Optimal Sampling Theory: An Overview of Its Application to Pharmacokinetic Studies in Infants and Children

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ABBREVIATIONS. Vd, volume of distribution; Cl, clearance; AUC, area under the plasma concentration time curve; OST, optimal sampling theory.

Sick neonates, infants, and children often require drug therapy to ameliorate or cure disease. The success of drug therapy is directly dependent on administration of the optimal dose at the ideal dosing interval.[1,2] Determination of the optimal dose and dosing interval for a therapeutic agent requires a fundamental understanding of the complex interplay between a drug's pharmacokinetic and pharmacodynamic characteristics.[1] Unfortunately, pediatric practitioners often are confronted with the challenge of selecting a medication and defining a dose and dose interval without a clear understanding of the drug's pharmacokinetic and/or pharmacodynamic profiles or interactions. Our lack of understanding of these important, drug-specific pharmacologic characteristics places patients at tremendous risk for both suboptimal therapeutic results and serious untoward effects. Fortunately, over the past decade, we have witnessed great strides in our acceptance of performing pharmacokinetic studies in ill infants and children and the application of these data to the design of age-specific dosing regimens.[3,4] Nevertheless, unique challenges and limitations remain that complicate the performance of detailed, critical pharmacokinetic assessments of drugs in sick infants and children. The purpose of this article is to address some of the more important variables that influence the design and successful execution of pharmacokinetic evaluations in pediatric patients.

PHARMACOKINETICS

The determination of a drug's pharmacokinetic profile involves a detailed, critical assessment of the processes of absorption, distribution, metabolism, and excretion. As noted above, a fundamental knowledge of each of these processes is required for the design of an optimal dosing regimen for the treatment of specific disorders. Each of these pro-

cesses must be integrated with patient-specific factors that influence directly a drug's disposition in the body. The more important clinical variables that influence a drug's disposition in the body are shown in Table 1. Of the variables outlined in Table 1, age would appear to be the most important. The normal, dynamic changes that occur in organ function with age will influence dramatically a drug's disposition profile. Most notably, changes in the functional capacity of major organs can substantially impact on a drug's clearance (Cl) from the body.[1,2] Similarly, the ontogeny body water content and its anatomic distribution and protein content can directly influence a drug's distribution within the body. An understanding of a drug's distribution volume, ie, volume of distribution (Vd), permits an accurate determination of the individual dose to be administered, whereas an understanding of a drug's rate of Cl permits an accurate determination of the dosing interval. Further, the profound influence technology may and will have on a drug's disposition profile cannot be overemphasized (Table 1). Hemofiltration and extracorporeal membrane oxygenation can have varying influences on a drug's disposition profile that can only be determined with adequate study in patients receiving these and other such procedures.[5,6] Depending on the physicochemical characteristics of the drug, these processes may enhance drug Cl by adherence to equipment surfaces or via membrane capture.[6]

The most common approach to determining a drug's primary pharmacokinetic parameter estimates, elimination half-life ($t_{1/2}$), Vd, and Cl is to perform an individual, patient-specific pharmacokinetic evaluation. To perform such an evaluation, multiple blood and/or biologic fluid concentrations are obtained at predetermined, specific times over a specified time interval. Once these samples are analyzed for the compound in question and the values quantitated, a drug concentration–time curve is constructed (Fig 1), permitting an accurate computation of $t_{1/2}$, Vd, and body Cl. The construction of a drug concentration–time curve is necessary to describe a drug's pharmacokinetic profile. A working knowledge of a drug's $t_{1/2}$, Vd, and Cl is necessary for the design of effective and safe dosing regimens.

The performance of detailed pharmacokinetic evaluations of old and new drugs are well accepted in adults. After the administration of a known dose of drug to an adult, it is common to obtain multiple blood samples at predetermined time points, usually

TABLE 1. Clinically Important Factors That Influence a Drug's Pharmacokinetic Profile

Age
   Ontogeny of organ function
Disease
   Influence on organ function
Technology
   ECMO/cardiopulmonary bypass
   Dialysis/hemofiltration

ECMO indicates extracorporeal membrane oxygenation.

