Pharmacokinetics in the Child

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Pharmacokinetic studies have made many significant contributions to rational therapeutics in children. Pharmacokinetic data have helped distinguish between differences in drug disposition and drug sensitivity in children as compared to adults and led to the establishment of age-specific dosage guidelines. Factors influencing the observed differences between drug disposition in children and adults are reviewed. Specific examples utilizing anticancer drugs are presented. The use of model substrates to study hepatic drug metabolism and renal excretion in children is described and some results are discussed. The significance of genetic polymorphic drug metabolism is presented and the use of model substrates to determine individual metabolic phenotypes is described. The use of pharmacokinetic data to define the maximum-tolerated systemic exposure rather than the maximum-tolerated dosage of anticancer drugs in children is presented. — Environ Health Perspect 102(Suppl 1):111–118 (1994)

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Introduction

The application of pharmacokinetic principles and drug assay technology has been of significant benefit in recent therapeutic advances in pediatrics. Pharmacokinetics has aided in the detection and elucidation of the mechanism of numerous drug–drug and drug–disease interactions, the refinement of specific pediatric dosages of many drugs, and more specific individualization of therapy for children with a wide variety of diseases. The last decade has seen the development of rapid, sensitive, and specific assays for many drugs along with refinement of pharmacokinetic study design and use of sophisticated computerized modeling approaches that make optimal use of limited data. These developments have enhanced the ability to conduct comprehensive pharmacokinetic studies to define the population pharmacokinetics of drugs in the pediatric population and clinical monitoring studies to define the optimal use of measured drug concentrations in serum or plasma and to individualize drug therapy. This is important because for ethical reasons clinical studies of drugs can rarely be carried out in healthy volunteer children. For drugs used primarily in pediatrics, limited data from adults may be available. As a result, pharmacokinetic studies must often be performed on sick children under treatment when a variety of logistical factors (limited access to blood samples, limited volume of blood samples, etc.) as well as ethical concerns make performance of such studies difficult. Therefore, it is not surprising that, compared to adults, the amount of pediatric pharmacokinetic data available for many drugs is quite limited and for other drugs there is no pediatric information available at all. Despite these limitations, thorough pharmacokinetic studies of a number of drugs in children have yielded some very useful data.

There are a number of reasons that pharmacokinetic data must be generated from studies in children rather than simply extrapolating from adult studies. First, children are not simply miniature adults. There are a number of physiologic and metabolic processes which differ qualitatively as well as quantitatively when compared to adults. Different metabolic pathways may predominate in the biotransformation of some drugs, for example. Children often receive treatment for different diseases that don’t afflict adults. This may require treatment with different drugs or drug combinations than are typically used in adults. In addition, the pathophysiology of the disease may affect the disposition of these drugs. Finally, children may have different inherent sensitivity to drug effects, yielding significantly different dose–response or dose–toxicity curves. Pharmacokinetic data help differentiate between drug disposition differences that may be responsible for alterations in the dose–response relationship and inherent differences in drug–receptor interactions.

In the latter case, altered concentration–response relationships may be identified.

This review will discuss the use of pharmacokinetic data in children other than neonates or infants. For purposes of this discussion, the definition of age ranges used by the National Library of Medicine’s Index Medicus will be observed. Neonates are defined as less than 1 month of age, and infants are defined as 1 to 23 months of age. Children are 2 to 12 years of age, while adolescents are 13 to 18 years old. This discussion will focus on the latter two groups, pediatric patients from 2 to 18 years old.

Physiologic Factors Influencing Drug Disposition in Children

Absorption. Absorption of drugs from the gastrointestinal tract is influenced by factors such as gastric acidity, gastric and intestinal motility, enzymatic activity, permeability and maturation of the mucosal membrane, biliary function, bacterial flora, and dietary components (1). Although many of these factors undergo significant maturational changes during the first 2 years of life, less is known about changes between 2 and 18 years of age. In general, younger children may have higher gastric pH and increased gastric and intestinal
motility. Increased gastric pH slows the absorption of weak acids in these patients; conversely, weak bases are preferentially absorbed due to the effect of both pH and increased motility. Consistent with these theoretical considerations, increased phe-nobarbital absorption has been shown in older pediatric patients, while digoxin absorption is much less predictable and consistent in children compared to adults. Few additional examples are available, in part due to the difficulty of performing crossover bioavailability studies, which require administering a drug both intravenously and orally.

