As research into the action of ocular antibiotics continues, more published reports are incorporating the concepts of pharmacokinetics and pharmacodynamics into study designs, and some may draw conclusions about the effectiveness of antibiotics in the eye. Much of this research includes terms such as AUC (area under the curve) and the $C_{\text{max}}$ (maximum achieved concentration of a drug) and ratios such as $AUC/\text{MIC}$ (AUC/minimum inhibitory concentration) and $C_{\text{max}}/\text{MIC}$. Eye care specialists may be uncertain what these really mean and how to apply them to clinical decision making. It is therefore worthwhile to review and simplify these concepts.

Although the science of pharmacokinetics can be quite complex mathematically, it is applied practically in the early stages of drug development to determine therapeutic dosing regimens while avoiding toxic effects. Pharmacokinetics charts the level of an administered drug in various tissues of the body after one or more doses. A mathematical analysis allows characterizations to be made that can predict how different doses and regimens would distribute the drug throughout the body and affect drug levels in tissue, drug excretion rates, efficacy, and toxicity. Pharmacokinetic calculations are used daily for hospitalized patients given antibiotics such as the aminoglycosides and vancomycin, for example, to determine optimal dosing while avoiding renal and/or hepatic toxicity.

In contrast, however, the study of the pharmacokinetics of ocular antibiotics after their administration via topical drops has remained fairly basic in recent years. By and large, it has focused on actual measured levels that approximate peaks or the highest level achieved. Additional random levels measured at more distant time points have been used to estimate the rate of drug removal or decline in certain ocular compartments, although such data are sparse and rarely obtained. From these measured points, mathematical calculations have been made to estimate parameters such as the AUC.

**A REVIEW OF BASIC PARAMETERS**

Some basic pharmacokinetic/pharmacodynamic parameters that appear in the ophthalmic literature can be explained as follows:

- $C_{\text{max}}$. The maximum concentration of drug achieved. This is generally a single point that represents the highest level achieved, as shown in Figure 1.
- $T_{1/2}$. The amount of time required for the level of the drug to be reduced by one-half.
- AUC. The area under the time/concentration curve represents a mathematical calculation of the total amount of drug present during a given period of time. AUC is usually measured during the 24 hours after a dose or during a typical dosing interval (eg, $AUC_{0-24}$, $AUC_{0-t}$).
- MIC. The minimum inhibitory concentration represents the lowest concentration of an antibiotic that inhibits bacterial growth, as determined under laboratory conditions.
- AUIC. This variation of AUC represents the area under the inhibitory curve or the total amount of drug during the time interval in which antibiotic levels remained above the MIC.
- T>MIC. The amount of time during a period (eg, 24 hours) in which antibiotic levels remain above the microbial MIC (Figure 1).

Because the measurement of achieved antibiotic levels is meaningless without a comparison to the MICs of targeted microbes that infect the eye, the parameters of C_{max}, AUC, and AUIC are compared to the MICs of interest by looking at their ratios (eg, C_{max}/MIC, AUC/MIC, AUIC/MIC, etc.). These ratios are represented by numbers or fractions. For example, if the C_{max} is 10 times higher than the microbial MIC (eg, 10 µg/mL and 1 µg/mL, respectively), the ratio C_{max}/MIC is 10. Similarly, if the AUC is 100 (units as in Figure 2) and the MIC is 1 (µg/mL), the AUC/MIC ratio is 100.

These, or any, ratios obviously depend greatly on that fraction’s denominator. That is, if the organism considered has an MIC of 0.1 µg/mL as opposed to 1 µg/mL, then the ratios will be 10 times higher (not 10 and 100 but 100 and 1,000, respectively). Therefore, it is important to carefully determine if the bacterial MICs chosen in a report are reflective of typical ocular isolates or are artificially low, thereby creating an inflated ratio.

**WHAT DO THESE RATIOS MEAN CLINICALLY?**

Pharmacokinetics is the simple mathematical measurement or modeling of drug levels within the body, whereas pharmacodynamics is the study of the impact of these drug levels on the microorganism. Do they affect the microbe in vitro, are they bacteriostatic or bactericidal, or is there clinical improvement in vivo? These ratios have been tested in in vitro and in vivo models in an attempt to determine which ratios are most closely associated with bacterial eradication and/or clinical cures.

