Dosage individualization in children: integration of pharmacometrics in clinical practice

Wei Zhao, Stéphanie Leroux, Evelyne Jacqz-Aigrain
Paris, France

Background: **Children are in a continuous and dynamically changing state of growth and development. A thorough understanding of developmental pharmacokinetics (PK) and pharmacodynamics (PD) is required to optimize drug therapy in children.**

Data sources: **Based on recent publications and the experience of our group, we present an outline on integrating pharmacometrics in pediatric clinical practice to develop evidence-based personalized pharmacotherapy.**

Results: **Antibiotics in septic neonates and immunosuppressants in pediatric transplant recipients are provided as proof-of-concept to demonstrate the utility of pharmacometrics in clinical practice. Dosage individualization based on developmental PK-PD model has potential benefits of improving the efficacy and safety of drug therapy in children.**

Conclusion: **The pharmacometric technique should be better developed and used in clinical practice to personalize drug therapy in children in order to decrease variability of drug exposure and associated risks of overdose or underdose.**

World J Pediatr 2014;10(3):197-203

Author Affiliations: Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, China (Zhao W); Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP, Paris, France (Zhao W, Leroux S, Jacqz-Aigrain E); Clinical Investigation Center CIC1426, INSERM, Paris, France (Zhao W, Jacqz-Aigrain E); EA7323, Université Paris Diderot-Université Paris Descartes, Paris, France (Zhao W, Leroux S, Jacqz-Aigrain E); Division of Neonatology, Department of Child and Adolescent Medicine, CHU de Rennes, Rennes, France (Leroux S)

Corresponding Author: Wei Zhao, Pharm D, PhD, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, China; Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, 48 Boulevard Sérurier, 75935 Paris Cedex 19, France (Tel: 0033 140033656; Fax: 0033 140035779; Email: wei.zhao@rdb.aphp.fr)

doi: 10.1007/s12519-014-0493-x

Key words: **developmental pharmacokinetics; developmental pharmacology; pediatric pharmacology; personalized therapy; pharmacometrics; quantitative pharmacology**

Review article

Introduction

Children are in a continuous and dynamically changing state of growth and development. Marked differences in the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of many drugs are reported between children and adults due to the developmental changes in physiological parameters during childhood.[1,2] Yet, the favorable balance between efficacy and adverse events of drugs has often been demonstrated in adults only; as a result, there is not sufficient information about safety and efficacy of drugs in children. The lack of pediatric clinical trial data directly results in the variation and uncertainty of drug therapy in pediatric clinical practice. The pediatric dosage regimen is often empirically extrapolated from adults on basis of weight. Clearly, this empirical use of drug in children increases the risk of either sub-therapeutic or toxic treatments. Off-label drug use becomes a major concern in pediatrics.[3] Many drugs used in pediatric clinical practice lack a validated dosage regimen. Indeed, approximately 70% of drugs prescribed to children, and more than 93% to critically ill neonates, are unlicensed or used in an off-label manner.[4,5]

The urgent need to improve pediatric drug therapy has been recognized by regulators and public health professionals. The introduction of the Pediatric Regulation by the European Union, together with the renewal of the Pediatric Rule by the Food and Drug Administration (FDA) on the requirements for pediatric labeling, has provided an impetus to stimulate pediatric clinical investigations and improve pediatric prescribing information in drug labels.[6] Meanwhile, the major challenges in pediatric drug evaluation related to developmental physiological and pharmacological changes, and ethical and practical constraints have been highlighted.

Pharmacometrics

There has been a growing interest in exploring innovative methodology to optimize drug evaluation and establish evidence-based pharmacotherapy in clinical practice. In this context, pharmacometrics presents a promising and valuable approach.[7,8] Pharmacometrics is the science of quantitative pharmacology. In application to pediatrics, it involves primarily developmental pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation, which can combine information from many diverse sources as drug characteristics, developmental clinical pharmacology, physiological changes during childhood, pediatric disease and statistics.

PK-PD modeling

PK has been defined as "how the body handles the drug" and describes the relationship between drug dosing and the drug concentration-time profile in the body.[9] The drug concentration can be determined in plasma, serum, blood or other biological samples (i.e. cerebrospinal fluid). As shown in equation 1, in a simple case of a one-compartment PK model with first order elimination, the concentrations decline from an initial concentration (C_0) with time *t* by an exponential function.

$$C(t)=C_0\times e^{(-k_e\times t)} \quad \text{(Equation 1)}$$

Where k_e is the elimination constant, which can be estimated based on the concentrations-time data.