**Distribution.** Two major factors determine the differences in drug distribution between children and adults. The first is the relative proportion of total body water, total extracellular water, and total body fat present in children. The second is differences in protein binding, which may result from decreased albumin concentrations in some pediatric age groups. Total body water decreases from approximately 75% in full-term infants to adult values of about 55% by 12 years of age (1). The result is that children compared to adults, approximately 35% of total body weight in children versus 20 to 30% in adults. Similarly, fat content increases between 5 and 10 years of age, followed by a decrease in boys to age 17. These changes are shown graphically in Figure 1. In girls there is a rapid increase at puberty and from age 13 years, females have approximately two times greater percentage body fat compared to boys (1). Drugs that are lipophilic, such as diazepam, have a larger volume of distribution in children with higher percentage of body fat.

Plasma protein concentrations do not change appreciably between 2 and 18 years of age in healthy children (1). However, other factors (disease, malnutrition, plasma protein loss, etc.) that result in decreased albumin concentrations may increase the free fraction of highly protein-bound drugs, which results in higher concentrations of unbound active drug.

**Metabolism.** Biotransformation is important in the detoxification of many drugs. Oxidation–reduction (phase I) reactions may inactivate, activate, or convert a drug into a form in which it can undergo conjugation (phase II) reactions. Conjugation results in the attachment of a sulfate or glucuronide moiety to a drug, yielding a more polar and water-soluble compound that is more rapidly excreted in the urine. Both processes undergo maturation during the pediatric period, and some pathways may be proportionally more active in children than in adults. This can result in different metabolic profiles for a particular drug in children and adults.

There is also substantial interpatient variability in the activity of these pathways for children of the same age. This may translate into 2- to 3-fold variability in the systemic clearance of some drugs, even in children with no underlying pathophysiology that might affect drug disposition. In addition, some pathways may be completely absent in a subset of individuals as a result of a genetic defect (2). This yields a multimodal distribution of drug clearance with significantly lower clearances and much higher drug concentrations in patients who lack the enzyme required to metabolize compounds by that pathway. Such polymorphic drug metabolism can result in potentially lethal drug exposure following normal therapeutic dosages in patients who are genetically poor metabolizers.

**Excretion.** Renal function increases over the first year of life, but it is essentially at adult (corrected for body size) level by the age of 1 year and remains constant over the pediatric and adolescent age range, as shown in Figure 1. Thus, there is no general age-related change in renal function over this age period. However, there is substantial variability in renal function within the general population, and the kidneys are very sensitive to the toxic effects of a number of drugs. This can result in decreased renal function and clearance of a number of compounds or potentially toxic metabolites excreted in the urine. For those compounds primarily excreted in the urine, this can result in increased exposure and likelihood of toxicity in patients with reduced renal function. Unlike metabolic function, a number of methods have been developed that reliably and accurately estimate glomerular filtration rate (GFR). These estimates of GFR can be used to individualize the dosage of drugs and thereby increase the likelihood of efficacy and reduce the chances of toxicity in an individual patient.

**Effects of Disease.** In both children and adults, underlying diseases may affect the disposition of drugs. This has been far more extensively studied in adults than children. The most well-documented differences in drug disposition secondary to an underlying disease occur in children with cystic fibrosis. For most drugs studied, clearance is faster in children with cystic fibrosis than in healthy children or those treated for other conditions. As a result, higher dosages are required for children with cystic fibrosis both to yield a therapeutic benefit and to achieve similar serum drug concentrations as in children who do

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**Figure 1.** Developmental changes in total body water, intracellular and extracellular water, body fat, and kidney function in infants and children expressed as percentages of body weight and adult values. From Milsap et al. (1); reprinted with permission.
not have this disease. This subject recently has been reviewed extensively (3). It has also been suggested that at least part of this apparent difference in clearance may be an artifact secondary to normalizing clearance to body weight or surface area, because children with cystic fibrosis are often smaller and have less total body fat than other children (4). Therefore, although absolute clearance values may be similar in age- and sex-matched subjects with and without cystic fibrosis, clearances normalized to body weight or body surface area are larger in subjects with cystic fibrosis because they are smaller. However, other data suggest that differences in clearance persist even when clearances are normalized to ideal body weight or are left unnormalized (5). Several mechanisms may contribute to this apparently increased clearance, but the exact mechanism(s) responsible have not been established for any specific drugs.