without concern as to the volume of blood to be removed. The duration of sampling is most accurate when the sampling time encompasses at least three to four elimination $t_{1/2}$ values. If any portion of the drug is excreted from the body via the kidney, timed urine collections after a dose permit an assessment of the extent of renal excretion and determination of the drug's rate of renal Cl. An example of a detailed blood sampling strategy for a pharmacokinetic evaluation of a drug with a $t_{1/2}$ of 4 hours is shown in Fig 1A. This example includes 12 blood samples to define the drug's plasma concentration time profile. The construct of a best-fit line through these points allows the calculation of the area under the plasma concentration–time curve (AUC) and the slope of the terminal portion of the concentration–time curve. The latter value is used to calculate the drug's $t_{1/2}$ ($t_{1/2} = 0.693/\beta$, where β is the slope of the terminal portion of the plasma concentration–time curve) and the AUC for body Cl (Cl = drug dose/AUC). A drug's Vd can be estimated from the simplified equation Vd = drug dose/Cpo, where Cpo is the peak drug concentration. The vast majority of such detailed pharmacokinetic evaluations often are performed in healthy adult volunteers, with the results of these studies then extrapolated to adult and pediatric patients. Although very helpful in providing insight into the drug's general disposition characteristics, studies in healthy volunteers provide little information on the influence of disease on a compound's disposition profile or any insight into the possibility of drug–drug or drug–disease interactions. For these reasons, additional studies are performed in patients with the disease state the drug is intended to treat.

It is clear from the example shown in Fig 1A that the greater the number of blood samples obtained over a specified period, the more accurate the construction of the drug's plasma concentration–time curve and, thus, the more accurate the calculation of derived pharmacokinetic parameter estimates. Nevertheless, this sampling strategy pays little attention to the most optimal time to obtain samples, relying mostly on a large number of samples to define the curve more completely. Alternatively, it would appear highly desirable if an identical curve could be constructed with much fewer samples providing the same degree of accuracy while consuming the least number of clinical and laboratory resources[7–10] (Fig 1B).

In contrast to the approach often used in adults outlined above, a number of problems confront the clinical investigator or clinician who desires to perform a pharmacokinetic evaluation in pediatric subjects. Some of the more important constraints that complicate the performance of a pharmacokinetic evaluation in pediatric patients are outlined in Table 2. The majority of the concerns outlined in Table 2 are legitimate safeguards protecting the health and overall well-being of the child (eg, sample volume requirements relative to assay methodology), whereas other concerns may reflect an emotional posture emanating from a deficient understanding of the importance of defining a drug's pharmacokinetic profile to its clinical application (eg, perceived ethical
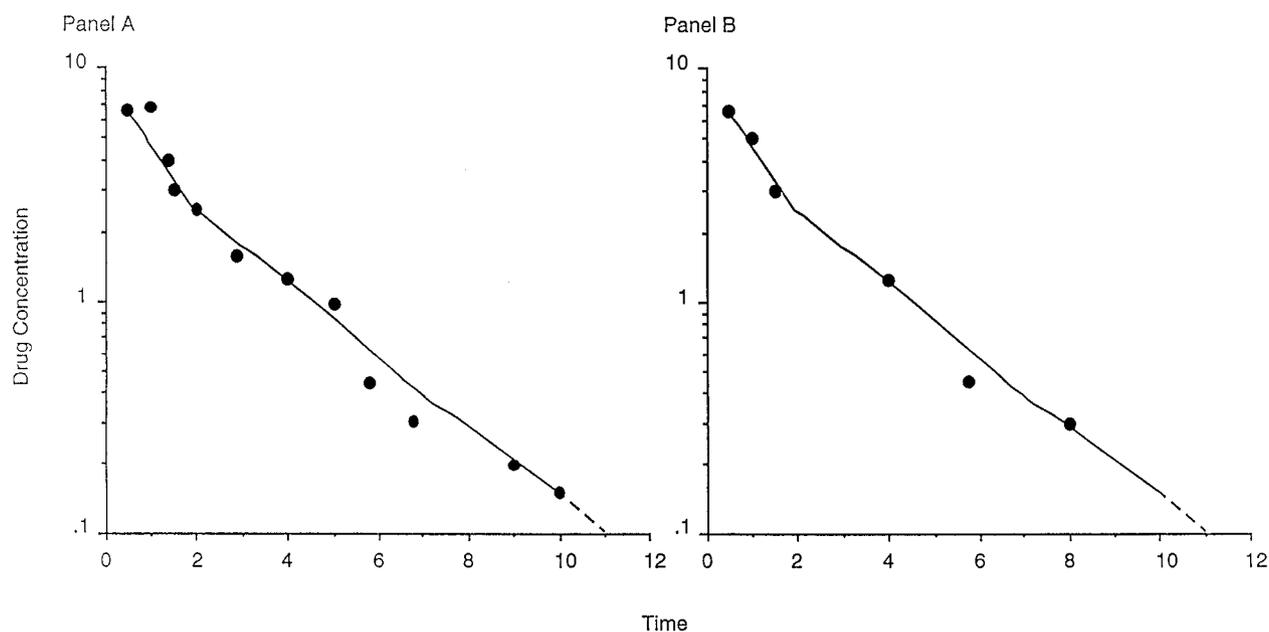
Fig 1. Typical drug concentration–time curve. Construction of a drug concentration–time curve from a traditional, aggressive sampling strategy ($n = 12$ samples, A) compared with an identical drug concentration–time curve constructed with sparse sampling ($n = 5$ samples) using optimal sampling strategy.