PD has been defined as "how the drug affects the body" and describes the relationship between concentration and effects, which can be either efficacy or adverse event.[9] The effect measurement at any given time is determined by a function of its value without drug (E_0) and the drug concentration (C). As shown in equation 2, a sigmoidal E_{max} model.

$$E(t)=E_0+(E_{max}\times C(t)^{Hill})/(EC_{50}{}^{Hill}+C(t)^{Hill}) \quad \text{(Equation 2)}$$

Where E_{max} is the maximum effect, EC_{50} is the drug concentration that results in half of maximum effect, Hill is the Hill or sigmoidicity coefficient.

PK-PD models are typically illustrated by compartments and schematic boxes. As illustrated in Fig. 1, a two-compartment PK model linked to a sigmoidal E_{max} PD model. Population PK-PD models are frequently applied to characterize concentrations and effects over time, and identify the covariates that can explain the variability. Once a PK-PD model has been developed, simulation can be performed to describe, explain, and investigate different scenarios i.e., different dosage regimens, can be investigated and predicted.[10,11]

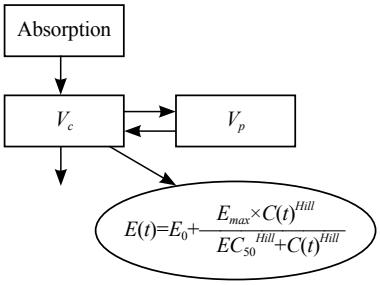

Fig. 1. Two-compartment PK model linked to E_{max} PD model. V_c: central volume of distribution; V_p: peripheral volume of distribution; E_{max}: maximum effect; EC_{50}: drug concentration that results in half of maximum effect; Hill: sigmoidicity coefficient.

Developmental PK modeling

The impact of development on the PK of a given drug is dependent, to a great degree, upon age-related changes in the body composition and the maturation of organs (i.e., renal maturation to determinate renal clearance and ontogeny of drug metabolism and transporter).[12,13] It is important to recognize that changes in physiology that characterize development may not correspond to predefined age groups (neonate, infants, children and adolescents) and are also not linearly related to weight.

The allometric model,[14,15] based on sound biological principles and supported by extensive observations, has been used to extrapolate the PK parameters between species, and has also been proposed for extrapolation between children and adults using the equations 3-4:

$$CL_{child}=CL_{adult}\times(WT_{child}/WT_{adult})^{PWR} \quad \text{(Equation 3)}$$

$$V_{child}=V_{adult}\times(WT_{child}/WT_{adult})^{PWR} \quad \text{(Equation 4)}$$

Where CL is clearance, V is volume of distribution and WT is body weight. The PWR exponents are: 0.75 for clearance and 1 for volume of distribution. It is of practical importance to report PK parameters in terms of a standard weight, allowing direct comparison between different studies and better understanding of developmental changes.[14,16] The allometric predictions are not changed by the choice of the standard weight.

Of note, allometric scaling is insufficient to describe clearance in neonates and infants.[17,18] The maturation and organ function have to be taken into account (equation 5).

$$CL_{neonate}=CL_{adult}\times(WT_{neonate}/WT_{adult})^{PWR}\times MA\times OF \quad \text{(Equation 5)}$$

Where MA is maturation and OF is organ function.

The maturation can be renal maturation or ontogeny of drug metabolizing enzymes or transporter. For example, the Hill model has been used to describe the renal maturation using equation 6.[19]

$$MA=PMA^{Hill}/(PMA_{50}{}^{Hill}+PMA^{Hill}) \quad \text{(Equation 6)}$$

Where PMA is postmenstrual age expressed in weeks, PMA_{50} is the PMA at which renal maturation reaches half its maximal value, which was reported to be 47.7 weeks, and Hill is the sigmoidicity coefficient with an estimated value of 3.4.[19]

Very recently, a neonatal amikacin maturation model has been reported that can serve as a renal maturation that is able to predict the developmental

changes of other renal eliminated drugs (i.e., vancomycin, gentamicin, netilmicin and tobramycin) and glomerular filtration rate in neonates.[20-22]

Proof-of-concept: integration of pharmacometrics in clinical practice

During pediatric drug development, pharmacometric analyses can provide a rational basis for making important choices when designing and conducting pediatric clinical trials, including first dose in children, rational dose range to be studied, sample size, optimal PK sampling, PK-PD target, efficacy and safety determinations, etc.[23-25] Impacts on decision-making throughout the pediatric drug development and regulatory review process have been certainly confirmed.[26] However, the clinical implication of pharmacometrics has rarely been reported in children and without real follow-up in clinical practice. The central question is now to convert complex research-based models into easy-to-use tools and integrate them into evidence-based personalized pharmacotherapy in clinical practice.