Normalization of Pharmacokinetic Parameters

As discussed above, in pediatric pharmacokinetics it is necessary to normalize clearance and volume of distribution parameters to body size in order to compare values in children of different ages. The most common methods are to normalize these parameters to total body weight, ideal or lean body weight, or body surface area. Body surface area is generally not measured directly but calculated from one of several equations that require body weight and height (6–10). The goal of normalization is to correct for differences in parameters that are due solely to differences in body size. After normalization, these parameters are usually uncorrelated with age. We have found for several drugs that normalization to body surface area eliminates more of the age-related differences in clearance than normalization to body weight (11,12). This suggests that dosages based on body surface area will result in less variability in serum drug concentrations than dosages based on body weight. However, the opposite might be true for other drugs, depending on their route(s) of biotransformation or excretion and protein and tissue binding.

Several equations are available for calculation of body surface area (Table 1). All of them have the same general form but use different coefficients and exponents. Although the oldest of these equations (6) is widely used in pediatrics, it yields biased results, particularly in very small or young children, probably because very few young individuals were used in the study population from which this equation was derived. The Haycock and Gehan–George equations yield very similar results. We recommend the Gehan–George equation, however, because it is based on direct measurements in over 400 subjects, including both children and adults. The Haycock equation is based on direct measurements in 81 pediatric subjects.

Examples

Anticancer Drugs. Anticancer drugs provide a useful model for assessing important differences in pharmacokinetic disposition between children and adults, particularly with regard to environmental exposure to toxins. Anticancer drugs are generally administered at their maximum tolerated dosage (MTD), at which significant systemic toxicity may be anticipated. As summarized in Table 2, for many anticancer drugs the MTD in children is greater than for adults (13,14). This may be due to faster clearance of some compounds, decreased sensitivity to the toxic effects, or both. Differences in clearance may be the result of greater organ reserve (i.e., better kidney and liver function) in children, compared to adults who have been exposed to other drugs or toxins that may damage these organs. In general, however, children are often able to tolerate higher dosages (on a mg/m² basis) than adults.

One example of somewhat greater drug clearance in children than adults is the disposition of methotrexate. As shown in Figure 2, children as a group have faster methotrexate clearance than adults, and there is a general trend toward decreasing methotrexate clearance with increasing age. However, it is apparent from Figure 2, that there is substantial variability at any individual age, and clearance values in children and adults overlap somewhat. The trend toward decreasing clearance in older patients is probably due to progressive decrease in renal function with increasing age.

We have seen similar trends for clearance normalized to body weight with other

### Table 1. Body surface area equations.

| Drug                                      | Equation                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------|
| Dubois–Dubois (6)                         | \[ \text{Surface area (SA)} = 0.007184 \times \text{height (ht)}^{0.75} \times \text{weight (wt)}^{0.43} \] |
| Boyd (7)                                  | \[ \text{SA} = 0.017827 \times \text{ht}^{0.43246} \times \text{wt}^{0.51456} \] |
| Gehan–George (8)                          | \[ \text{SA} = 0.02350 \times \text{ht}^{0.43246} \times \text{wt}^{0.5071} \] |

Where SA is in square meters, height is in centimeters, and weight is in kilograms.

### Table 2. Maximal tolerated doses (MTD) of some anticancer drugs in adults and children.

| Drug                                      | Schedule | MTD, mg/m² | MTD ratio children/adults |
|-------------------------------------------|----------|------------|---------------------------|
| Dianhydrogalactitol                       | qd × 5 days | 25         | 30 | 0.83 |
| 5-Fluorouracil                            | qd × 5 days | 200        | 225 | 0.89 |
| Piperazinedione                           | qd × 4 days | 3          | 3  | 1.0  |
| Etoposide (VP-16)                         | Biweekly  | 150        | 125 | 1.20 |
| Diglycoaldehyde                           | qd × 5 days | 7,500      | 6,000 | 1.25 |
| Amscarine                                 | qd × 5 days | 50         | 40  | 1.25 |
| Daunomycin (mg/kg)                        | qd × 4 days | 1.0        | 0.8  | 1.25 |
| Doxorubicin                               | qd × 4 days | 0.8        | 0.6  | 1.33 |
| Temodar (VM-26) mg/kg                    | Biweekly  | 4.0        | 3.0  | 1.33 |
| 3-Dezaauridine (leukemia patients)        | qd × 5 days | 8.2       | 6.0   | 1.40 |
| Azaserine (mg/kg, total dose)             | Daily     | 156        | 108  | 1.44 |
| Dihydroxyanthracenedione                  | Every 3 weeks | 18        | 12  | 1.5  |
| 3-Dezaauridine (solid tumors)             | qd × 5 days | 2.8       | 1.5  | 1.85 |
| Cyclophosphamide                          | qd × 10 days | 600       | 300  | 2.00 |
| IFU-187                                   | qd × 3 days | > 2750     | 1,250 | > 2.20 |

qd, once daily.
anticancer drugs (15,12). Because some of these drugs are not excreted renally to a significant degree, it is likely that other mechanisms such as distribution in body tissues is at least partly responsible for faster clearances in younger children than in adolescents or adults.

