Review Article

Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing

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ABSTRACT

Purpose: An understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) principles that determine response to antimicrobial therapy can provide the clinician with better-informed dosing regimens. Factors influential on antibiotic disposition and clinical outcome are presented, with a focus on the primary site of infection. Techniques to better understand antibiotic PK and optimize PD are acknowledged.

Methods: PubMed (inception–April 2016) was reviewed for relevant publications assessing antimicrobial exposures within different anatomic locations and clinical outcomes for various infection sites.

Findings: A limited literature base indicates variable penetration of antibiotics to different target sites of infection, with drug solubility and extent of protein binding providing significant PK influences in addition to the major clearing pathway of the agent. PD indices derived from *in vitro* studies and animal models determine the optimal magnitude and frequency of dosing regimens for patients. PK/PD modeling and simulation has been shown an efficient means of assessing these PD endpoints against a variety of PK determinants, clarifying the unique effects of infection site and patient characteristics to inform the adequacy of a given antibiotic regimen.

Implications: Appreciation of the PK properties of an antibiotic and its PD measure of efficacy can maximize the utility of these life-saving drugs. Unfortunately, clinical data remain limited for a number of infection site–antibiotic exposure relationships. Modeling and simulation can bridge preclinical and patient data for the prescription of optimal antibiotic dosing regimens, consistent with the tenets of personalized medicine. (*Clin Ther.* 2016;38:1930–1947) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: antibiotic, dosing, exposure, pharmacodynamics, pharmacokinetics.

INTRODUCTION

Antibiotics are a key component of modern medicine, utilized in over half of all US hospitalizations, with >250 million additional treatment courses provided in the outpatient setting per year.[1,2] Along with other classes of anti-infectives, they represent a uniqueness in pharmacotherapy, where one patient's prescription can have a direct effect on others', as antimicrobial utilization remains the primary driver of organism resistance.[3,4] Despite antibiotic resistance having long been declared a major threat to global public health,[3,5,6] the landscape of antimicrobial development has remained arid: no agents with novel mechanisms of action against resistant Gram-negative organisms are currently in late-stage clinical trials.[7–9] It is abundantly clear that optimization of antibiotic prescribing is necessary to preserve our current armamentarium. Although stewardship practices focusing on the restriction of use and shortening of treatment duration are well-cited,[10,11] further research on

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antibiotic pharmacokinetic (PK) and pharmacodynamic (PD) properties that maximize the probability of a successful outcome is needed.

The present review serves to provide the clinician with the principal PK/PD considerations for the most common antibiotics encountered in US hospital settings (β-lactams, vancomycin, fluoroquinolones, and aminoglycosides). The information contained herein can assist in producing dosing regimens that maximize clinical benefit while minimizing the risk of toxicity. While such concepts remain salient to antifungal and antiviral agents, these drugs are beyond the scope of this review. Particular emphasis is placed on the site of infection when applying these concepts to patient care. This review is by no means exhaustive, and the interested reader is encouraged to access the provided references and available textbooks[12,13] for a more in-depth discussion of antimicrobial PK/PD. Instead, the goal is to discuss the key principles related to rational selection of an antibiotic dosing regimen, which remain applicable to agents not discussed here in addition to new agents as they enter clinical practice.

MATERIALS AND METHODS

PubMed (inception–April 2016) was searched for relevant publications using combinations of the search terms "antibiotic," "penicillin," "cephalosporin," "carbapenem," "vancomycin," "fluoroquinolone," "aminoglycoside," "penetration," "blood," "bloodstream," "lung," "epithelial lining fluid," "soft tissue," "interstitial fluid," "bone," "central nervous system," "cerebrospinal fluid," "pharmacodynamic," and "outcome." Reference lists of identified publications were also reviewed for relevant articles.

ANTIMICROBIAL PHARMACOKINETICS

General Considerations

The kinetics of a drug refer to its rate of change as it traverses through a biological system, and is governed by the four essential processes of absorption, distribution, metabolism, and excretion. While antibiotic PK is often considered in terms of the body's effect on the drug, the agent's physicochemical properties must also be considered to predict its disposition. Chief among them is the relative solubility of the antimicrobial, which can have a significant impact on its volume of distribution (V_d) and thus may prove key in selecting agents expected to attain adequate penetration to the site of infection.[14,15] Also influential is the extent of protein binding the antibiotic exhibits, as only free, unbound drug is capable of exerting antimicrobial effects.[16–19] As albumin is the primary plasma-binding protein for the majority of antibiotics, its concentrations should be considered when implementing and adjusting dosing regimens, with highly protein bound agents being most affected.[14,20–22] Finally, the agent's major route of elimination warrants appreciation, particularly in times of changing clinical condition where development of end-organ dysfunction or critical illness can greatly enhance (renal failure)[23,24] or reduce (augmented renal clearance) antibiotic exposures.[25–27] Table I summarizes these properties for the most commonly used parenteral antibiotics in the US hospital setting.

Site-Specific Considerations

With these PK properties in mind, it becomes clear that the primary infection site is a crucial variable in considering whether sufficient antibiotic exposures are likely to be attained for a given agent

Table I. Representative pharmacokinetic properties of commonly administered antibiotics.

Antibiotic	Solubility	Plasma Protein Binding	Clearance
β-Lactams*	Hydrophilic	Low to moderate	Renal
Vancomycin	Hydrophilic	Moderate	Renal
Fluoroquinolones†	Lipophilic	Low to moderate	Renal
Aminoglycosides	Hydrophilic	Low	Renal

*Exceptions: cefazolin (highly protein bound), ceftriaxone (highly protein bound), ertapenem (highly protein bound), nafcillin/oxacillin (highly protein bound, hepatically cleared).
†Exception: moxifloxacin (hepatically cleared).