Antibiotics in septic neonates and immunosuppressants in pediatric transplant recipients were used as "proof-of-concept" to demonstrate the utility of pharmacometrics in clinical practice. Dosage individualization is a key problem faced by pediatricians and pediatric pharmacologists to ensure personalized therapy in children.

Antibiotics in neonates

Neonatal bacterial sepsis, classified as early and late onset sepsis, is a major cause of mortality and morbidity.[27] According to regulatory guidelines,[28-30] antibiotic is a class of drugs for which the pharmacometric approach can be used to establish pediatric dosage recommendations. Antibiotics are active against well defined bacteria and their PK-PD relationship can be assumed to be similar across all age ranges including neonates, as the target is the bacterium. Following the pediatric study decision tree defined by FDA, two types of studies are required to evaluate antibiotics in neonates: a PK study to achieve the levels similar to adults and a safety study. Traditionally, the neonatal PK study of antibiotics focused on average drug exposure to achieve adult levels. The neonatal recommended dose is defined on a mg/kg basis. This approach obviously simplifies the impacts of developmental factors and clinical conditions on PK parameters. It assumes an "average newborn" with an "average weight" and a simple linear maturation relationship between weight and drug clearance.

The commonly used antibiotics in neonates, including ampicillin, gentamicin, meropenem and vancomycin, are taken here as the illustrative examples to demonstrate how to use pharmacometrics to optimize antibiotic therapy in neonates.

Ampicillin features actively against many of the most common etiological agents of early-onset neonatal sepsis, including *group B Streptococci*.[31] It displays time-dependent antimicrobial activity, which means that the PD parameters that have been most strongly correlated with maximal bacterial killing is the time above the minimum inhibitory concentration (T>MIC).[32] In order to define the optimal dose of ampicillin in neonates, Tremoulet et al[33] conducted a population pharmacokinetic study in 73 neonates. A one-compartment model with first order elimination was fitted to the PK data. Postmenstrual age, weight and serum creatinine were covariates for ampicillin clearance. Based on simulation results, an optimal dosage regimen of 50 mg/kg twice daily for gestational age (GA) ≤34 weeks and postnatal age (PNA) ≤7 days; 75 mg/kg twice daily for GA ≤34 weeks and PNA ≥8 and ≤28 days; and 50 mg/kg thrice daily for GA >34 weeks and PNA ≤28 days achieved the pre-specified surrogate efficacy target (steady-state trough concentration ≥8μg/mL) in 90% of simulated neonates. Compared to the dosing regimens currently recommended in pediatric references (Neofax and Harriet Lance), this optimal dosage regimen provides fewer dose groups and less frequent dose, which are more convenient for neonatal clinical practice.

Gentamicin is primarily used for the treatment of gram-negative sepsis. The American academy of pediatrics recommends that the optimal treatment of early-onset neonatal sepsis include therapy with broad-spectrum antimicrobial agents, including ampicillin and an aminoglycosides.[31] The PD parameter that has been most strongly associated with gentamicin antimicrobial activity is the area under the curve (AUC).[34] Nephrotoxicity and ototoxicity have been reported in neonates. High trough concentration above 2 μg/mL and peak concentration greater than 12 μg/mL were associated with increased risks of nephrotoxicity and ototoxicity, respectively.[35,36] In addition to the high inter-individual PK variability, therapeutic drug monitoring (TDM) and dosage individualization are mandatory to optimize gentamicin therapy in neonates. Nielsen et al[37] performed a population PK study in 61 neonates. A three-compartment model with first order elimination was fitted to the PK data. Gentamicin clearance increased with the weight, GA and PNA. Based on final PK model, the dosage regimen of 4-5 mg/kg given at dosing intervals of 24-48 hours was proposed for neonates. Individual gentamicin dose can be predicted based on weight and age (GA and PNA) in neonates.

