Published in final edited form as:

Curr Pharmacol Rep. 2020 October ; 6(5): 260–266. doi:10.1007/s40495-020-00234-5.

The Utility of Pharmacometric Models in Clinical Pharmacology Research in Infants

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Abstract

Purpose of commentary—Acquiring knowledge on drug disposition and action in infant is challenging because of the problem of sparse and unbalanced data obtained for each individual infant due to the limited blood volume as well as the issue of extensive inter-subject and intra-subject variability in drug exposure and response due to the fast growth and dynamic maturation changes in infants. This commentary highlights the importance of using population-based pharmacometric models to improve knowledge on drug disposition and action in infants.

Recent findings—Pharmacometric modeling remains to be critical in clinical pharmacology research in infants. Many pediatric covariate models developed for scaling of drug clearance use a combination of allometric weight scaling to account for size change and a sigmoid function of antenatal development and postnatal maturation to characterize the age-related maturation. To expedite the development of safe and effective dosing regimens in infants, a number of strategies have been proposed recently, including the use of pediatric covariate model obtained from one drug for extrapolation to other drugs undergoing similar elimination pathways, as well as the combination of opportunistic clinical studies and population-based pharmacometrics models.

Summary—Population-based pharmacometric modeling plays a pivotal role in clinical pharmacology research in infants. Most of the covariate models reported so far focus on antibiotics undergoing renal elimination. Novel modeling strategies have been proposed recently to facilitate clinical pharmacology research and expedite the dose optimization process in infants.

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Conflict of Interest

None

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Keywords

Pharmacometric modeling; population pharmacokinetics; infant; pediatric covariate model; opportunistic clinical study; erythropoietin pharmacokinetics

Introduction

Although great progress has been made in drug testing in children in the past decade, due to practical and ethical reasons, there is only a small number of drugs studied in infants. It has been reported that 65~ 90% of the drugs used in infants are either outside the product license (off-label) or without a license at all (unlicensed) [1]. Therefore, there is an urgent need to improve the knowledge on drug disposition (i.e. pharmacokinetics, PK) and action (i.e. pharmacodynamics, PD) in this vulnerable population. It is particularly challenging to acquire knowledge on drug PK/PD in infants due to the problems of small body size and extensive biological changes. One promising approach to overcome these problems is to perform a population based pharmacometric modeling. This commentary highlights the importance of using population-based pharmacometric models to improve knowledge on drug disposition and action in infants and provides modeling strategies to expedite the safe and effective dosing regimen optimization process.

Infants still lack drug data to guide therapy

Infants, the ultimate therapeutic orphans

More than 5 decades ago, Harry Shirkey coined the term “therapeutic orphans”, referring to the lack of pediatric studies demonstrating drug safety and efficacy when children receive drugs [2]. Since early 2000s, extensive efforts have been spent in drug testing in children after a series of federal US legislations on pediatric research, including the Best Pharmaceuticals for Children Act (BPCA, passed in 2002) [3] and Pediatric Research Equity Act (PREA, passed in 2003) [4], were in place. By the end of 2016, these legislative implementations resulted in 665 drug label changes that included new pediatric prescribing information, and 57% of the drugs used in children have adequate pediatric labeling [5]. Although great progress has been made, unfortunately infant population does not benefit much from these regulatory efforts and the number of drugs studied in infants has remained very small [1]. Among the drug label changes on pediatrics population, only 6% is on infants [5, 6]. As a result, infants, particularly neonates, still remain therapeutic orphans.

Uniqueness of infant population

Infants are truly a special population considering the rapid and variable maturation of their physiologic processes, the fast changes in body composition and body size, as well as diseases that are unique to this period of life [7, 8]. Because of these unique conditions, infants by no means are small adults. Consequently, extrapolation of drug studies from adult indications to infants is rarely appropriate. Despite this, most drugs used in infants have been introduced based on their efficacy in adults [6]. As a result, pediatric doses for infant population are often derived empirically with unknown safety and unproven efficacy.

