ELSEVIER

CONCLUSION

Future of Ophthalmic Anti-infective Therapy and the Role of Moxifloxacin Ophthalmic Solution 0.5% (VIGAMOX®)

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Abstract. The vintage antibiotics that were available in the 1950s–1980s were sometimes toxic, had limited spectra, and were bacteriostatic agents, and they have been replaced by significantly broader-spectrum therapies. We ask more of our future antibiotic products for ophthalmology: they must be 1) broad spectrum, 2) convenient to use, 3) useful prophylactically, 4) effective therapeutically, 5) benzalkonium chloride–free, 6) comfortable, and 7) nontoxic. The emergence of antibiotic resistance has focused us on more potent agents effective against resistant strains of bacteria. Fluoroquinolones have become a dominant family of ophthalmic antibiotics. But even the older fluoroquinolones (e.g., ofloxacin, ciprofloxacin) have lost much of their effectiveness against some important ocular isolates. Considering all of the characteristics for an ideal ophthalmic antibiotic product available today, moxifloxacin ophthalmic solution 0.5% represents a primary antibiotic product of choice for treating and preventing ophthalmic infections. (**Surv Ophthalmol 50**:S64–S67, 2005.

Key words. benzalkonium chloride • ciprofloxacin • fluoroquinolones • gatifloxacin • levofloxacin • moxifloxacin • ofloxacin • ophthalmic therapy • VIGAMOX®

Product Evolution and Demands

Gone are the days in the 1950s and 1960s when there was a wide range of choices for antibiotic therapy. Eye care practitioners no longer use sulfonamides, chloramphenicol, polymyxin, or bacitracin to treat ophthalmic infections. The use of aminoglycosides (neomycin, gentamicin, tobramycin) is waning as better agents in the fluoroquinolone family become available. These 1950s vintage antibiotics were sometimes toxic, had limited spectra, were bacteriostatic agents, and have been replaced by significantly broader-spectrum therapy. We ask more of our future antibiotic products for ophthalmology. They must be very effective against a wide range of infectious agents. They must be convenient to use for the surgeon and patient. They must cure quickly or sterilize the surgical eye area effectively. They should be able to be used prophylactically to prevent infections and therapeutically to cure infections. They must be able to be used in a wide variety of people, from neonates to geriatric patients. They must be broad enough to be used prophylactically and strong enough to cure serious, specific infections. Their dosage regimens must be simple, yet effective. They

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must be comfortable and nontoxic to the eye. They should be useful in treating or preventing a wide range of ocular infections (e.g., conjunctivitis, keratitis, endophthalmitis, blepharitis, dacryocystitis).

Growing Antibiotic Resistance

Growing microbial resistance to current antibacterial agents and widening gaps in antibiotic coverage create a need for a more potent and genetically smart fluoroquinolone. When ciprofloxacin, the first ocular fluoroquinolone, became available for ophthalmic use roughly a decade and a half ago, there was tremendous excitement. This was our knockout punch in the fight to prevent ocular infection, especially after cataract and refractive surgery. Today, however, our most impressive weapon has lost some of its punch.[13,16,24] Several microorganism groups have developed resistance to ciprofloxacin and its sister fluoroquinolones, ofloxacin and levofloxacin, more quickly than imagined, and resistance levels are increasing each year (**F1**).[16]

The bacteria hold most of the cards for the future. They will evolve and respond to their environment and produce progeny that will be resistant to today's antibiotics. Humans can only try to keep ahead of these clever creatures. Abandoning the old antibiotics and taking on the new is the only way to keep abreast of and even stop resistant trends. Continuing to use older, previous-generation antibiotics will only facilitate the continued development of resistant strains.[11] To our knowledge, there are no studies that prove or suggest topical application of moxifloxacin has the potential to induce microbial resistance distal to the site of instillation.

Conjunctivitis

Conjunctivitis occurs worldwide and affects people of all ages, all social strata, and both sexes. It has been cited as one of the most frequent causes of self-referral in the practice of comprehensive ophthalmology.[8,12,14,18] According to the American Academy of Ophthalmology (**F2**), conjunctivitis infrequently causes permanent visual loss or structural damage, but the economic impact of the disease in terms of lost work time, although undocumented, is doubtless considerable.

Fluoroquinolones

The fluoroquinolones are an evolving and powerful class of broad-spectrum antimicrobial agents used in the prevention and treatment of a variety of ocular infections; however, resistance to currently available agents in the class has been emerging among ocular pathogens.[2,4] They interfere with bacterial deoxyribonucleic acid synthesis, and newer generations of these compounds have improved broad-spectrum coverage. The topical fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, were approved in 2003 by the US Food and Drug Administration for ocular indications. These antibiotics represent the most advanced group of compounds within the class, offer a unique dual-binding mechanism of action in gram-positive organisms, and have activity against otherwise resistant species.[4] Recent reports (**F3**) have indicated that the fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, are more effective than earlier generations of fluoroquinolones and tobramycin, based on minimum inhibitory concentrations (MICs) and susceptibility results. Several recent *in vivo* studies using prophylactic models with rabbits have shown the potency of these antibiotics in preventing infections by common pathogens.[3,9,17] Although further clinical evidence of their efficacy in prophylaxis and treatment of human ocular infections is required, there is a growing need for compounds with this potential to combat emerging resistance.[4,6]