Meropenem, a carbapenem antibiotic with a broad spectrum of antimicrobial activity, is stable against hydrolysis by most extended-spectrum beta-lactamases and AmpC chromosomal beta-lactamases, increasing the drug's activity against many antibiotic-resistant gram-positive (e.g., *Penicillin-resistant S. pneumoniae*) and Gram-negative (e.g., *P. aeruginosa*) bacteria.[38] It is labeled for pediatric patients older than 3 months of age for treatment of bacterial meningitis and complicated intra-abdominal infections. Currently, its use in neonates is off-label partly because of lack of pharmacokinetic studies. Smith et al[39] conducted a population pharmacokinetic study in 188 premature and term infants <91 days old with suspected intra-abdominal infections. A one-compartment model with first order elimination was fitted to the PK data. Postmenstrual age, weight and serum creatinine were covariates for meropenem clearance. Based on PK results, an optimal dosage regimen of 20 mg/kg twice daily for GA<32 weeks and PNA<14 days; 20 mg/kg thrice daily for GA<32 weeks and PNA≥14 days and for GA≥32 weeks and PNA<14 days; and 30 mg/kg thrice daily for GA≥32 weeks and PNA≥14 days achieved therapeutic target of T>MIC (2 μg/mL) for 75% of the dosage interval in 92% infants. This population PK study provided evidence-based dosage regimen of meropenem in neonates and young infants.

Vancomycin is a glycopeptide antibiotic used for more than 50 years in neonates.[40] It became the treatment of choice for *staphylococcal* infection in the 1950s, when *Staphylococcal* strains developed resistance to treatment with penicillin,[41] and was then replaced by methicillin in the 1960s, but when the incidence of late onset sepsis in neonates increased due to *coagulase negative Staphylococci* (*CoNS*) and *Methicillin-resistant staphylococci* (*MRSA*), the use of vancomycin re-emerged and is today the current treatment of choice for many *Staphylococcal* infections.[41,42] Its pharmacokinetics has shown large inter-individual variability.[43] As vancomyin is primarily eliminated by glomerular filtration, renal maturation, renal function and body weight should be the most important factors influencing pharmacokinetics.[44,45] "Classical" mg/kg basis dosing regimens integrated these factors as categorical variables and correspondent dose was calculated in the different neonatal age groups. In our recent study of vancomycin continuous infusion in neonates,[46] the classical mg/kg based dosing regimens, taking into account age and/or serum creatinine allowed obtaining the expected average concentration in the population, but variability was extremely large. Only 41% of neonates had concentrations in the target range of 15-25 mg/L. Applying pharmacometrics, a patient-tailored dosing regimen, taking into account current weight, birth weight, postnatal age and serum creatinine as continuous variables, was developed based on a one-compartment population PK model. A prospective validation study showed a major improvement in individual vancomycin therapy. The percentage of neonates achieving the target concentrations increased to 71%. The corresponding tool has been set up in our NICU to individualize vancomycin dose and undoubtedly optimization of prescription is applicable for other antibiotics in neonates.

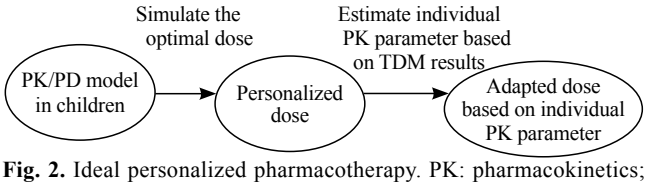

Fig. 2. Ideal personalized pharmacotherapy. PK: pharmacokinetics; PD: pharmacodynamics; TDM: therapeutic drug monitoring.

Immunosuppressants in pediatric transplant recipients

Immunosuppressants are widely used in pediatric solid organ and bone marrow transplant recipients to prevent transplant rejection. The desired therapeutic effect is obtained with an acceptable tolerability within a narrow range of blood concentrations while between-individual PK and PD variability is very large.[47,48] Dosage individualization and TDM are crucial in daily practice to optimize treatment efficacy, reduce rejections, and prevent adverse reactions. Most transplantation centers are using whole blood trough concentrations (C_0) and/or drug exposure (AUC) to adjust the individual dose, with the primary goal to maintain the C_0/AUC within a predefined therapeutic range according to the type of transplantation, post-transplant period and protocol of immunosuppression.[49,50]