Therefore, there is an urgent need to improve knowledge on drug PK and PD in infants so that drug can be used in this unique population in a safe and effective manner.

Population based pharmacometric modeling is a valuable tool to improve knowledge on drug disposition and action in infants

Unique barriers in acquiring knowledge on drug PK/PD in infants

Acquiring knowledge on drug PK/PD in infant is challenging due to two barriers that are unique to this special population. One barrier is that traditional PK/PD studies, which involve the predetermined and rich blood sampling schedule, are not feasible in this special population since infants only have limited blood volume. As a result, usually sparse and unbalanced PK/PD data are obtained for each individual infant in pediatric clinical studies. For this type of data, it is difficult to extract meaningful information (e.g. drug exposure, elimination half-life, etc) if each individual's data is analyzed alone (i.e. the way that the traditional rich data is handled). Another barrier is the extensive inter-subject and intra-subject variability in drug exposure and response due to the fast growth and dynamic maturation changes in infants [9, 10]. Because of the extensive variability caused by these developmental changes, performing dosing adjustment across different age groups based on body weight alone will not be adequate. Due to these barriers mentioned above, new approaches to support infant data analysis and dose regimen optimization in infants are needed.

Population based pharmacometric modeling is the key to unlock these barriers

One promising approach to overcome the barriers mentioned above is population based pharmacometric modeling [11, 12]. Population based pharmacometric modeling is a nonlinear mixed-effect modeling approach which includes 3 model components: a) a structural model component which characterizes the overall trend in the data using fixed effects parameters (e.g. clearance (CL), volume of distribution (V)); b) a stochastic model component which accounts for variability within population using multiple level of random effects, such as inter-individual variability (IIV), residual variability (RV), and (if applicable) inter-occasion variability (IOV); and c) a covariate model component in which subject covariates (e.g. age, bodyweight, renal function) are explored for their ability to account for inter-subject and/or intra-subject variability. As population based pharmacometric modeling can perform simultaneous analysis of all data of the entire population while still taking into account different observations derived from different subjects, this approach is capable of analyzing sparse and/or unbalanced data. In addition, the influence of developmental changes in underlying physiological processes on drug PK parameters can be evaluated in the covariate model component of the population model. Therefore, population based pharmacometric modeling is particularly powerful and suitable for pediatric clinical pharmacology as it can handle both sparse and unbalanced data (i.e. barrier 1) using its stochastic model component and the ontogeny of organ function (i.e. barrier 2) using its covariate model component.

Development of pediatric covariate model to expedite the development of safe and effective dosing regimens in infants

As noted earlier, covariate analysis is an important step in the pharmacometric model building process as covariates characterize inter- and intra-variability of PK parameters. As growth, development and dynamic maturation processes in infants lead to large inter- and intra-variability of drug disposition, development of pediatric covariate model is particularly important when handling infant PK data and it provides the opportunity to personalize dosing strategies based on patient specific factors. The evaluation of covariate effects on drug disposition in infants has been mainly limited to antibiotics (e.g. various aminoglycosides and β -lactams) as well as ontogeny of renal function. This is not surprising since antibiotics are the most frequently prescribed medications in infants and most of the antibiotics used in pediatric population are primarily eliminated by the kidneys [13–15]. Based on developmental pharmacology principles, pediatric covariate model should include components reflecting both growth and maturation processes that influence drug PK parameters such as V and CL. In line with this concept, the clearance of renally eliminated antibiotics is often expressed as a function of growth (size) and age-dependent maturation [15] (Figure 1). Regarding the size, most of the reported covariate models used weight to account for organ size/growth with CL being scaled to weight either linearly or parameterized as a power function using a fixed component (0.75) [15–17]. Regarding the maturation changes over time, covariates that have been commonly explored include gestational age (GA, time elapsed between the first day of the last menstrual period and the day of delivery), postnatal age (PNA, time elapsed from birth), postmenstrual age (PMA, calculated as GA plus PNA), and corrected age (CA, calculated as PNA reduced by the number of weeks born before 40 weeks of gestation). As PMA describe time since conception, it relates to both antenatal development and postnatal maturation. Many reported covariate models use PMA based sigmoidal maturation function to account for progressive increase in clearance during the first year of life [18–20]. On the other hand, Wilbaux and co-workers proposed that it is important to account for different dynamics of development before birth and maturation processes after birth and they recommended including separate antenatal (GA) and postnatal (PNA) effects to describe time dependent changes in drug clearance in infants [15] (Figure 1). In addition to growth (size) and maturation, many reported covariate models also include a kidney function factor, such as serum creatinine, cystatin C or other relevant biomarkers, to account for deviation from normal kidney function such as nephrotoxicity induced by co-administered drugs (e.g. indomethacin) [15].

