Available online at

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com

Thérapie

ELSEVIER

PEDIATRIC PHARMACOLOGY/DRUGS AND CHILDREN

Principles and applications of pharmacometrics in drug evaluation in children

Stéphanie Leroux[a,b], Valéry Elie[a], Wei Zhao[c,d],
Sophie Magreault[a], Evelyne Jacqz-Aigrain[a,c,e,*]

[a] Department of paediatric pharmacology and pharmacogenetics, Robert-Debré hospital, Assistance publique—Hôpitaux de Paris (AP—HP), 75019 Paris, France
[b] Neonatology, CHU Rennes Sud, 35033 Rennes, France
[c] University of Paris Diderot Sorbonne Paris Cité, 75013 Paris, France
[d] Clinical pharmacy department, pharmaceutical sciences university, Shandong university, 266510 Shandong Sheng, China
[e] Clinical investigation center (CIC1426), Inserm, AP—HP, 75019 Paris, France

Summary   Drug evaluation in children is difficult for many well-identified reasons and many drugs are still used off-label. Innovative approaches are particularly adapted to the paediatric and neonatal populations, as clinical trials are difficult to conduct, need adapted designs in order to define the optimal dosage regimen in many diseases and therapeutic areas. Population approaches to define pharmacokinetics and pharmacokinetic/pharmacodynamics are now more currently used to define dosing regimens, adapted to the different paediatric and neonatal age groups, that allow to increase efficacy and reduce toxicity, by taking into account factors explaining variability in drug response. Such approaches are presented and the evaluation of vancomycin in neonates is detailed as different steps allowed validation of the optimal strategy to administer vancomycin in neonates.
© 2018 Published by Elsevier Masson SAS on behalf of Société française de pharmacologie et de thérapeutique.

 * Corresponding author: Department of pediatric pharmacology and pharmacogenetics, Robert-Debré Hospital, 48, boulevard Sérurier, 75019 Paris, France.
    E-mail address: evelyne.jacqz-aigrain@aphp.fr (E. Jacqz-Aigrain).

Abbreviations

CoNS   coagulase negative staphylococci
LOS   late onset sepsis
LSS   limited sampling strategy
MRSA   methicillin-resistant staphylococci
PBPK   physiology based pharmacokinetic modeling
PG   pharmacogenetics
PK   pharmacokinetic
PK—PD pharmacokinetic—pharmacodynamic

Introduction

There are important interindividual differences both in terms of efficacy and toxicity when considering one drug and one disease. This is even more accentuated in children, as childhood is the period with the most important physical and physiological changes. Changes are not linearly related to age, resulting in a highly heterogeneous pediatric population explaining the division of the pediatric population in age groups and the requirement for age-dependent dosing adaptation [1,2].

Since 2007 and the application of the European pediatric regulation, drug evaluation and safe drug use in children have become of public health importance. The lack of evaluation is of major concern for specific pathologies and specific age groups. Reasons for insufficient evaluation are multiple, including methodological difficulties, particularly the low number of eligible patients in clinical trials and the difficulty to collect blood samples in comparable volumes to adults. Therefore, modeling and simulation techniques are now a mainstay to support clinical drug development [3,4].

Modeling and population approaches to pharmacokinetics and pharmacodynamics

Drugs are administered to very different patients/groups of patients from neonates to adults, in diverse levels of growth/maturation and physiopathological conditions. In this context, drug pharmacokinetics and dynamics need to be linked to explicative individual characteristics whether constitutional (age, weight, genetics, etc.) or environmental (pathology, drug interactions for example). The use of population modeling allows to assess and to quantify sources of variability in drug exposure and response in the target population, even under sparse sampling conditions [4].

Population pharmacokinetics and pharmacodynamics

Pharmacokinetics determines the disposition of a drug in the body by analyzing its concentration versus time profile, while pharmacodynamics aims to investigate the relationship between drug dosage regimen and response, both therapeutic and toxic. Of note, the concentration-time or concentration-effect relationships frequently differ between pediatric and adult patients and that variability in pharmacodynamics is frequently as wide as that observed in pharmacokinetics.

When concentration—time and concentration—effect datasets are considered for analysis, two different methods can be applied: the two-stage and the population approaches [5—7].

When using the standard two-stage or classical approach, parameters are estimated in each individual based on concentration—time profiles, summarized by calculating the mean or median of the parameters and the variability between subjects. This method requires a high number of ''planned'' samples per individual, each of them contributing the same number of samples. However, this approach makes it difficult to distinguish between interindividual (variability between subjects) and intra-individual or residual variability (variability within one subject, measurement error...).

The one-stage approach analysis is based on simultaneous analysis of population data from different patients. Pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK—PD) population modeling are mathematical methods for predicting drug disposition and effect. The term ''population'' refers to ''non linear mixed-effects' modelling'', a mixture of fixed and random effects. Fixed (structural model) effects are parameters such as clearance and factors that significantly influence clearance (for example weight, age). Random effects (variance model) parameters include the inter-subject variability, and the variability, which remains unexplained after fitting the model to the data (data collection and measurement error, model misspecification...). The population approach is used in situations where multiple measurements cannot be made (data-sparse situation), and now currently performed in pediatrics, particularly in the younger patients to quantify and explain variability. Population modeling particularly permits to take into consideration repeated measures in the same patients. Multiple programs are used to conduct these types of analysis starting from a Bayesian approach (NonMEM, Monolix, R, etc.).

The immediate interest of this methodology is a precise adaptation of drug posology taking into account all identified variability factors based on simulations. It can be used to optimize individual dosage based on data obtained from therapeutic drug monitoring [8], for selection of dose in a given pediatric population or subgroups based on simulation (Figs. 1 and 2). It is also possible to improve trial design by simulations and/or determination of optimal times to collect observations [9].

PBPK — physiology based pharmacokinetic modeling

The previous modeling approaches require preexisting/preliminary data on the populations of interest and thus to expose patients to a drug without knowing the optimal dose, effect and risks of toxicity. To limit patients' risks and reduce the number of exposed subjects, physiological or PBPK modeling is a model-based method, integrating all knowledge available on developmental physiology and pharmacology (including for example biological parameters such as maturation of metabolic pathways impacting