

An Imperfect Science: Antibiotic Tissue Penetration

Will this fluoroquinolone reach the site of infection?

Anna Seto, Pharm.D.

Most infections do not occur in the plasma, but rather in extravascular tissues. Depending on the site of infection, it can be unwise to choose antibiotic therapy solely on the basis of *in vitro* laboratory sensitivity reports.¹ Furthermore, knowledge of plasma concentrations is not a reliable method for assessing appropriateness of therapy if the antibiotic does not achieve sufficient concentrations within target tissues. In fact, suboptimal antibiotic concentrations within the infected tissue site may lead to the emergence of resistant subpopulations of pathogens.² Thus, the capacity of an antibiotic to reach target tissues must be evaluated to assure the best possible treatment outcome for patients.

Due to the enormous volume of published literature and the inconsistent methods used to study antibiotic tissue penetration, consolidation and comparison of experimental results are difficult. Rather than a comprehensive review of the tissue-penetration characteristics of all antibiotics, this article explores the pharmacokinetic (PK) principles predictive of tissue penetration, with the intent of allowing clinicians to apply this knowledge for rational selection of an antibiotic and an appropriate dosing regimen to enhance bacterial killing and reduce resistance. In addition, this article will review tissue-concentration measurement methodologies and compare the tissue-penetration characteristics of UW Medicine Drug Formulary fluoroquinolones (FQs): ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin (ophthalmic), and gatifloxacin (ophthalmic).

Tissues are not homogenous compartments.³ As alluded to above, the pattern of drug distribution is determined by specific PK parameters that must be considered in order to calculate a dose of antibiotic appropriate to achieve the desired tissue concentration. Volume of distribution (Vd) is the key pharmacokinetic property related to the extent of drug distribution since the drug traverses and equilibrates through the body prior to elimination. Vd is a drug property driven by physiochemical interactions between various body compartments and the drug molecule. Physiological characteristics that influence drug distribution are determined by blood volume, tissue and organ volumes, and protein binding within intravascular and extravascular tissues.⁴ Vd is also dependent on the relative solubility of the drug in adipose tissue versus body water. Physiologic and drug variables that can ease tissue distribution are inflamed tissues, well-vascularized tissues, active transport mechanisms (i.e., excretion of drug molecule by the kidney), and neutral or non-ionized drug molecules. Similarly, variables that obstruct distribution to tissues are presence of necrotic tissue or anatomic barriers (i.e., blood-brain barrier) and increased drug protein binding affinity.^{1,3} The ability of a compound to diffuse across membranes and concentrate in tissues is determined by the interchange and balance between these variables.

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A University of Washington Drug Information Center publication
Distributed monthly by authority of the Pharmacy and Therapeutics Committee
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
Department of Pharmacy Services / School of Pharmacy

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Concentration-dependent killing

A pharmacodynamic parameter describing the rate and extent of bactericidal activity as a function of antibiotic concentration, where higher levels of antibiotic produce a better effect.

FQs exhibit concentration-dependent killing.

Only free, nonprotein-bound antibiotic molecules are able to distribute through body tissues and only free antibiotic concentrations at target sites are available for antibacterial activity.³ While the desirability of measuring unbound interstitial antibiotic tissue concentrations seems straightforward, there is disagreement regarding the most appropriate method to use for any particular tissue type. Antibiotic concentrations measured in tissue homogenates, blister fluid, and saliva are used as surrogates for measuring concentrations directly in tissues, skin, and interstitial fluid, respectively (see Table I). Limitations of these methods likely contribute to reported inter-study measurement differences. Recent advances in experimental tissue-sampling techniques such as the ability to extract tissue from the actual site of infection have increased the pool of penetration data and the increased availability of chromatographic methods to measure free antibiotic levels is improving the reliability of newer tissue-concentration data. Local free antibiotic concentration measurements are better representations of tissue distribution compared to measurements obtained from tissue homogenates, blister fluid, and saliva.³

Table I: Tissue concentration methods³

Methods	Limits
Tissue homogenate	Tissue homogenate antibiotic concentration overestimates actual tissue levels due to contamination of the sample with capillary blood, which may contain both "free" (nonprotein-bound) and protein-bound drug. To be accurate, tissue homogenate drug levels should be corrected for blood contamination.
Blister fluid	Blister fluid antibiotic concentration reflects free drug and is a surrogate marker for skin concentration. Blisters are induced by suction and fluid composition is dependent on blister site and suction pressure. Thus, blister fluid is not an absolute representation of skin concentration.
Saliva	Saliva antibiotic concentration reflects "free" drug and is a surrogate marker for interstitial fluid concentration. However, the acidity of saliva can result in measurements that are different from the comparator tissue.