Extrapolation of a pediatric covariate model between drugs that are eliminated through similar pathways

To avoid the conduction of the systematic and time-consuming PK/PD analysis for each new or existing drug, new approaches are urgently needed to expedite the development of safe and effective dosing regimens in infants. One recently proposed approach is the extrapolation of pediatric covariate model obtained from one drug to other drugs with similar elimination pathways [21, 22]. The central hypothesis is that the covariate model established contains system-specific information reflecting underlying physiological changes and therefore can be used between drugs. Kinbabe's group has tested this concept

through a number of interesting investigations [21–23]. In one study, they used the extensively validated covariate model for amikacin to predict the clearance of 4 other antibiotics, namely netilmicin, vancomycin, tobramycin, and gentamicin, all of which are mainly eliminated through glomerular filtration and have similar physicochemical properties as amikacin [22]. Their results showed that the descriptive and predictive performance of the models developed using the amikacin covariate model were good and similar to the independent reference models developed based on a systematic covariate analysis for each compound [22]. In another study conducted by Kinbabe's group, the same concept was tested using morphine and zidovudine, both of which are primarily eliminated via the UDP2B7-mediated glucuronidation [21]. In this study, a pediatric covariate model for morphine glucuronidation, extensively validated both internally and externally, was directly incorporated into a population model for zidovudine glucuronidation in infant population [21]. Their results indicated that using the covariate model established from morphine can adequately characterize zidovudine disposition in infants, further supporting their hypothesis that pediatric population PK covariate models contain quantitative information on the influence of maturational changes in the biological system on drugs PK and can be extrapolated between drugs with similar elimination pathways. It's worth emphasizing that the prerequisite of a successful extrapolation is that the pediatric covariate models containing system-specific information are established from a large patient cohort with varying characteristics (e.g. GA, birth weight, PNA) and are extensively validated. When these requirements are met, the covariate model extrapolation approach could expedite the development of safe and effective dosing regimens in infants as model development of the unstudied drugs may be accomplished using even more limited number of data, which is a clear advantage as both the number of subjects and the burden for each participant in the study can be reduced.

The utility of opportunistic clinical studies and population-based pharmacometric models to optimize dosing regimens in infants

Conducting clinical studies in infants is challenging due to the ethical concerns, low parental informed consent rates, as well as difficulty in obtaining PK samples due to the critical medical condition and limited blood volume of the infants. Conducting clinical studies in infants is also time consuming due to the slow enrollment. One attractive strategy to overcome these difficulties is to perform opportunistic clinical studies in infants, where leftover blood from laboratory testing (i.e. scavenged samples) are used [24–27]. As the blood samples used for drug concentration measurement are obtained from discarded blood from other clinical lab tests (such as hematology and chemistry tests), this means no additional phlebotomy for PK samples is involved in this type of studies, which represents an advantage and can increase parental informed consent rates. Another advantage of opportunistic clinical studies is that the blood samples are collected randomly (i.e. not at predetermined time points) and the different subject could contribute different number of samples at various times since the frequency and time schedule of clinical lab tests are different among infants. Once the sparse and/or unbalanced PK data in each subject are obtained, they can be pooled together for further quantitative characterization using population based pharmacometrics modeling.