**PHARMACOKINETIC/PHARMACODYNAMIC RATIOS FOR FLUOROQUINOLONES**

Broadly speaking, C_{max}/MIC ratios of 10 or more and AUC/MIC ratios of nearly 50 to 100 have been identified as desirable goals during fluoroquinolone therapy.¹² There is considerable variation in these ratios according to the bacterial strain in question, and as mentioned previously, any change in the denominator of the fraction can profoundly affect the resulting number (ratio). The modern fluoroquinolones commonly used in ophthalmic drops are associated with lower MICs for the common gram-positive (vs gram-negative) bacteria. Therefore, lower ratios may suffice for certain gram-positive species.

When it comes to the eye, however, a number of specific considerations must be emphasized to distinguish from...
assumptions drawn from the general literature. The ophthalmic versus systemic treatment of infections differs in many ways. For example, the immune system in compartments of the eye differs from the systemic circulation and other infection sites. Moreover, some drug doses (eg, intravenous/intravitreal injections) are often not repeatable intermittently, as are oral or parenteral doses. In addition, T1/2 is an important variable when the rapid drainage of tears, or turnover time of the aqueous humor, determines the majority of drug loss. Drug levels in adjacent compartments of the eye will also vary dramatically after a single dose, because levels in tears are much higher (but short-lived) than in the adjacent conjunctiva, cornea, or aqueous humor.

Lastly, the MICs of strains of ocular bacteria may differ from others reported in the literature. Therefore, data reflecting recently reported MICs of ocular isolates, preferably from surveillance studies, will better reflect what is needed to treat or prevent ocular infections. These data also serve to reflect current trends in the bacterial resistance of ocular strains.

**WHAT ARE THE TARGETED PHARMACOKINETIC/PHARMACODYNAMIC PARAMETERS FOR TOPICALLY APPLIED FLUOROQUINOLONES?**

Because of the many variables discussed, each compartment of the eye and each organism targeted should be analyzed separately. Compared with the management of systemic infections, few guidelines exist for the treatment or prevention of ocular infections. Frequent tissue sampling or dosing is often impossible for the most challenging ocular infections, making definitive pharmacokinetic/pharmacodynamic guidelines difficult to establish.

Eye care specialists can, however, be aware of guidelines set forth in the general literature from other infectious disease specialties and may couple these with unique considerations for the eye. Although the levels of fluoroquinolones in tears are extremely high initially, they are quickly reduced. Therefore, the Cmax/MIC may be adequately high, but the AUC/MIC may not be. If bacterial eradication in the aqueous humor is the goal for topically applied drops, then both Cmax/MIC and AUC/MIC are likely to be inadequate—except for the most sensitive organisms—because topical drops have poor penetration into the aqueous humor.3,5

It is interesting to compare the AUCs of fluoroquinolones in the aqueous humor after the application of multiple topical drops with the AUCs of similar drugs for the treatment of, for example, pulmonary infections (where fluoroquinolones are also widely used). Figure 2 compares such AUCs obtained in pulmonary tissue versus aqueous humor.3,5 It is clear that, with systemic administration, the behavior of fluoroquinolones in nonocular tissues may differ dramatically from the ocular circumstance. This underscores the need to better understand and investigate specific pharmacokinetic/pharmacodynamic parameters that will translate into clinically useful antibiotic regimens for the treatment or prevention of infections in the eye.

Whereas gram-positive microorganisms account for the majority of postoperative ocular infections and are more prevalent on the ocular surface, gram-negative microorganisms can be sight threatening and difficult to treat. When topical drops are the mode of the drug’s delivery, there is almost 100% interpatient variability in the amount of drug delivered/retained on the ocular surface. This high variability will also carry forward to any calculated Cmax/MIC or AUC/MIC ratios expected in the eye for an individual patient.

**CONCLUSION**

Topical antibiotic drops are used for various purposes. The treatment of conjunctivitis involves different considerations than the treatment or prevention of more serious infections such as corneal ulcers or endophthalmitis prophylaxis. Pharmacokinetic and pharmacodynamic parameters may vary widely with compartments of the eye and the specific microbial strain in question. It is best to tailor antibiotic regimens to the intended goals. Mathematical analyses of pharmacokinetic/pharmacodynamic parameters published in the general literature do, however, offer valuable guidelines. These parameters support the use of the most potent antibiotic that is present over the longest period of time, while maintaining safety, to achieve the pharmacokinetic/pharmacodynamic parameters that are currently associated with successful fluoroquinolone use.

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