Benzalkonium Chloride–Free Products

Agents that are innately antibacterial, such as antibiotics, like the fluoroquinolones, have the opportunity of being formulated in multiple-dose containers without added antimicrobial preservative agents, such as benzalkonium chloride. This preservative has served the ophthalmic community well over the last 50 years and is still required for preserving antiglaucoma and other ophthalmic products. But researchers should take the opportunity to avoid additional chemicals in any ophthalmic formulation, if possible, unless new data suggest some previously unrecognized benefits. Moxifloxacin ophthalmic solution (VIGAMOX®, Alcon Laboratories, Inc., Fort Worth, TX) is the first fluoroquinolone antibiotic preparation available in the US that does not need benzalkonium chloride to be adequately preserved (**F4**). There are a number of benzalkonium chloride–free fluoroquinolone products for ophthalmology available in Japan.

[F1] Alfonso EC: Why is the next generation of antibiotics so important? Refractive Eyecare Ophthalmol 7(Suppl):1, 2003.

[F2] AAO, Cornea/External Disease Panel and the Preferred Practice Patterns Committee: Conjunctivitis. San Francisco, AAO, 2003.

[F3] Tepedino ME: Microbiological analyses of the activity of 7 anti-infectives against isolates from patients with acute bacterial conjunctivitis (abstract). Invest Ophthalmol Vis Sci 45(Suppl): 4914, 2004.

[F4] Schlech BA, Sutton S, Rosenthal RA, et al: Antimicrobial preservative effectiveness of VIGAMOX®™ (abstract). Invest Ophthalmol Vis Sci 45(Suppl):4913, 2004.

Therapeutic Usage

Topical therapy for treatment of infections remains an important and convenient avenue for the physician. The ability of an antibiotic to cure an ocular infection quickly and prevent serious vision loss is a paramount consideration for evaluating the effectiveness of therapeutic antibiotics. The ability of the antibiotic to penetrate the ocular tissues and kill and eradicate the pathogens at the site of the infection is an important goal. At this time, antibiotics such as moxifloxacin have better ocular penetration qualities than earlier fluoroquinolones, such as ciprofloxacin or ofloxacin (**F5**, **F6**, **F7**).[15,22]

Prophylactic Usage

The prevention of infections before, during, and after surgery and the use of prophylactic antibiotic products will undoubtedly continue in the future.[1,7,20,21,25] With this use, the antibiotic with the widest spectrum, lowest number of resistant strains, and fewest side effects should be the agent of choice for prophylaxis. The broad, shotgun approach still has merit in the surgical suite (**F8**).[10,17,23,25]

Antibiotic Susceptibility Testing and Breakpoints

The future of susceptibility testing is uncertain. The links between tests that define a pathogen as resistant or susceptible to a particular antibiotic are coming under fire. Standards have been set for systemic breakpoints for most antibiotics, but it is argued that these levels are not really relevant to the antibiotic levels achievable in ocular tissues via topical dosing.[19] The relatively poor predictive value of *in vitro* susceptibility is even dramatized more when systemic breakpoints are applied to ophthalmic antibiotics and their usage.[26] However, MICs are still of great value for rank ordering the power of various antibiotics or comparing the organisms that make up the most resistant or less sensitive groups.[5]

Culturing Bacterial Pathogens

Isolating and identifying an infecting organism is still a key principle of the 1883–1884 postulates defined by Robert Koch. Microbiologists will continue to show the virtue of culturing, isolating, or detecting the main pathogen in ophthalmic infections. It has been shown that culture confirmation affects the antibacterial therapeutic response rate of ulcerative keratitis.[28] Corneal infections by relatively ciprofloxacin-resistant bacteria respond more slowly to ciprofloxacin therapy. Antibacterial susceptibility testing of corneal cultures may predict the fluoroquinolone therapeutic response rate of bacterial keratitis.[27]

Ideal Antibiotic Product for Ophthalmology

For today's time and considering all of the characteristics for an ideal ophthalmic antibiotic product, moxifloxacin ophthalmic solution 0.5% (as VIGAMOX®) represents a primary antibiotic product of choice for treating and preventing ophthalmic infections. This includes improved effectiveness and potency, spectrum breadth, utility in treating and preventing infections, greater solubility, enhanced ocular penetration, acceptable safety, lack of benzalkonium chloride, and lower risk of resistance development. These virtues have been highlighted in this supplement. Nevertheless, the future will require even more advanced medications and therapy options. Such is the nature of infectious disease control for ophthalmology.

Method of Literature Search

We performed a literature search for this article based on MEDLINE database searches from 1990 to 2005, using varying combinations of the search terms *ocular infections, ophthalmic antibiotics, moxifloxacin, gatifloxacin, ciprofloxacin, ofloxacin, fluoroquinolones, therapy, prophylaxis,* and *future.* Relevant English journal articles and/or abstracts were selected for review.[6]

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