Zwitterion

A chemical compound that is electrically neutral but carries formal positive and negative charges on different atoms.

FQs are zwitterions.

Fluoroquinolones (FQs) are a class of antibiotics that demonstrate concentration-dependent bactericidal activity (see sidebar) mediated by the inhibition of bacterial DNA gyrase or topoisomerase IV. FQs are amphoteric zwitterions (see sidebar) with a pKa of 5.5-6.3 for the carboxylate functional group and a pKa of 7.6-9.3 for the amino functional group.⁵ This unique amphoteric property theoretically renders FQs ideal agents to traverse membranes and penetrate tissues while maintaining water solubility in both acidic and basic environments.⁶ While FQs share structural similarities, it is a common misconception that all agents within an antibiotic class display comparable PK characteristics (see Table III). However, as demonstrated in Table II, even slight variations in Vd and a drug's propensity for protein binding may translate into significant tissue concentration differences.

Amphoteric

Ampholytes are molecules that contain both acidic and basic groups, and are therefore said to be amphoteric. Amphoteric substances exist as zwitterions at a certain pH and can act as buffers by accepting or donating hydrogen ions in the presence of acids or bases, respectively.

FQs are amphoteric.

Table II (see insert) summarizes the results of FQ penetration studies into fourteen distinct tissue sites. For each site, peak antibiotic tissue concentrations were compared with corresponding plasma concentrations to elucidate the degree of penetration. In general, the formulary FQs show tissue concentrations that were comparable or greater than plasma levels in prostate and lung tissues, pulmonary epithelial lining fluid (ELF), alveolar macrophages (AM), bronchial mucosa (BM), sinus mucosa, and synovial fluid. Ciprofloxacin has been more extensively studied than others and is associated with data that demonstrate good penetration into thoracic abscesses, gynecologic tissues, and heart tissues. FQ penetration into bones, cerebrospinal fluid (CSF), vitreous and aqueous humor (ophthalmic preparations), ascitic fluid, peritoneal fluid and tissues, and prostatic fluid is generally poor while penetration into skin and soft-tissue structures and the urinary tract depends on the specific FQ. As a general rule, all antibiotics attain higher concentrations in inflamed compared to non-inflamed tissues. Human data were not available for some FQs and standard deviations were generally wide when the data were included. Penetration data derived from single-dose studies do not reflect concentrations that can be achieved clinically at steady state and some studies employed dosing regimens different from those routinely used in clinical practice. Lastly, studies that reported tissue concentrations in $\mu\text{g/g}$ cannot be readily compared to microbial MICs.

**Table III:
Selected Pharmacokinetic
Characteristics of Systemic
Fluoroquinolones**

	Vd (L/kg)	Protein Binding (%)
Ciprofloxacin	1.2-2.7	20-40
Levofloxacin	1.25	24-38
Moxifloxacin	1.7-3.5	30-50

Reminder

Only free, nonprotein-bound antibiotic molecules are available for antibacterial activity.

While most published studies report peak concentrations, some pharmacokinetics experts argue that tissue concentrations for antibiotics exhibiting concentration-dependent killing are best calculated as the ratio between 24-hour area-under-the-curve (AUC_{24}) and minimum inhibitory concentration (i.e., $AUC_{24}:MIC$).

Antibiotic tissue concentrations do not consistently correlate with the ability of an antibiotic to cure an infection. Likewise, low tissue concentrations do not automatically preclude the use of that antibiotic for a particular infection type.

Note: The editor and author gratefully acknowledge the assistance of Doug Black, Pharm.D. & Jeannie Chan, Pharm.D., M.P.H. in reviewing this article.

According to Cunha et al., antibiotic tissue concentrations do not consistently correlate with the ability of an antibiotic to cure an infection.⁷ Achieving levels several fold above the MIC_{90} (typically four or more times are recommended)^{8,9} within the infected tissue does not always translate to clinical response. In spite of adequate tissue concentrations, the antimicrobial activity of certain antibiotics can be thwarted by the presence of factors such as exudate pH, local hypoxemia, and white-cell debris.⁷ Likewise, low tissue penetration does not automatically preclude the use of an antibiotic for a specific infection type (i.e., FQs are the agents of choice in prostatitis). Thus, clinicians should avoid making decisions based wholly on antibiotic sensitivity and favorable target tissue penetration data. Rather, additional literature should be reviewed to examine whether cases of clinical cure have been found for indications lacking FDA approval and an infectious disease specialist should be consulted if uncertainty regarding the most appropriate treatment options persists.

