances that have reduced the incidence and improved the treatment of ocular infection. Included among these developments, of course, is the advent of fluoroquinolones for ophthalmic use.

BEFORE FLUOROQUINOLONES

Prior to using fluoroquinolone antibiotics, we relied heavily on tobramycin and chloramphenicol. In chloramphenicol we had an extremely potent and effective broad-spectrum antibiotic. However, its use quickly dropped off in the United States due to potentially lethal side effects—although a very rare occurrence, chloramphenicol induced aplastic anemia in some patients.[1,2] Worse yet, this condition is not dose-dependent—a single drop could cause death in susceptible individuals. Moreover, there was no way to screen for risk in advance.

Thus, chloramphenicol was withdrawn from our armamentarium, but we would have new opportunities with the arrival of fluoroquinolone antibiotics.[1,2] These drugs offered attractive qualities that contribute to their continued widespread use today: potent broad-spectrum coverage, good tissue penetration, and low toxicity. They also presented an advantage over aminoglycosides, which can cause chemical blepharitis after one or more weeks of use.

EVOLUTION OF FLUOROQUINOLONES

As the years went by, "generations" of fluoroquinolone antibiotics made their way into the ophthalmic practice. Novel formulations would eventually yield drugs with a broader spectrum of coverage, improved pharmacokinetics, and better tolerability.[3]

As antibiotic resistance has become more prevalent, an emphasis has also been placed on formulations that inhibit the emergence of resistant bacteria. The more recently introduced topical fluoroquinolones, such as gatifloxacin, moxifloxacin, and besifloxacin, target both DNA gyrase and topoisomerase IV, enzymes that are essential for bacterial growth.[4,5] This was a departure from early fluoroquinolones, which preferentially target one enzyme or the other.[5] Due to this modification, more recent fluoroquinolones have broader coverage and are less susceptible to resistance developing from single-step topoisomerase mutations.

In addition, newer topical fluoroquinolones penetrate tissue well and can produce tissue concentrations in the eye that are fairly high in relation to minimum inhibitory concentration (MIC) values of susceptible organisms. In a 2009 study, Karpecki and associates compared the MIC_{90}s of various antibiotic agents against clinical isolates from patients with culture-confirmed bacterial conjunctivitis.[6] They found that the MIC_{90}s for gatifloxacin, moxifloxacin, and besifloxacin were substantially lower than those for ciprofloxacin against *Staphylococcus aureus* and *Streptococcus pneumoniae*. The MIC_{90}s of these newer fluoroquinolones were the same or lower than that of ciprofloxacin against *Staphylococcus epidermidis*. (The biggest difference against *S. epidermidis* was seen with besifloxacin, the newest fluoroquinolone, which had an MIC_{90} of 0.06 µg/mL compared with moxifloxacin (0.125 µg/mL), gatifloxacin (0.25 µg/mL), and ciprofloxacin (0.25 µg/mL).[6] In addition, the more recently developed fluoroquinolones have generally demonstrated somewhat lower rates of bacterial resistance than older fluoroquinolones.[7-9]

BACTERIAL RESISTANCE: CAUSES AND CONSEQUENCES

Despite these advantages, antibiotic resistance has become a growing problem among

both older and newer generations of these drugs. In the most recent reports from the nationwide Ocular TRUST (Tracking Resistance in U.S. Today) study, for example, the majority of tested methicillin-resistant *S. aureus* (MRSA) isolates were resistant not only to ciprofloxacin, but also to levofloxacin and the newer topical fluoroquinolones gatifloxacin and moxifloxacin.[10]

One factor that has contributed to the development of antibiotic resistance is the widespread use of the fluoroquinolones themselves, particularly their application in systemic medicine and their even more liberal use in agriculture. A 2002 study by Smith and associates reported that up to 80% of the antibiotics produced in the United States are used in agriculture, mostly to promote animal growth.[11] Resistant bacteria can develop within these animals due to chronic antibiotic exposure. In such cases, the bacteria can be transferred to humans when the animal meat is commercially sold and eaten.[12] These microorganisms can also spread beyond the farm when manure leaches into the soil and water of surrounding areas (Table 1).[13]

TABLE 1.

Factors that Promote Bacterial Resistance

- Liberal use of antibiotics in agriculture
- Increasing amounts of antibiotics in water/soil
- Patient noncompliance (missed doses; tapering; stopping prematurely)
- Taking antibiotics unnecessarily for extended periods, especially at low or ineffective doses

Among eyecare practitioners, additional factors that contribute to antibiotic resistance include inappropriate prescribing and patient noncompliance. In PRK and LASIK prophylaxis, for example, patients may be told to take their drops four times daily after surgery. After a day or two, these patients may feel that, since there is nothing noticeably wrong with them, there is no harm in missing doses or reducing their number. On the physician's side, prescribing low-dose antibiotics for extended periods can also promote resistance.

