Injection volume and intracameral moxifloxacin dose

We read with interest the recently published article of Shorstain and Gardner, which highlights the importance of adequate intracameral (IC) moxifloxacin dosing and injection protocols in achieving consistent bactericidal levels for postoperative endophthalmitis prophylaxis in cataract surgery. In their study, mathematical models of the anterior chamber (AC) concentrations of moxifloxacin and its elimination rates were calculated following laboratory experimentation with 3 concentrations/injected volumes (0.5%/0.05 mL, 0.5%/0.10 mL, and 0.15%/0.50 mL). Two different AC volumes representing the human pseudophakic eye (0.19 mL and 0.33 mL) for each dosing method were used for their calculations. They concluded that larger injection volumes yielded more reliable aqueous concentrations.

In our recent publication, we share the authors’ viewpoint that larger injection volumes, with similar total dosing, offer greater precision and reliability. We concluded that an IC injection dose of 600 μg moxifloxacin in 0.4 mL (yielding an AC concentration of about 1200 μg/mL), replacing most of the AC and intracapsular volume as the final step of surgery, enables more consistent antibiotic delivery into the AC. Our proposed IC injection method, after hydration of the main incision to avoid leakage, also enables slight adjustments of the intraocular lens position while injecting. It is important to understand that with IC injection, the IC drug concentration continuously accumulates within the AC by logarithmic growth throughout the injection, gradually approaching the injected solution’s concentration as aqueous is replaced, rather than providing a complete exchange or wash, an overly simplistic concept.

We chose our injection technique, because our research led us to results somewhat divergent from those of Shorstain and Gardner. Their model’s assumption of the human pseudophakic AC volume of 0.19 mL and 0.33 mL was derived from Kanellopoulos and Asimellis, whose Scheimpflug imaging measurements were taken 3 months after cataract surgery. This is long after postsurgical equilibration (ie, fibrosis and closure of the capsular bag) has taken place. Our calculation of 0.5 mL volume of the AC and a just-evacuated capsular bag after phacoemulsification was derived by summing the preoperative anterior and posterior chamber volumes with that of the mean preoperative capsular bag.

As a result of smaller AC volume estimates, Shorstain and Gardner arrived at a half-life elimination of moxifloxacin from the AC of 1.2 hours. This differs from our calculation of 2.89 hours, as illustrated in Figure 1, which is consistent with the literature. At our calculated abatement rate, the IC moxifloxacin does not dilute to below the bactericidal level of minimum inhibitory concentration greater than 64 μg/mL (the minimum inhibitory concentration of 90% of strains tested of the most moxifloxacin-resistant endophthalmitis pathogens, published in the ARMOR [Antibiotic Resistance Monitoring in Ocular Microorganisms] study) until 7.4 hours (with efficacy to 10.4 hours due to the postantibiotic effect of fluoroquinolones) after injection. This compares favorably with Shorstain and Gardner’s estimation of 5.4 hours for moxifloxacin levels to fall to the same level.

Practical and ethical limitations preclude frequent postoperative AC sampling of antibiotic levels in humans. Improved understanding of moxifloxacin’s complex pharmacokinetics as clinical and bacteriological data accumulate will help us refine mathematical models representing IC abatement profiles. We arrived at greater immediate postphacoemulsification AC volume and IC moxifloxacin half-life than Shorstain and Gardner.

