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Review

Dose optimisation of antibiotics in children: application of pharmacokinetics/pharmacodynamics in paediatrics

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ABSTRACT

The judicious use of antibiotics to combat infections in children relies upon appropriate selection of an agent, dose and duration to maximise efficacy and to minimise toxicity. Critical to dose optimisation is an understanding of the pharmacokinetics and pharmacodynamics of available drugs. Optimal dosing strategies may take advantage of pharmacokinetic/pharmacodynamic (PK/PD) principles so that antibiotic dosing can be individualised to assure effective bacterial killing in patients who have altered pharmacokinetics or who have infections with less susceptible or resistant organisms. This review will outline the fundamentals of antimicrobial pharmacokinetics/pharmacodynamics through discussion of antibacterial agents most often used in children. We aim to highlight the importance of dose optimisation in paediatrics and describe non-conventional dosing strategies that can take advantage of PK/PD principles at the bedside.

1. Introduction

Antibiotics are among the most commonly administered medications in children. In ambulatory settings in the USA, antibiotics are prescribed during as many as one in five paediatric visits [1]. Cross-sectional point prevalence studies have shown that more than 35% and 40% of hospitalised children are receiving antimicrobials at any given time in European and non-European countries, respectively [2].

Whilst the judicious use of antibiotics is clearly needed in all paediatric settings, appropriate drug selection and dose optimisation are also important to improve the management of bacterial infections. An understanding of pharmacokinetic/pharmacodynamic (PK/PD) principles may allow for the selection of the best drug to treat a specific bacterial pathogen whilst utilising the ideal dosing regimen to eradicate the infection, limit toxicity and reduce development of bacterial resistance.

As Dr Abraham Jacobi formally acknowledged more than 100 years ago, children are not little adults. Responses to medications differ depending on organ function, size and maturation of the child [3]. Age-related differences in absorption, distribution, metabolism and elimination of drugs preclude the use of a one-dose-fits-all approach for prescribing medications in children [4]. In addition, there are special populations within paediatrics—individuals with critical illness, cystic fibrosis, morbid obesity, immune compromise, and others—for whom 'standard' age-based dosing regimens may be inadequate. These groups often demand optimal antibiotic exposure to assure eradication of infection and limit the development of resistant pathogens. Therefore, it is crucial to understand and apply PK/PD principles when using antimicrobials and to appreciate how dosing regimens can be individualised to optimise therapy in these vulnerable patients. The goal of this review is to provide a general overview of PK/PD principles and to discuss how strategies can be employed in clinical practice to optimise antibiotic therapy in paediatric patients. Particular attention will be given to special populations to highlight the importance of dose optimisation.

2. Pharmacokinetics/pharmacodynamics of antibiotics

Pharmacokinetics refers to the drug concentration in serum, tissues and other body fluids over time and is dependent on the absorption, metabolism, distribution and elimination of the drug.

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Table 1
Pattern of activity of different antibacterial drugs and their associated pharmacokinetic/pharmacodynamic (PK/PD) targets.[a]

Mechanism of bactericidal effects based on in vitro data	Antibiotic class	PK/PD parameter(s) associated with efficacy	Goal of dosing regimen
Concentration-dependent killing with moderate-to-persistent bactericidal effects	Aminoglycosides Fluoroquinolones Metronidazole Daptomycin Ketolides	C_{max}/MIC $AUC_{0–24}$/MIC	**Maximise concentration**: increase dose
Time-dependent killing with minimal-to-no persistent bactericidal effects	β-Lactams: Penicillins Cephalosporins Carbapenems Aztreonam Erythromycin	$T_{>MIC}$	**Maximise the duration of exposure**: increase duration of infusion or frequency of administration
Time-dependent killing with moderate-to-prolonged persistent bactericidal effects	Macrolides Tetracyclines Glycopeptides Clindamycin Linezolid[b]	$AUC_{0–24}$/MIC	**Maximise drug exposure**: increase dose, frequency of administration or duration of infusion

C_{max}, maximum serum concentration; MIC, minimum inhibitory concentration; $AUC_{0–24}$, area under the concentration–time curve over a 24-h period; $T_{>MIC}$, percentage of the dosing interval above the MIC.

[a] Adapted with permission from Taylor and Francis Group LLC Books [10].

[b] $T_{>MIC}$ has also been reported to be an appropriate PK/PD target for linezolid [9].