Tacrolimus, which is a calcineurin inhibitor and an effective alternative to cyclosporine for preventing rejection after solid organ transplantation, is taken here as a second example. A uniform initial dose of 0.15 mg/kg twice daily is recommended for children. However, with this standard dose, adolescents are overdosed, whereas young children are underdosed,[51,52] indicating that this mg/kg basis dosing regimen is not adapted to children. Pharmacometrics can be implicated in two ways to individualize tacrolimus pediatric therapy in clinical practice. The first one is to personalize starting dose. As tacrolimus is primarily metabolized by cytochrome p450 (CYP) 3A4/A5,[53] the developmental pharmacogenetics of CYP3A5 has been integrated into the population PK model to develop CYP3A5 genotype based pediatric dose of tacrolimus.[54,55] Despites the continuing efforts to identify the covariates influencing pediatric PK of tacrolimus, the residual variability is

still very high, making the posterior dosage adaption mandatory. Such observation explains the second way of integrating pharmacometrics in clinical practice, which is posterior dosage adaption via maximum a posteriori (MAP) Bayesian estimation.[56] MAP Bayesian dosage estimation utilizes information from the already available population PK model (typical drug clearance, volume of distribution, expected associated variability) and limited concentration-time data from an individual, to obtain the most likely PK parameter estimates for this particular individual. The individual PK values that are obtained can be used to devise the dosing regimen that will allow achieving the required target AUC in this particular individual. Using this strategy, we demonstrated that the mean absolute prediction error between MAP Bayesian estimated and observed AUCs was less than 7.5% for tacrolimus.[57,58]

Mycophenolate mofetil (MMF), 2-morpholinoethyl ester of mycophenolic acid (MPA), is the prodrug of the active compound MPA. Currently, it use in combination with calcineurin inhibitor to prevent rejection after solid transplantation. Large intra- and inter-variability was reported in children related to weight, plasma albumin concentration, post-transplantation time, corticoid dose, and kidney functions.[59] Concomitant immunosuppressive medication has a differential effect on MPA apparent clearance (CL/F). Higher MPA CL/F was reported in patients treated with cyclosporine–MMF than those treated with tacrolimus–MMF. Consequently, the recommended dose in renal transplant children is 900 mg/m^2 twice daily with concomitant cyclosporine and 600 mg/m^2 with concomitant tacrolimus, respectively.[60] AUC-guided MMF monitoring was recommended with the target window of 30 to 60 mg/h in conjunction with full-dose calcineurin inhibitor therapy.[60] In order to facilitate the clinical use of AUC-based dosing individualization, Barau et al[61] conducted a population PK study in 28 liver transplant children. A Bayesian estimator of T_0, T_1 and T_4 was developed to predict the individual AUC based on a one-compartment model with first order elimination. Payen et al[62] evaluated the population PK in 45 renal transplant children. A model-based Bayesian estimator of T_1 and T_4 provided precise prediction of individual AUC in an independent group of children. Pharmacometrics provided useful tools to individualize immunosuppressant therapy in pediatric transplant recipients.

The integration of pharmacometrics in pediatric clinical pharmacometrics has certainly a further to personalize drug therapy in children. It requires a close collaboration between pediatrician and pediatric clinical pharmacologist. The pediatric pharmacometric training program is still under development. There is limited number of tutors. In addition, pediatric population PK-PD analysis is often based on limited number of patients. The covariate-PK relationship[63] and inter-center (study) variability[64] should be carefully interpreted in order to correctly apply the model in pediatric clinical practice. The general points to consider for pharmacometrics in children are presented in the Table.

Table. Pharmacometrics in children

- ► Developmental factors (i.e. age and weight) should be taken into account to develop population PK/PD model in children.
- ► Variability is more important in children compared to adults. The identification of covariates has more benefits in children in order to personalize drug therapy.
- ► Dose extrapolation across the age groups should consider impact of age and disease on PK-PD relationship.
- ► Population PK meta-analysis is a useful tool in pediatric PK analysis. The covariate-PK relationship and inter-center (study) variability can be better defined and evaluated in children.

PK: pharmacokinetics; PD: pharmacodynamics.

Conclusions

The pharmacometric technique should be better developed and used in clinical practice to personalize drug therapy in children in order to decrease variability of drug exposure and associated risks of overdose or underdose. A general approach of "ideal personalized pharmacotherapy" should be to start treatment with an optimal dose, simulated from pediatric PK/PD model, followed by a posterior dosage adaptation based on individual PK/PD parameters (Fig. 2).

Funding: Zhao W and Jacqz-Aigrain E receive supports from the European commission for their work in pediatric clinical pharmacology (FP7 Treat infection in neonates TINN1, grant agreement no. 223614; FP7 Treat infection in neonates TINN2, grant agreement no. 260908; FP7 Global research in paediatrics GRIP, grant agreement no. 261060; FP7 NeoVanc, grant agreement no. 602041)
Ethical approval: None.
Competing interest: None.
Contributors: Zhao W and Leroux S contributed to concept, design and drafting of the paper. Jacqz-Aigrain E made a critical revision for the paper.

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Received January 12, 2014
Accepted after revision June 18, 2014