The diminishing susceptibility of ocular isolates to fluoroquinolones is frightening because it limits our options for managing common eye infections.[14-16] A future direction of ocular drug development will, therefore, be to find ways of circumventing pathogen drug resistance.[14-17] Currently, we employ a variety of strategies—with varying degrees of efficacy—to combat resistant organisms. These include the use of combination therapy, monitoring drug interactions, customizing prescribing patterns, frequent patient follow-up visits, and incorporating the preservative benzalkonium chloride (BAK) to improve antibiotic potency (Table 2).

TABLE 2.

Strategies for Dealing with Bacterial Resistance

- Combination therapies
- Monitoring drug interactions
- Customized prescribing
- Patient follow-ups
- Incorporating BAK to boost antibiotic efficacy
- Development of new fluoroquinolones

BENZALKONIUM CHLORIDE

In several studies, the addition of BAK has resulted in enhanced in vitro potency. Hesje and associates found that adding BAK to gatifloxacin and moxifloxacin caused dramatic reductions in the mutant prevention concentration against MRSA isolates.[18] (The mutant prevention concentration is the minimum drug concentration needed to kill quickly enough to prevent the generation of mutant organisms.) Additionally, the MIC_{90} of gatifloxacin and moxifloxacin against MRSA was substantially lower when BAK was added (≤0.008 µg/mL) versus when the same drugs were used without BAK (MIC_{90} ≥ 4 µg/mL and MIC_{90} = 4 µg/mL for gatifloxacin and moxifloxacin, respectively) (Table 3).[18] A similar association has been noted in animal studies—in a rabbit model, adding BAK to gatifloxacin resulted in increased efficacy (supported by the finding of lower MICs in vitro) than when the drug was used without BAK.[19]

Although the addition of BAK to antibiotics has certain advantages that have been documented in the laboratory, the incorporation of BAK also presents certain challenges. First, there is the common problem that exists for all topical applications, which is that a significant amount of BAK can be lost from the eye due to tear turnover.[20] In addition, the prolonged use of BAK, or the use of BAK in high concentrations, can have toxic effects on the eye. This is particularly an issue when BAK is added to glaucoma medications—drugs that are used daily for years, usually by older

TABLE 3.

MPCs and MICs of Gatifloxacin, Moxifloxacin, and BAK Against Clinical MRSA Isolates

	MICs						MPCs		
	without BAK			with BAK*			without BAK	with BAK	
	MIC_{50}	MIC_{90}	MIC_{range}	MIC_{50}	MIC_{90}	MIC_{range}	0 µg/mL	7–9 µg/mL	10 µg/mL
Gatifloxacin (µg/mL)	≥ 4	≥ 4	0.063 to ≥ 4	≤ 0.008	≤ 0.008	≤ 0.008 to ≥ 8	≥ 4	≤0.004 to 0.125	≤ 0.004
Moxifloxacin (µg/mL)	0.063	4	0.031 to ≥ 8	≤ 0.008	≤ 0.008	≤ 0.008 to ≥ 8	≥ 4	≤0.004 to 0.063	≤0.004

*BAK was added at concentrations of 3.125 µg/mL to 6.25 µg/mL.

Abbreviations: BAK = benzalkonium chloride; MPC = mutant prevention concentration; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*.

patients who already have dry eyes. However, this ocular surface toxicity is less of an issue in antibiotic treatment, as most patients take antibiotics for only a few days.

BESIFLOXACIN

A final factor that may help us to overcome antibiotic resistance, even if only temporarily, is the development of new fluoroquinolones. One such example, besifloxacin, is the newest of these broad-spectrum agents to become available in a topical formulation and was FDA approved in 2009 strictly for ophthalmic use. It is formulated in a polymeric mucoadhesive wetting agent that has been shown to enhance residence time of the drug on the eye.[21]

Many clinical efficacy studies have been performed on this drug. In one study, for example, after besifloxacin treatment of 656 conjunctivitis isolates, no resistant strains emerged.[22] Additionally, data compiled from three clinical studies show the in vitro MIC_{90} activity of besifloxacin, moxifloxacin, gatifloxacin, and azithromycin against a variety of clinical isolates (Table 4).[23] A sizeable number of isolates of both *S. aureus* and *S. epidermidis* were tested; for both organisms, besifloxacin had the lowest mean MIC_{90} values: 0.5 µg/mL for *S. aureus* and 0.5 µg/mL for *S. epidermidis*. This compares with 2 µg/mL and 4 µg/mL, respectively, for moxifloxacin, 4 µg/mL and 2 µg/mL for gatifloxacin, and >8 µg/mL and >8 µg/mL for azithromycin.

Cambau et al found that besifloxacin showed lower frequencies of resistant variants in studies of representative ocular pathogens than ciprofloxacin and moxifloxacin.[18] This is due to its balanced dual targeting of DNA gyrase and topoisomerase IV.