Model Substrates. In recent years, the use of model substrates to determine drug clearance by specific elimination pathways has been developed. Specifically, our group has conducted studies with lorazepam, antipyrine, and indocyanine green to study hepatic drug clearance mechanisms (11) and technetium-99m diethylene triamine pentaacetic acid to measure glomerular filtration rate in children (16). This approach has the advantages of being able to study specific drug-metabolizing pathways using low (nontherapeutic) doses of relatively safe substances in large numbers of pediatric patients. This provides valuable information about hepatic function without exposing the children to potentially toxic effects of drugs. Lorazepam, indocyanine green, and antipyrine are administered simultaneously as a 5-min iv infusion as an assessment of glomerular filtration (lorazepam), which is removal of high extraction ratio drugs (indocyanine green), and hepatic mixed-function oxidase activity (antipyrine), as shown in Figure 3.

We have observed that clearance of two of these model substrates, indocyanine green (17) and antipyrine (18), is correlated with age when clearance is normalized to body weight (ml/min/kg). Younger children have faster clearance than adolescents or young adults (Figures 4,5). There is no difference in clearance among these three groups when clearance is normalized to body surface area (ml/min/m²). No differences were seen in lorazepam clearance among these three groups when clearance was normalized by either method (18). These results suggest that, for drugs eliminated by similar pathways to antipyrine and indocyanine green (hepatic microsomal metabolism and high-extraction ratio compounds), dosages based on body weight will yield lower serum concentrations in younger children, while dosages based on body surface area are more likely to result in similar concentrations in children and adults. One explanation for this result is the observation (Figure 6) that liver volume, estimated by ultrasound studies, is similar in children and adults when expressed as a percentage of body surface area but is greater in children when normalized to body weight, and the ratio of liver volume to weight decreases with increasing age. It has been suggested (17,18) that for several drugs, including antipyrine, "functional hepatic parenchymal mass," which approximates to liver volume, is a major determinant of hepatic drug metabolism. Our results suggest that this relationship may also be true for indocyanine green but that lorazepam is not dependent on functional hepatic parenchymal mass.

We have also used this methodology to study drug clearance in patients with cystic fibrosis (5). As mentioned earlier, patients with this disease have faster clearance for many drugs and require larger dosages to achieve equivalent clinical results. We compared results in nine patients with cancer who were treated only with surgery or radiation not involving the liver to 14 patients with cystic fibrosis. In this study, results were compared for unnormalized clearance as well as clearances normalized to body weight and body surface area. Antipyrine clearances were not different between the

![Figure 3](image.png)

Figure 3. Summary of hepatic transformation routes for lorazepam, indocyanine green, and antipyrine.
two groups, regardless of the method of normalization. However, lorazepam and indocyanine green clearances were significantly faster in the patients with cystic fibrosis. These results for lorazepam are consistent with increased glucuronidation activity, which has been demonstrated in experimentally induced cholestasis (19,20). The mechanism underlying the increased clearance of indocyanine green has not been elucidated.

Similarly, we demonstrated a significantly faster clearance, normalized to body weight, of lorazepam in six moderately malnourished children with acute lymphocytic leukemia, compared to 13 well-nourished matched controls with acute lymphocytic leukemia (21). The malnourished children also had a shorter terminal lorazepam half-life. However, clearances normalized to body surface area were not significantly different between the two groups. As with the patients with cystic fibrosis, it is possible that this may partly be due to the decreased body size of children who are malnourished. This may be particularly important when clearances are normalized to body weight. These results need to be further studied and confirmed.

In summary, model substrates are useful in comparing groups of children with different diseases to determine the effect of disease states on specific drug metabolism pathways. In addition, model substrates can help explain changes in drug metabolism during growth and maturation.