Our group has recently demonstrated the utility of this approach to characterize the PK of recombinant human erythropoietin (rhEPO) in premature infants [24]. Neonatal anemia is the most common hematological problem for very low birth weight (VLBW) infants (i.e. weight < 1,500 g at birth). For neonatal anemia, in addition to red blood cell transfusion (RBCTx), an alternate therapy is the administration of rhEPO. As information of rhEPO PK in infants is limited, the current rhEPO dose regimen in infants is mainly empirically derived from the dosing regimen used in adult population. Current Epo therapy in VLBW infants has only modestly reduced the number of RBCTxs, indicating that the empirical Epo dosing schedules used in infants is inadequate [28, 29]. To address this therapeutic opportunity, we conducted a clinical study to investigate the PK of Epo in VLBW premature neonates following multiple i.v. and s.c. Epo doses administered within the first 4 weeks of life [24]. In this study, leftover blood samples from laboratory tests were used to measure plasma rhEpo concentrations. As our study subjects were premature infants in the neonatal intensive care unit, for many subjects we were able to get extensive sampling (especially during the first week of life) where frequent phlebotomies were performed due to numerous clinical laboratory testing, along with a sparse later sampling (e.g. in week 4) because the severity of illness decreased and consequently less clinical laboratory testing was scheduled (Figure 2c). Because of the opportunistic sampling strategy, the plasma rhEpo data we obtained provided comprehensive information about the rhEpo kinetics. During model development process we tested several different models, including linear PK model, nonlinear Michaelis-Menten (M-M) PK model, as well as a target-mediated drug disposition (TMDD) model. Results from our population-based pharmacometric modeling indicated that neonatal rhEpo PK was best characterized by the TMDD model containing a target-mediated saturable, nonlinear, elimination pathway that incorporated the mechanism of rhEpo binding to its receptors along with a parallel linear, central elimination pathway [24] (Figure 2a, Figure 2b). Several lines of evidence indicate that Epo is mainly degraded by its pharmacological target (i.e. Epo receptor, Epo-R) which is in greatest abundance on erythroid progenitors located primarily in bone marrow [30, 31]. Therefore, our final TMDD model not only provides the best fit but also is consistent with current knowledge on the mechanism of Epo elimination. In addition, our modeling result showed that rhEpo total clearance was significantly higher in preterm infants compared to adults [32, 24]. For example, the total clearance of Epo in infants and adults were 8.53 ml/h/kg and 4.64 mL/h/kg, respectively, at the dose of 500 U/kg [32]. The higher clearance of rhEpo in infants than that in adults may be caused by the higher expression of Epo-R in infants. It has been reported that infants have a higher proportion of bone marrow erythroid volume and a greater erythroid progenitor cell mass per kilogram of bodyweight than adults [33]. Indeed, based on our model prediction, the total Epo receptor concentration (R_{max}) was estimated to be 133 pM in infants, which is higher than the R_{max} of 88.8 pM that was estimated in adults [24, 32]. Our further investigation indicated that at doses > 500 U/kg, the rhEPO receptor-mediated nonlinear elimination is the dominant rhEpo elimination pathway in premature infants, and parallel linear elimination was dominant in adults [32]. This is not surprising since the expression of Epo-R is lower in adults than that in infants, and consequently Epo-R mediated nonlinear elimination will be saturated sooner. As a result, linear elimination pathway plays more important role in the overall elimination process of Epo in adults at high doses. The significantly higher rhEPO clearance in infants as well as different dominant elimination

pathway between these two populations indicated that 1) the empirical dose regimen used in infants may be too low; and 2) the simple bodyweight-based dose extrapolation from adult to infant is not appropriate for rhEPO because of the complicated rhEPO receptor-mediated nonlinear elimination. Our work, accomplished by the combination of opportunistic study and population-based modeling, are valuable in guiding and predicting future rhEpo dosing regimens in VLBW infants. Most of the previously reported Epo population PK analysis in various human populations have used either a linear PK model or a non-mechanistic M-M model [34, 35]. Our TMDD model is advantageous because it is mechanism-and physiology-based, and the model results are more valuable since it incorporates the mechanism of receptor binding and degradation. This TMDD model arose naturally because of the comprehensive information about the rhEpo kinetics embedded in the data that were collected using an opportunistic sampling strategy.

