Therapeutic Drug Monitoring for Anti-infective Agents in Pediatrics

The Way Forward

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OPTIMAL ANTI-INFECTIVE DRUG DOSES FOR CHILDREN

Anti-infective agents are among the most commonly prescribed drugs in children. What is considered the optimal dose of an anti-infective agent is determined by how the child handles the drug and the resulting drug concentration in the body (pharmacokinetics, PK) as well as by the effect of the drug on the target pathogen (pharmacodynamics, PD). Among pediatric patients, considerable PK differences exist, including age-related variation in drug absorption, distribution, protein binding, metabolism and elimination. For many anti-infective agents, there is therefore no direct evidence for pediatric dosing recommendations and, as a consequence, adult-based dose recommendations are modified based on body weight or surface area. This may be an oversimplified approach, as it fails to account for many key maturational and developmental changes that influence drug concentrations and ultimately efficacy of treatment (Fig. 1). In addition, there are a number of specific patient groups, including individuals with cystic fibrosis, critical illness, obesity and immunocompromise, as well as preterm and term neonates for whom PK and PD properties are even more complex.

OPTIMAL ANTI-INFECTIVE DRUG DOSE TO KILL THE PATHOBEN

For many infections, an accurate dosing might not always be critical, either because of a broad therapeutic range of the chosen drug and the resulting minimal risk of toxicity or because the pathogen is highly sensitive to low drug concentrations. The latter relates to anti-infective PD, which describes the relationship of the dose observed in the body and the ability to kill and/or inhibit the growth of the pathogen. To define this relationship, the minimal inhibitory concentration (MIC) of a particular pathogen is the key factor which is used to define PK/PD targets for anti-infective agents. Traditionally, the majority of anti-infective agents can be classified into 2 broad groups depending on their PK/PD properties: time-dependent anti-infective agents (efficacy dependent on the time or the area under the curve (AUC) during which the drug concentration is above MIC; T>MIC; and AUC/MIC) or concentration-dependent anti-infective agents (efficacy dependent on the ratio of peak concentration over MIC; C_{peak}/MIC).

WHAT IS THERAPEUTIC DRUG MONITORING?

Decisions on optimal drugs used to treat infections are based on many assumptions, including that a given dose will lead to a certain drug concentration in the body (PK) and that this drug concentration will be sufficient to kill and/or inhibit growth of the pathogen (PD). However, in certain clinical situations such assumptions are inaccurate, and it has been shown that outcome improves when drug concentrations are measured (as opposed to be assumed) as part of therapeutic drug monitoring (TDM). TDM is defined as measuring drug concentrations in serum or plasma with subsequent dose adjustment for the individual patient. TDM can be used to both minimize toxicity and maximize efficacy. Today, routine measurement of drug concentrations for a number of anti-infective agents is available; these include aminoglycosides, antiretroviral drugs, antiviral drugs, triazoles and vancomycin. The challenge of TDM is the accurate interpretation of the measured concentrations, for which a multidisciplinary team is required including specialists in pharmacology, microbiology and pediatric infectious diseases. Decisions on dosing recommendations are based on a careful evaluation of a number or criteria including: dose and interval of administration, time since initiation of treatment, exact time of drug administration, total duration of infusion for intravenous drugs, exact time of TDM blood specimen taken, age, weight or body surface area, renal and hepatic function, expected or confirmed pathogen, resistance profile of the pathogen, including MIC, underlying diseases and concomitant medication and nutrition. Typically, drugs and diseases most suitable for TDM are those where a correlation between drug concentration and efficacy (PK/PD target) and/or toxicity is established. In addition, a number of drugs have unpredictable concentrations as a result of human genetic variation in drug metabolism making TDM essential.

EXAMPLES OF CURRENT USE OF TDM FOR ANTI-INFECTIVES

Aminoglycosides

TDM of aminoglycosides has become standard clinical practice in pediatrics, and traditionally, the prevention of toxicity has been the main reason for use of TDM in this drug class. Many studies evaluating toxicity of aminoglycoside trough concentrations in adults and children, comparing multiple daily doses with extended-interval (eg, once daily) doses, have shown that the latter results in lower trough concentrations with reduced nephrotoxicity in adults. However, this has not been consistently observed in the pediatric population, possibly because children generally exhibit lower aminoglycoside-associated nephrotoxicity. The mechanisms underlying ototoxicity are still controversial. It has been suggested that ototoxicity is mainly related to the cumulative dose of aminoglycosides over time. In addition, it is also related to a genetic predisposition resulting from mutations in mitochondrial DNA, and that in individuals affected a single dose can cause ototoxicity. Several mutations in mitochondrial DNA are linked to increased susceptibility to aminoglycoside-associated ototoxicity, and the prevalence of the most common mutations is estimated to be around 1–2%. These findings challenge the view of routinely monitoring aminoglycoside trough concentrations in pediatrics, and selective-targeted TDM has been advocated in children who have prolonged treatment or are exposed to concomitant nephrotoxic drugs.
TDM of aminoglycosides to optimize effect, including \( C_{\text{max}} \) measurements, is less commonly performed. \( C_{\text{max}} \) is usually determined 30–60 minutes after the end of intravenous administration, and a second concentration is ideally measured before the lower limit of detection is reached. These measurements should be obtained after steady state has been reached, which is commonly considered to be the case after approximately 5 half-lives of the drug have elapsed (see also below). Barriers to the implementation of TDM for efficacy optimization in aminoglycosides are the need for multiple blood samples as well as the lack of information on the optimal \( C_{\text{max}}/\text{MIC} \) ratio. In adults, maximal efficacy seems to be achieved when \( C_{\text{max}}/\text{MIC} \) is 8–10 or \( \text{AUC}/\text{MIC} \) is 75–260.4 In children, however, only indirect evidence is available from a meta-analysis suggesting that once daily dosing, associated with higher \( C_{\text{max}} \) tends to have a better efficacy and improved microbiological eradication rates when compared with multiple daily dosing.5