When faced with unusual infections, clinicians should develop a mental checklist to guide antibiotic choices. Local susceptibility patterns must be considered in conjunction with tissue-penetration characteristics of the antibiotic of choice. Will the antibiotic reach the site of infection? If so, what was the approximate antibiotic level achieved? Are tissue sample concentration measurements representative of concentrations necessary at the site of infection? Was the dosing and sampling times used in the penetration study rational? Have studies shown clinical cure using this antibiotic? Were patient characteristics in the study population similar to my patient? Lastly, are contraindications to the use of this antibiotic present?

As an example, an elderly patient with *P. aeruginosa* meningitis requires therapy. The culture and sensitivity report indicates that the strain is resistant to β -lactams, carbapenems, and monobactams but remains sensitive to aminoglycosides and to ciprofloxacin at an MIC $0.5\mu\text{g}/\text{mL}$. Monotherapy with aminoglycosides alone is known to increase the risk of resistance development¹⁰⁻¹² and regrettably, ciprofloxacin is not approved for the treatment of central nervous system infections and may have adverse CNS effects.¹³ Drawing ciprofloxacin levels, whether in the plasma or in tissue samples, is not routinely practiced, so we must refer to tissue-penetration data published in the literature. The study by Wolff et al. found a mean peak CSF concentration of $0.56 \pm 0.39\mu\text{g}/\text{mL}$ at steady state using a regimen of ciprofloxacin 200mg IV every 12 hours.¹⁴ Case reports have shown that high-dose intravenous ciprofloxacin has garnered treatment success in *P. aeruginosa* meningitis after first-line treatment options have failed.¹⁵⁻¹⁷ Thus, by a preponderance of evidence, ciprofloxacin in combination with an aminoglycoside may be an option for this life-threatening infection as long as higher doses are used and the patient is carefully monitored for evidence of improvement and for CNS-related adverse events.

Therapeutic success in the treatment of infections is contingent on the selection of an antibiotic that appropriately covers the suspected pathogenic organism and with correct dosing has the ability to concentrate adequately at the site of infection. Vd, a key determinant of antibiotic tissue distribution patterns, is dictated by interactions between physiological characteristics of the target tissue and the chemical properties of the drug molecule. Data on tissue penetration have grown enormously with improvements in sampling methodologies and availability of more reliable concentration measurement tools. FQ tissue-concentration data was extracted from published literature to garner better understanding of penetration patterns for select tissues. However, as mentioned previously, administering antibiotics at doses in hopes of exceeding the MIC of the infecting pathogen is not always associated with response and can increase the potential for patient harm. Published literature should always be reviewed to learn whether clinical cure has been reported and if favorable outcomes data are lacking, infectious disease specialists should be consulted.

References available on request.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Exenatide (Byetta [®])	Injection: 5mcg/dose (1.2mL); 10mcg/dose (2.4mL)	Incretin mimetic	Diabetes	5mcg SQ BID 1h prior to AM/PM meals
	Added to formulary restricted to patients approved by a UWMC Diabetes Care Center or by the HMC Glycemic Control Team.			
Posaconazole (Noxafil [®])	Suspension: 40mg/mL (105mL)	Imidazole antifungal	Serious fungal infections	Indication specific
	Added to formulary limited to use for the treatment of <i>Zygomycetes spp.</i> , as salvage therapy for <i>Aspergillus spp.</i> in patients not responding/tolerating voriconazole, or for secondary prophylaxis against aspergillus and other susceptible molds as an alternative to voriconazole.			
Pramlintide (Symlin [®])	Injection: 0.6mg/mL (5mL)	Amylin analog	Diabetes	15mcg sq prior to meals
	Added to formulary restricted to patients approved by a UWMC Diabetes Care Center or by the HMC Glycemic Control Team.			
Testosterone (Testim [®])	Gel: 1% (5g)	Androgen	Replacement therapy	Topical, 5g daily
Formulary Deletions	Form(s) & Strength(s)	Classification	Comment	
Caspofungin (Candidas [®])	All strengths and forms	Antifungal	Replaced by micafungin (Mycamine [®])	
Testosterone (Androgel [®])	All strengths	Androgen	Replaced by Testim [®] brand testosterone gel	
Other Actions				
Digoxin Immune Fab	DigFab [®] and Digibind [®] were deemed therapeutically equivalent. Pharmacy will dispense whichever product offers the best cost advantage at the time of purchase.			
Disposable Insulin Pens	The Novolog FlexPens [®] , Novolog 70/30 Premix FlexPens [®] , and Innolet [®] (NPH,70/30, and Regular) will replace the current Lilly disposable insulin pen devices stocked by pharmacy due to patient and provider preference.			
Entecavir (Baraclude [®])	The restriction on the use of entecavir (as a 2nd-line therapy for chronic hepatitis B) was removed.			

[‡] Contact pharmacy for information on drug costs.

* Refer to product labeling for full prescribing information.

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 Box 354735
 Seattle, WA 98195-4735

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