While opportunistic clinical study leveraging scavenged samples represents an attractive strategy to expedite the development of safe and effective dosing regimens in infants, it should be conducted with extra caution for drugs with stability issue. In our institution, the general practice is that the leftover blood samples are not discarded right away after the clinical test is done. Instead, the leftover samples are usually kept within the clinical labs for additional 1–3 days (under room temperature or 4°C) in case repeated analysis is needed. This means that the scavenged samples are already a few days old before research team picks them up and put them in –80°C freezer. This is not an issue for our rhEPO project as rhEPO is very stable in blood under room temperature or 4°C. However, using scavenged samples may be problematic for PK studies of some antibiotics. A typical example is β -lactams, a class of antibiotics that are frequently prescribed in infant patients. We conducted short-term stability of cefepime, meropenem, piperacillin, and tazobactam and found that all four antibiotics were unstable after 24 hours at room temperature, with average degradation ranging from 30.1% for cefepime to 75.6% for meropenem [36]. In addition, meropenem was even unstable after 24 hr at 4°C with an average degradation of 25.9% [36]. Although we did not test their 3-day stability, it is reasonable to anticipate that the stability data can only be worse than the 24 hr stability data we have. Therefore, before conducting opportunistic clinical study, stability of the studied drug should be evaluated first to make sure that using scavenged samples has no negative impact on the data quality.

Conclusions

Population-based pharmacometric modeling plays a pivotal role in the conduct of clinical pharmacology research in infants. Pediatric covariate analysis represents an important step in the population-based model building process. Most of the covariate models reported so far focus on antibiotics undergoing renal elimination. Development of pediatric covariate models for other classes of drugs used in infant population as well as other elimination routes are needed. There is a consensus that infants are not small adults and size-based adjustment alone is inadequate. Many pediatric covariate models developed for CL scaling use a combination of allometric weight scaling to account for size change and a sigmoid function of antenatal development and postnatal maturation to characterize the age-related maturation. To expedite the development of safe and effective dosing regimens in infants, a number of approaches have been proposed, including the use of pediatric covariate model

obtained from one drug for extrapolation to other drugs that are eliminated through similar pathways, as well as the combination of opportunistic clinical studies and population-based pharmacometrics models. Current pharmacometrics modeling effort for infants is mainly on drug disposition. Much less attention has been paid to the scaling and developmental changes of drug effects in infants. Future investigations are warranted to fill in this knowledge gap by collecting more PD endpoints and establishing population PK/PD modeling.

Acknowledgement

This work is partially supported by National Institute of Health (R21 DK113073; P01 HL046925).

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Figure 1.

Reference covariate model for characterizing clearance of drugs that are primarily eliminated through kidneys in infants. BW, body weight; PWR, power coefficient; CL, clearance; GA, gestational age; PNA, postnatal age; SCr, serum creatinine. Adapted from Wilbaux et al. JCP 2016.

Figure 2.

a) Final TMDD model describing the PK of Epo. This model characterizes the distribution of Epo between a central compartment (C_p , V_p), and a peripheral compartment (C_t , V_t) determined by a distribution clearance (Q). Epo in the central compartment interacts with Epo receptors (R) with a second-order association rate constant (k_{on}) to form a Epo-R complex (RC). The complex can dissociate back to free Epo and free Epo receptors with a first-order dissociation rate constant (k_{off}). Epo can be eliminated either from the central compartment via a linear pathway (CL) or via internalization of the Epo-R complex (k_{int}). b) Key equations used to characterize the TMDD model; and c) Time courses of observed (symbols) and the final population pharmacokinetic model predicted (lines) Epo plasma concentrations in four representative neonates receiving multiple i.v. and s.c. dose regimens during the first 4 weeks of life. The observed Epo concentration data were obtained from scavenged plasma samples. Adapted from D'Cunha et al. EJPS 2019.