TABLE 2. Limitations to the Performance of Pharmacokinetic Studies in Infants and Children

Perception of ethical conflicts
   Requires diligence in safeguarding pediatric patients
Colleague ignorance of need for pediatric pharmacokinetic data
   Underestimating value for dose projections, particularly age-
      disease-related
Analytical
   Small sample volume requirement
   Sensitivity/precision constraints
   Number of samples needed to define drug disposition profile
      accurately

constraints). For example, ethical guidelines have been established for the performance of clinical studies, including drug evaluations/pharmacokinetic studies in pediatric subjects.[3,4] Such studies clearly are necessary for the safe and effective use of new compounds in pediatrics. Nevertheless, a perception still remains with some practitioners, investigators, and most importantly, many innovators that pharmacokinetic evaluations in neonates, infants, or children should not be performed because of ill defined ethical concerns and/or perceived insurmountable risks. Actually, the opposite is true. The lack of age-specific pharmacokinetic data subjects the pediatric patient to greatest risk from the administration of a drug without adequate knowledge of its disposition characteristics. Although well-intentioned, such perceptions unfortunately and unduly deprive the pediatric patient from realizing the full benefits of advances in medical science.

A number of practical limitations challenge the performance of clinical pharmacokinetic studies in infants and children. Recognizing the importance of the plasma concentration–time curve (Fig 1) to defining a drug's systemic disposition profile, the quantity of blood necessary for each sample and the number of samples necessary to describe adequately the concentration time profile are two extremely important variables that impact directly on the ability to perform such an evaluation. Furthermore, the sensitivity and precision of the analytic methodology used to quantitate the drug in the collected samples (eg, plasma, any biologic fluid) will influence the selection of sampling times and ultimately define the number of samples to be obtained (Table 2). These variables are of particular importance in pediatric patients, because the amount of blood that can be obtained is limited by the patient's age, size, and underlying disease(s), underscoring the necessity for developing accurate analytic methods that accommodate small sample volumes. The amount of blood that can be or is obtained from adult subjects in the performance of a pharmacokinetic study is rarely a focus of the study design. Unfortunately, this lack of focus on sample volume requirements has fostered the common request/requirement by most clinical and research laboratories for unnecessarily large sample volumes for analysis. Most of these laboratory determinations can be performed accurately on substantially smaller quantities of blood/biologic fluid.

Another important variable that is germane to

studies performed in both adult and pediatric subjects is cost. The greater the number of samples obtained, the greater the consumption of clinical (equipment, personnel time, etc) and laboratory resources, with an obvious increase in overall study cost. Similarly, the longer the sampling duration (eg, ≥12–24 hours), the greater the cost. One viable approach to maximize efficacy, accuracy, and safety and to minimize cost is to incorporate optimal sampling strategies in the design of clinical pharmacokinetic evaluations. Defining the optimal times to collect only those samples necessary for the construction of an accurate drug concentration–time curve minimizes the negative impact of these legitimate, clinical and logistic constraints imposed on the performance of a pharmacokinetic evaluation while preserving the integrity and validity of the data obtained.[7–10] An example of an optimal sampling design that is capable of defining accurately a drug's dis-position profile with far less sampling is shown in Fig 1A (traditional, extensive sampling) versus 1B (sparse sampling). The pharmacokinetic results obtained with both sampling strategies would be identical but far less invasive, with less blood volume removed and less costly, using the optimal sampling strategy shown in Fig 1B.