Vancomycin

Vancomycin is another example of a drug for which monitoring of serum concentrations is recommended by product labels as well as national and institutional guidelines. However, the implementation of these recommendations in pediatrics is challenging. A study in the US showed implementation of vancomycin TDM to be variable, with only 81% of children on vancomycin for more than 3 days having at least 1 serum concentration measured.6 As for aminoglycosides, specific PK/PD targets for vancomycin TDM in pediatrics are missing. In adults, \( \text{AUC}_{24}/\text{MIC} > 400 \) has been suggested as the best predictor for treatment outcome of invasive methicillin-resistant \( \text{Staphylococcus aureus} \) infections. However, calculation of the AUC is not feasible in a routine clinical setting as this requires concentration measurements on multiple samples and the use of prediction equations. Therefore, in 2011, the Infectious Diseases Society of America suggested the use of trough concentrations of 15–20 mg/L as a surrogate for \( \text{AUC}_{24}/\text{MIC} > 400 \), explicitly stating that this recommendation “requires additional study” in children.7 Indeed, several studies comparing predicted or measured \( \text{AUC}_{\text{trough}} \), with trough concentrations in children found a poor correlation and/or that lower trough concentrations corresponded with a \( \text{AUC}_{24}/\text{MIC} > 400 \) in children (reviewed by Neely et al8). In addition, studies investigating efficacy of vancomycin \( \text{AUC}_{\text{trough}}/\text{MIC} > 400 \) in children with different types of infections as well as other pathogens for which vancomycin is used are lacking, as the number of patients with positive cultures included in the currently available studies are limited. This results in the problematic situation in which dose adjustments based on trough concentrations alone may be inaccurate, but evidence to change this practice is currently lacking.

Triazoles

One example of a drug class with unpredictable concentrations is the class of triazole antifungal agents. Itraconazole, posaconazole and voriconazole have variable metabolism as a result of polymorphisms in the specific enzymes of the cytochrome P450 system and also variable oral absorption caused by nutrition.9 This results in considerable interindividual variability in the measured drug concentrations, and therefore, TDM is commonly offered for this class of drugs. Evidence is accumulating on both concentration–efficacy and concentration–toxicity relationships. For example, a voriconazole trough concentration <1 mg/L has been shown to be associated with increased mortality in children,10 whereas concentrations above 5.5 mg/L were associated with increased phototoxicity and neurotoxicity. Recent guidelines therefore suggest routine triazole TDM in the majority of patients with published target concentrations.11

Antiretroviral Agents

Several antiretroviral agents (ARVs) have considerable interindividual variability in drug concentration but only some ARVs have known drug concentrations associated with improved virologic response and/
or reduced toxicity. TDM is generally not indicated for nucleotide reverse transcriptase inhibitors as the serum or plasma concentrations do not reflect intracellular concentrations of the drugs adequately. For non-nucleoside reverse-transcriptase inhibitors and protease inhibitors, several centers provide drug concentration measurements. However, routine TDM of ARVs is not recommended for adults or children, and selective TDM for special situations, including suspected drug interactions and toxicity or adherence, is instead advised.12

**FUTURE APPLICATIONS AND IMPROVEMENT OF TDM IN PAEDIATRIC INFECTIOUS DISEASES**

**β-Lactam Antibiotics in Critically Ill Patients**

β-Lactam antibiotics are the most commonly used group of anti-infective agents in critically ill pediatric patients. Classically, β-lactam TDM is not offered because of the generally wide therapeutic window and relatively predictable drug concentrations. However, in an intensive care setting, considerable PK changes occur resulting in highly variable drug concentrations not only between patients but also within the same patient. Most clinicians are concerned about increased drug concentrations and potential toxicity of anti-infective agents in critically ill patients as a result of renal impairment. Subtherapeutic drug concentrations may equally be a challenge in these patients resulting from extravascular volume expansion and glomerular hyperfiltration. In pediatrics, data on TDM of β-lactam antibiotics in critically ill patients are lacking and data on adults from a recent survey in 9 intensive care units showed significant variations in practice. This also requires target PK/PD from available concentrations. Moreover less-invasive patient samples are being investigated for TDM use. For example, a recent study showed a good correlation of fluconazole concentrations in saliva and serum.17

**Optimization of Blood Sampling**

Drug concentrations are measured using serum or plasma and generally require a volume of 1–2 mL. To minimize the volume of blood required, for example, in the neonatal intensive care setting, and reduce preanalytic sample handling errors, the use of dried blood spots is being explored. Dried blood spots–based levels can be determined for many anti-infective agents, but the current lack of validation compared with serum or plasma concentration precludes introduction into routine clinical practice. Moreover, less-invasive patient samples are being investigated for TDM use. For example, a recent study showed a good correlation of fluconazole concentrations in saliva and serum.17

**CONCLUSION**

TDM in pediatric infectious diseases is currently used in selected patient groups and for certain anti-infective agents only. Better understanding of PK for many anti-infective agents in children has led to improved dosing recommendations. Integration of pathogen data, including MIC, is of critical importance to further improve TDM practice. This also requires target PK/PD ratios to be specifically assessed for pediatric infections. In the future, applications, including software-based early TDM, may be possible and be particularly useful for critically ill children.

**ACKNOWLEDGMENTS**

The authors would like to thank Frederique Rodieux and Aline Fuchs for helpful discussions.

**REFERENCES**