Figure 1. Abatement rate of intracameral moxifloxacin 600 μg in 0.4 mL against the background of the MIC90 for the indicated strains from the ARMOR study. The calculated abatement of the concentration of moxifloxacin in the AC shows that the AC level will not fall below the ARMOR-reported MIC90 of MSSA, the most frequent pathogen, for almost 37 hours, or below its mutant prevention concentration for 27 hours. Even for the most resistant strains ever reported, ARMOR CoNS MIC90 = 64 and ARMOR MRSA MIC90 = 32 mg/L, the level of moxifloxacin exceeds those MICs for 7.4 and 10.4 hours, respectively (AC = anterior chamber; ARMOR = Antibiotic Resistance Monitoring in Ocular Microorganisms; CoNS = coagulase-negative Staphylococcus; MIC = minimum inhibitory concentration; MIC90 = minimum inhibitory concentration of 90% of strains tested; MPC = mutant prevention concentration = 10 × MIC for dose-dependent fluoroquinolones; MRSA = methicillin-resistant Staphylococcus aureus; MSSA = methicillin-sensitive Staphylococcus aureus).
However, we agree that larger volume IC injection with similar total dose is a more precise and reliable method to achieve consistent antibiotic delivery.

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**Reply:** Arshinoff and Modabber call into question two assumptions of our mathematical model describing the residence times of moxifloxacin in the anterior segment with two different intracameral injection strategies. The authors of the letter agree with us on the underlying principle of our publication but disagree on the volume of the anterior chamber (AC) and the half-life of antibiotics.

We selected two representative mean pseudophakic AC volumes (0.19 mL and 0.33 mL), substantiated by the literature, to demonstrate the principle that injecting the same dose of antibiotics (eg, 500 μg) into ACs with varying volumes produces varying concentrations of antibiotics within the total aqueous humor volume. The larger volume of 0.33 mL of Matsuura was derived from aqueous humor sampling immediately after intracameral injection in humans, before any possible fibrosis of the capsule. Libre and Mathews also agree with this volume. Arshinoff and Modabber’s estimation of 0.5 mL is based on a mean phakic AC volume in the human eye of 0.25 mL; however, measurements of the AC volume in the elderly phakic eye average only 0.15 mL. With this experimentally derived volume, Arshinoff’s estimation of the mean pseudophakic aqueous volume would be 0.4 mL, close to Matsuura and Libre’s reported value of 0.33 mL.

The AC size is known to vary from patient to patient, which cataract surgeons recognize when operating on smaller eyes and myopic eyes with longer axial lengths and larger chambers. Therefore, attempting to replace the aqueous contents with an antibiotic solution of known concentration will achieve the more consistent final concentration of drug, irrespective of the patient’s pseudophakic AC volume. This same principle would have been demonstrated had we chosen two different AC volumes.

There is a wide variation in the reported half-life elimination of antibiotics in the AC. Generally speaking, interdrug variation in elimination times, especially in the eye, may be due to factors such as differences in the drug molecular size, tissue binding, active pump mechanisms, and obstructions or reductions to outflow and drug elimination. Asena obtained antibiotic half-lives between 1.2 hours and 13 hours in rabbits, depending on which time points were used; Lipnitzki et al. found between 0.64 hours and 1.8 hours in rabbits. Matsuura et al. demonstrated a half-life in rabbits and humans that averaged 1.2 hours over most time points. We chose 1.2 hours as it agrees with the 1% per minute aqueous turnover rate noted by Goel et al. The varied measured drug life-half-life elimination time of moxifloxacin and other antibiotics in the AC may be due to imprecision in injection and sampling techniques, pharmacokinetics that are not single compartment, and variations in individual subject anatomy and physiology. We would caution against the speculation of postantibiotic effects in regard to half-life because efficacy should be related to the target microorganism. Furthermore, principles that apply to the multidose administration of antibiotics in the treatment of systemic infections should not be presumptively applied to the scenario of single-dose intraocular injection without empirical evidence.

Our study used two different and substantiated aqueous volumes and demonstrated that injecting small volumes of an agent can result in unequal final drug concentrations in the AC. Given the patient-to-patient variations, the “flushing” or large-volume injection technique should offer some degree of standardization and assurance of a more uniform final drug concentration in the pseudophakic AC as compared with smaller-volume-injected aliquots, thereby minimizing the interpatient variable of AC volume differences during cataract surgery.—Neal H. Shorstein, MD

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