CHALLENGES WITH MODERN DRUGS

There are, of course, several potential challenges with new drugs. First, we have less clinical data to work with than we do with older antibiotics. New drugs may also incur higher costs for patients. At the pharmacy, these drugs are very likely to be priced in Tier 3 and require a higher

TABLE 4.

In Vitro (MIC_{90}) Activity vs Clinical Isolates

		MIC_{90} (µg/mL)			
Pathogen	**N**	**Besifloxacin**	**Moxifloxacin**	**Gatifloxacin**	**Azithromycin**
All isolates	1324	0.25	0.5	0.5	> 8
Gram(+) isolates	886	0.25	0.5	1.0	> 8
Gram(–) isolates	438	0.5	0.25	0.25	> 8
H. influenzae	344	0.06	0.06	0.03	4
S. aureus	190	0.5	2	4	> 8
S. epidermidis	111	0.5	4	2	> 8
S. pneumoniae	302	0.125	0.125	0.5	> 8

*Data pooled from 3 clinical studies. FDA Advisory Committee Briefing Document. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4397b1-00-Index.htm.

copay than Tier 1 or Tier 2 drugs—or, the drug may not be covered by insurance at all. In such cases, the patient may be switched to a generic, such as ciprofloxacin, as a more affordable alternative. The downside is that, although a fluoroquinolone, ciprofloxacin is an older drug, and there is a higher level of resistance; so switching medications to save money may result in taking a drug that does not efficiently resolve the infection. This could lead to extra physician visits and equate to more copays. Meanwhile, there is also the risk of spreading the infection to others.

CONCLUSION

The evolution of ocular antiinfectives has brought about several new options for killing bacteria. Today, we have ready access to antibiotics that provide a broad spectrum of coverage, excellent pharmacokinetics, and good tolerability. At the same time, growing bacterial resistance continues to limit treatment options and pose new challenges. Physician efforts (eg, appropriate prescribing and working to ensure patient compliance) and the development of new drugs should help us to meet these challenges.

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1. Chloramphenicol drops fell out of use in the United States due to:
   A. Loss of efficacy due to antibiotic resistance.
   B. Replacement by lower cost fluoroquinolones.
   C. Rare but potentially fatal side effects in some patients.
   D. Lack of broad-spectrum activity.

2. Targeting both DNA gyrase and topoisomerase IV:
   A. Reduces the chances of resistance developing from a single-step mutation.
   B. Results in the emergence of resistant strains of bacteria.
   C. Increases the chances of resistance developing from a single-step mutation.
   D. Is a characteristic of older fluoroquinolone antibiotics.

3. Compared with previous generations, "third generation" fluoroquinolones had:
   A. Improved antimicrobial activity, except against anaerobes.
   B. Roughly the same level of antimicrobial activity.
   C. Improved antimicrobial activity and stronger activity against anaerobes.
   D. Improved antimicrobial activity, but the same level of activity against anaerobes.

4. Pharmacokinetic parameters that describe drug behavior include:
   A. The AUC (area under the curve).
   B. The relation of the AUC to the MIC (minimum inhibitory concentration).
   C. The AUIC (area under the inhibitory curve).
   D. All of the above.

5. Ciprofloxacin and ofloxacin:
   A. Are both "first generation" fluoroquinolones.
   B. Target bacterial DNA gyrase and topoisomerase IV enzymes equally.
   C. Target primarily only DNA gyrase.
   D. Had less broad-spectrum activity than norfloxacin.

6. Incorporating benzalkonium chloride into a topical antibiotic drop has been found to:
   A. Improve patient compliance.
   B. Enhance residence time of the antibiotic on the eye.
   C. Increase in vitro potency.
   D. Lower antibiotic potency.

7. Halogenation, such as chlorination at C-8, has historically been associated with:
   A. Antibiotic activity against many resistant bacterial strains.
   B. Relatively low MICs.
   C. Neither A nor B is true.
   D. Both A and B are true.

8. Factors that may contribute to the development of antibiotic resistance include:
   A. Liberal use of fluoroquinolones in agriculture.
   B. Patient noncompliance.
   C. Extensive use of antibiotics in systemic medicine.
   D. All of the above.

9. Modern fluoroquinolones have characteristics that are conducive to:
   A. The development of bacterial resistance.
   B. Producing high tissue concentrations relative to MIC values.
   C. Producing higher tissue concentrations and higher MICs than older fluoroquinolones.
   D. None of the above is correct.

10. Besifloxacin is a new fluoroquinolone antibiotic that:
    A. Lacks a chlorine atom at the C-8 position.
    B. Is approved for ophthalmic and systemic use.
    C. Commonly causes phototoxicity.
    D. Is specialized for ophthalmic use only as an eyedrop.

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ANSWERS:

1.	A	B	C	D	6.	A	B	C	D
2.	A	B	C	D	7.	A	B	C	D
3.	A	B	C	D	8.	A	B	C	D
4.	A	B	C	D	9.	A	B	C	D
5.	A	B	C	D	10.	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

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