OPTIMAL SAMPLING STRATEGY

The underlying premise of optimal sampling theory (OST) is logical, constructive, and appropriate. OST incorporates mathematical models to define the optimal sampling times that allow the clinician/investigator to obtain the least number of biologic fluid samples while targeting the most "information-rich" areas of the drug concentration–time curve.[7–10] Although the total number of samples obtained over a specified time frame is a critical decision in the design of any pharmacokinetic study, the exact time a sample is collected may be more crucial (Fig 1). The important influence sampling strategy has on defining a drug's disposition profile and resultant variability in dose projections attributable to sample duration is exemplified by the propofol pharmacokinetic data presented in Table 3.[11–14]

Propofol, an alkylphenol sedative/hypnotic/anes-

TABLE 3. Important Influence of Sampling Strategy in Defining a Drug's Pharmacokinetic Profile: Propofol

Parameter	Data Presented as Mean (±SD)			
	Gepts et al[11]	Raoof et al[12]	Kantaria et al[13]	Reed et al[14]
n	18	6	53	49
Age (y)	Adult	1–3.6	3–11	0.01–16
Sample n	16	11	5–18	20
Sample duration (h)	8	4	~2.5	24
$t_{1/2}\alpha$ (min)	2.8 (1.2)	—	2	3.5 (4)
$t_{1/2}\beta$ (min)	31 (15)	—	27	38 (25)
$t_{1/2}\gamma$ (min)	355 (227)	100 (3)	329	1102.8 (106)
V_c (L/g)	16.9 (7)	—	0.32	0.67 (.07)
V_2 (L/g)	—	—	1.0	1.6 (1.4)
V_3 (L/g)	4.3 (3)	2.4 (1.4)*	5.9	30.3 (30)
Cl (mL/kg/min)	26.7	38.7 (6.8)	37	55.8 (21)

$t_{1/2}$ Indicates half-life during the α, β, and γ phases; V, volume of distribution for the central (C) and peripheral (2, 3) compartments.

thetic, is commonly used for conscious sedation to facilitate mechanical ventilation in critically ill patients and is an integral component of many intravenous anesthetic regimens. The drug has numerous advantages over other anesthetic agents including a very rapid onset of action, dose titratable level of sedation/anesthesia, and rapid dissipation of effects on discontinuation of the drug infusion. The pharmacokinetics of propofol are characterized by a complex disposition profile that is best described by a three-compartment pharmacokinetic model.[14] A number of studies have been performed to assess the drug's pharmacokinetic profile in infants and children and to determine its optimal dose in this patient population. Table 3 outlines four studies that evaluated propofol pharmacokinetics: three studies in pediatrics and, for comparative purposes, one in adults. As can be seen from the data presented in Table 3, most studies obtained a large number of samples (5–20 blood samples) per study patient over a predetermined, fixed period. The primary difference in design among these studies is the duration of time over which blood samples were obtained. After administration of a dose or discontinuation of a constant propofol infusion, blood samples were obtained for only ~2.5 hours in the study by Kataria et al,[13] 4 hours in the study by Roof and associates,[12] and 24 hours in the study by Reed and colleagues.[14] Of paramount importance is the impact the differing durations of sampling had on the resultant estimates of important propofol pharmacokinetic parameters (Table 3). Those studies with a shorter duration of sampling[12,13] tended to underestimate the drug's three volumes of distribution and overall Cl. The differences in the calculated Vd and Cl values led each group of investigators to project different dosing recommendations. These results clearly demonstrate that not only are the absolute number of samples obtained integral to defining accurately a drug's pharmacokinetic profile but also the specific time they are obtained after drug administration. Optimal sampling strategy accounts for both of these important variables by defining the most important times to obtain samples for the construction of the most information rich concentration–time curve with the least number of samples.