Polymorphic Drug Metabolism. It has been recognized for some time that for certain drug-metabolizing enzymes, a stable percentage of the population lacks or has greatly reduced enzyme activity (2,22). The first such genetic polymorphism to be described was N-acetylation. More recently, debrisoquin–sparteine oxidation and mephenytoin oxidation have been described. The debrisoquin hydroxylase deficiency has important potential clinical significance because over 30 other drugs have been identified as substrates for this enzyme. In addition, it is a fairly rare deficiency, with only about 5% of Caucasians classified as poor metabolizers (PMs) of this enzyme. In contrast, about 50% of Caucasians, 10% of Japanese, 5% of Canadian Eskimos, and 80 to 90% of Egyptians and Moroccans are slow acetylators. Because both of these polymorphisms can have serious adverse effects in children treated with conventional doses of drugs metabolized by one of the affected enzymes, we have developed a simple method to simultaneously phenotype patients for both these polymorphisms (23). This method involves administration of dextromethorphan, an over-the-counter antitussive that is a substrate for debrisoquin hydroxylase, and caffeine, an ingredient in Coca-Cola whose metabolite is a substrate for N-acetyltransferase. Urine is then collected over the next 4 hr, and the ratio of dextromethorphan to its metabolite, dextrorphan, in urine is determined to assign debrisoquin hydroxylase metabolizer phenotype. Similarly, the ratio of 5-acetylamo-6-formamidino-3-methyluracil to 1-methylxanthine, two metabolites of caffeine, is determined to assign acetylator phenotype. This method has been shown to be a reliable, innocuous, and noninvasive way to assess polymorphic drug metabolism in various pediatric populations (23).

Recently, this method has been used to demonstrate a lower prevalence of the debrisoquin oxidative PM phenotype in African–American subjects, compared to a comparable group of white subjects, as shown in Figure 7 (24). This study demonstrated a prevalence of the PM phenotype of 7.7% in 480 white subjects compared to 1.9% in 106 African–American subjects (p = 0.029). This difference suggests that differences in efficacy or toxicity may be seen in African–American versus white patients for drugs metabolized by this enzyme. There may also be differences in the incidence of certain diseases associated with the debrisoquin oxidative phenotype between these racial groups.

This study demonstrates how such innocuous model substrates can be used to determine the metabolic phenotype of a large population and to characterize differences between ethnic or geographic groups. In addition, this fast but relatively inexpensive method can be used to identify the small proportion of individuals who may be at risk of excessive toxicity for some drugs administered at conventional dosages. Additional studies are underway to further characterize the prevalence of the debrisoquin PM phenotype in other populations.

Pharmacodynamic Studies of Anticancer Drugs. The interpatient variability in the disposition of many drugs, including anticancer drugs, is a variable which confounds interpretation of phase I drug studies designed to determine the MTD and the dosage used in phase II studies (23). Figure 8 depicts the effect of a 3-fold range in clearance (which is quite common in children) of a hypothetical drug administered to all patients at a fixed dosage on the therapeutic or toxic effects of the drug. Although all subjects receive the same dosage of the drug, interindividual variability in clearance results in significantly different effects, as predicted by the hypothetical exposure versus effect curves.
pharmacokinetic data and principles to adjust dosages to achieve a target systemic exposure rather than administering a fixed dosage to all patients. As shown in Figure 8, when this approach is used successfully, the interpatient variability in drug disposition can be adjusted for and the actual systemic exposure (defined as the area under the concentration–time curve or area-under-the-curve [AUC]) will be much less variable than in fixed-dosage studies. This approach has been described in detail (28) and several studies using this design are currently underway.

Conclusions

Well-designed, carefully conducted pharmacokinetic studies can contribute a great deal to our knowledge of how to most appropriately use drugs in children. Children have unique physiologic and pathologic characteristics that distinguish them from adults, but in general, drug disposition is more variable than in adults, and, on average, children have faster clearances of many drugs and can tolerate larger dosages (based on body size) than adults. Pharmacokinetic parameters normalized to body surface area usually are less correlated with age than parameters normalized to body weight, suggesting that dosages based on body surface area will yield more consistent serum concentrations and therapeutic or toxic effects than dosages based on body weight. Model substrates are useful tools for noninvasively probing differences in drug disposition and identifying genetic polymorphisms. Drug disposition in children is highly variable and therefore dose-ranging studies must use pharmacokinetics to identify the optimal dosages of drugs administered near their maximum tolerated dosage. Other important differences in drug disposition between children and adults remain to be studied.

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