Pharmacodynamics denotes the pharmacological effects of the drug for a given exposure. Whilst pharmacokinetics is dependent on patient factors, antimicrobial pharmacodynamics also involves the pathogen. The susceptibility of a bacterium to antibiotic killing can vary widely based on the particular organism and the agent of interest. Traditionally, an in vitro measure of the minimum concentration of drug needed to inhibit bacterial growth, called the minimum inhibitory concentration (MIC), is the PD parameter most frequently utilised clinically to describe antibiotic activity against a pathogen. Knowledge of the MIC alone cannot predict antibiotic success because the MIC does not account for the dynamic in vivo processes that influence antibacterial killing over time. Integration of pharmacokinetics (exposure) and pharmacodynamics (antimicrobial activity) at the site of infection predicts the agent's efficacy against any given pathogen.

Antimicrobial effects are generally described as being either concentration-dependent or time-dependent [5,6]. Concentration-dependent drugs maximally kill bacteria with increasing concentrations, whereas the effect of increasing concentrations of time-dependent drugs plateaus; the latter are most effective when exposure is prolonged. Some drugs also have persistent or post-antibiotic effects (PAEs), referring to the continued suppression of bacterial growth following the removal of drug after exposure, varying based upon the mechanism of drug action, the pathogen and how the drug is administered [7,8]. Thus, based on optimal bactericidal conditions, antibiotics can be divided into three categories (Table 1): concentration-dependent killing with moderate-to-persistent PAEs; time-dependent killing with minimal-to-no persistent bactericidal effects; and time-dependent killing with prolonged persistent effects [10]. The PK/PD indices correlating with clinical efficacy differ depending on the mechanism of antimicrobial activity. Understanding which category best describes an antibiotic's mechanism allows for rational dose adjustments to maximise activity.

Historically, PK/PD relationships have been determined from in vitro or animal infection models [11] and confirmed in trials of adult patients [10]. Studies corroborating PK/PD endpoints in paediatric populations are often lacking. Nevertheless, the mechanism of action and PK/PD parameters that correlate with efficacy for the treatment of specific infections in adults should theoretically be similar for children. There are three primary PK/PD parameters that are most often described as the clinical targets for antibiotic exposure because they have been shown to correlate with clinical efficacy for different antibiotic classes (Fig. 1): the maximum serum concentration (C_{max}) to MIC ratio (C_{max}/MIC) for concentration-dependent drugs; the percentage of the dosing interval above the MIC ($T_{>MIC}$) for time-dependent drugs with minimal-to-no persistent effects; and the ratio of the area under the concentration–time curve over a 24-h period ($AUC_{0–24}$) to MIC ratio ($AUC_{0–24}$/MIC) for time-dependent drugs with moderate-to-prolonged persistent effects. It is important to note that drug molecules bound to plasma proteins are not free to act upon bacteria, thus PD parameters often relate to the free fraction of drug in serum [12]. In the next sections, we will discuss each of the categories of antimicrobial effects in more detail, using specific examples to demonstrate how PK/PD information can influence dose optimisation in paediatric clinical practice.

Before proceeding, two important points should be conveyed. First, PK/PD parameters are highly inter-related: dose adjustments influence multiple PK/PD parameters simultaneously. For instance, a higher dose will increase the C_{max} and $AUC_{0–24}$ in relation to

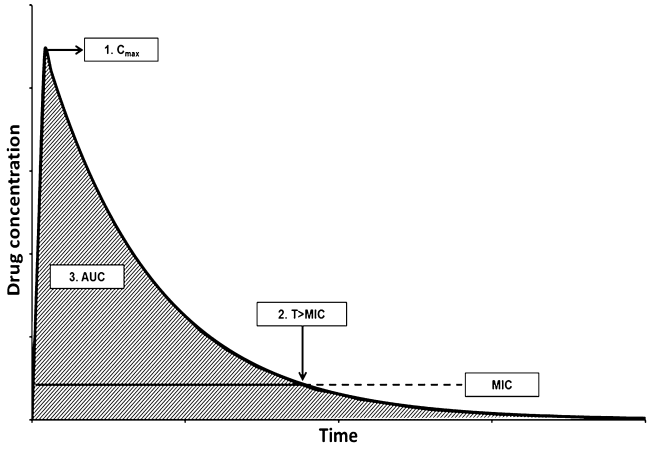

Fig. 1. Pharmacokinetic/pharmacodynamic (PK/PD) relationships between antibiotic concentrations relative to the minimum inhibitory concentration (MIC) over time. Three principal PK/PD parameters most often correlate with the clinical efficacy of different antibiotic classes: (1) maximum concentration (C_{max})/MIC ratio for concentration-dependent drugs; (2) percentage of the dosing interval above the MIC ($T_{>MIC}$) for time-dependent drugs with minimal-to-no persistent effects; and (3) area under the concentration–time curve (AUC, shaded area)/MIC ratio for time-dependent drugs with moderate-to-prolonged persistent effects.