The validity of optimal sampling strategies in the accurate determination of the pharmacokinetic profile for a number of drugs representing different classes and model characteristics has been described previously.[7–10,15–18] The mathematical basis for OST and its integrated computer applications is beyond the scope of this article. In general, optimal sampling times are determined according to specific computer programs.[8–10,17,18] Necessary to the application of such computer analysis is an accurate and complete description of the study compound's disposition profile in the system in question. The sensitivity and accuracy of any optimal sampling strategy for a given compound depends on a prior understanding of the drug's pharmacokinetic behavior. Thus, to identify which portion(s) of the plasma concentration–time curve provides the greatest information about a drug's pharmacokinetic behavior, a more

traditional, comprehensive pharmacokinetic evaluation incorporating an increased number of samples must be performed first (eg, Fig 1A). The pharmacokinetic results of this comprehensive, traditional analysis serves as the foundation for subsequent studies incorporating the recommendations derived from optimal sampling analysis. Although this approach can be very successful in adult subjects, it is less useful in pediatric patients because of the inherent need to limit sampling owing to age and concurrent disease. As a result, formal OST is less applicable across broad dose ranges and different diseases in pediatrics than in adult practice. These and other important limitations of OST, particularly when applied to the pediatric patient, are presented in Table 4.

POPULATION-BASED PHARMACOKINETICS AND BAYESIAN FORECASTING ENHANCE THE ACCURACY OF OPTIMAL SAMPLING METHODS

As described above, a major limitation to the use of OST is the absolute need for an accurate and complete description of the drug's disposition profile, which is then used to define optimal sampling times in subsequent evaluations. Further complicating this process in pediatrics is the need for an a priori definition of the drug's pharmacokinetic profile over broad age ranges encompassing physiologic and pathophysiologic variations in major organ function (eg, renal and liver function). Combining these challenges with the necessity for obtaining small sample volumes for any laboratory analysis performed in pediatric patients inherently limits the ability to define adequately a drug's complete pharmacokinetic profile in young infants and children. Fortunately, advances in our understanding of adaptive control theory and population-based pharmacokinetics[19–24] and the availability of user-friendly computer software capable of integrating the sophisticated software that performs such analysis (eg, NONMEM, NPEM) have provided powerful tools to partially overcome many of the limitations of OST presented in Table 4.

Population pharmacokinetic analysis can provide important pharmacokinetic and pharmacodynamic information from sparse data.[22–24] In contrast to the more traditional pharmacokinetic study that is conducted routinely in a small homogenous group of subjects incorporating an extensive blood sampling strategy after a defined dose of study drug, the population approach characterizes pharmacokinetic parameter estimates using data collected from a large number of treated patients without extensive blood sampling from any individual patient. The extensive

TABLE 4. Limitations of OST

Requirement for prior knowledge of PK behavior
    Must know appropriate model
    Need reasonable estimate of parameter values
    Need feasibility of sampling duration
Decreased sensitivity in specific circumstances
    Large interindividual variability
    If no single model best describes data
    OST cannot detect model misspecification

blood sampling design of the traditional "point estimate" pharmacokinetic analysis allows assessment of variability in plasma drug concentrations between individuals (ie, within a population) and can account for differences in disposition characteristics relative to specific fixed effects such as age and gender or other patient demographics. Population analysis expands the utility of point estimate analysis to provide information on the population central values, as well as inter- and intraindividual variability in drug disposition.[25] The overall clinical goal of these analyses are to apply the pharmacokinetic results to the ongoing care of patients by serving as the foundation for the design of an optimal drug dosing regimen. To use population-based pharmacokinetic data in the determination of individual pharmacokinetic parameters for a specific patient using sparse sampling, Bayesian methods are integrated with population-based methods, as shown in Fig 2.[22]

OPTIMAL SAMPLING METHODS IN PEDIATRIC PRACTICE

The need for an accurate description of a drug's disposition profile is a prerequisite for the design of the optimal dosing regimen for a specific disease in specific patient populations. In pediatrics, such descriptions must discriminate between patients of varying ages. As discussed above, pharmacokinetic evaluations requiring extensive and rigid blood sampling strategies often are very difficult to obtain accurately in sick infants and children, as well as in other populations including the elderly and selected patients with cancer and AIDS.[24] Population-based pharmacokinetic methods that incorporate a Bayesian estimator, as outlined in Fig 2, can circumvent these limitations, providing very useful data for both investigators and clinical practitioners. The incorpo-

ration of Bayesian estimation (forecasting) with population-based pharmacokinetic methods to basic optimal sampling algorithms enhances the accuracy and applicability of estimates based on less than complete descriptions of a drug's pharmacokinetic profile (Fig 2). Advances in computer technology has fostered the development of these tools and are necessary to apply these sophisticated techniques to data analysis.[22–25]

CONCLUSIONS

The recognition of the importance of defining a drug's pharmacokinetic profile across a broad age range has fostered a plethora of pharmacokinetic studies that describe specific aspects of the disposition profile for many of the drugs used routinely in clinical practice.[1–3] Despite the availability of these data, questions continue to surface that are unanswerable from these earlier studies because of limitations in study design and their lack of applicability to infants and children. The most notable of study design flaws include overdependence on data determined from healthy adult volunteers, analysis derived from incomplete sampling strategies, and sampling times that are too brief after a dose to describe adequately the drug's actual pharmacokinetic characteristics. In the absence of specific clinical pharmacology studies, clinicians often must resign themselves to scale down doses from accepted dose ranges for adults to provide their pediatric patients with the benefits of recent advances in drug therapy. Such therapeutic approaches can frequently lead to suboptimal therapy and/or serious adverse effects.

Advances in computer technology and newer techniques in computer data analysis have provided the tools to largely circumvent many of the limitations in our current understanding of drug disposition in
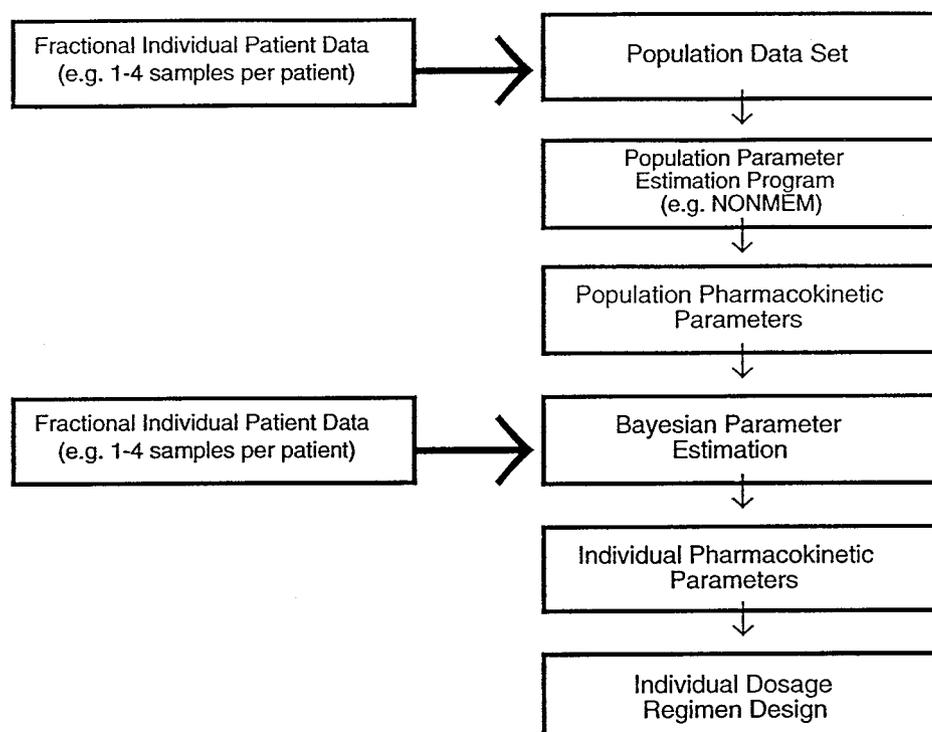

Fig 2. The interrelationship between Bayesian estimation and population pharmacokinetics (Reproduced with permission.[22])

pediatrics by providing needed pharmacokinetic information for drugs to be used in pediatric patients. Optimal sampling strategies can be determined using previously published data as the template for sample time projections. Unfortunately, the need for a prior description of a drug's disposition profile to define the optimal sampling times often limits this approach to a few, selected situations. More recently, our evolving database containing population-based pharmacokinetic data in infants and children has demonstrated the utility of sparse sampling strategies for individual patients when applied to large numbers of patients of varying demographics (eg, age, disease state, organ function) in defining important pharmacokinetic parameter estimates. Population-based data integrated with Bayesian parameter estimation capitalize on sparse, fragmented data that, when combined, describes population-specific characteristics while concurrently permitting individualization in dosage titration (Fig 2). As our database of pediatric pharmacokinetic data continues to evolve and discriminate among specific age groups, diseases, and so forth, the previous limitations placed on critical study by a perceived need for extensive sampling will become far less important in defining optimal dosing of drugs in sick infants and children.

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