Applicability of the Principles of Developmental Pharmacology to the Study of Environmental Toxicants

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ABSTRACT. Although nontherapeutic xenobiotics represent the vast majority of environmental exposures during childhood, study of these compounds in children has lagged behind drug studies. Some useful extrapolation can be made from the latter, however. An increased impetus for pediatric pharmacology studies resulted from evidence of shortcomings in algorithmic approaches to dosing and the recognition of differing efficacy and toxicity in children compared with adults. With some drugs, developmental differences resulted in increased toxicity or failed efficacy; however, in others, decreased toxicity has been demonstrated. Thus, pediatric patients may not be classified arbitrarily as a susceptible population but certainly a different one compared with adults. Better designed pediatric pharmacology studies use well-documented, nonlinear changes in body composition across childhood, as well as knowledge about the impact of physical growth, mediated by complex hormonal changes. Developmental differences in all components of drug disposition, including absorption, distribution, metabolism, and excretion, have been characterized. Of these, the ontogeny of metabolism, particularly tissue-specific metabolism, is the most complex. Many knowledge gaps persist within developmental pharmacology; however, recent Food and Drug Administration regulatory action likely will ensure continued accumulation of pediatric therapeutic data. Although these data can provide important a priori information for improved environmental study design, evaluation-specific toxicant disposition by pediatric patients is clearly needed.

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The physiologic processes and principles that determine drug response in children also have an impact on the response to environmental toxicants. Thus, developmental pharmacology offers insight for developmental toxicology that is particularly useful because in vivo human developmental toxicology data are limited. However, extrapolation of pediatric pharmacology data does not provide adequate information about many toxicants, particularly those that may bioaccumulate, such as metals and polychlorinated biphenyls. For these xenobiotics, the degree to which children differ from adults in disposition is not well defined and additional studies are needed. Nevertheless, information generated to improve therapeutics in children provides insights for the disposition of some toxicants.

The application of sound scientific data to therapeutic prescribing for children recently has made significant progress. In the past, dosing guidelines were not based on biological or pharmacologic data; rather, dosing used guidelines that were based on simplistic, mathematical calculations from adult information. Over decades, the shortcomings of Clark’s rule, which normalizes dosing on the basis of relative body weight, and Von Harnak’s and Kegel’s normograms, which normalize using surface area, were recognized (reviewed in 1). In some cases, developmentally altered disposition of substrates such as chloramphenicol contributed to severe neurologic outcomes or death.2,3 More common, lesser adverse events or failed efficacy from underdosing were observed. As increasing numbers of drugs were studied in children, it became apparent that children were not always more susceptible to adverse drug reactions than adults. In some cases, for example, the nephrotoxicity associated with aminoglycoside therapy, children, particularly infants, are less susceptible.4,5 Thus, generalizations about age-dependent relative efficacy and toxicity are not reliable. In addition, children have been shown to be a heterogeneous population with the process of growth and maturation from birth to adulthood occurring in a nonlinear manner. Body weight typically doubles by 5 months of age and triples by 1 year. Body length and surface area increase by 50% and 200%, respectively, by the first birthday. Growth rates slow down across childhood until the pubertal growth spurt. Nonlinearity of maturation is reflected in nonlinear changes in drug disposition. Frequently but not always, older infants and toddlers exhibit the greatest overall drug clearance. For example, the half-life of diazepam is shortest in infants and longest in premature newborns and the elderly, with the magnitude of differences being approximately 7-fold.6,7 By the 1990s, multiple demonstrations of significant developmental differences and the ethical premise that children deserve the same standards of safety and efficacy prompted regulatory action. The Food and Drug Administration’s issuance of the 1994 Pediatric Rule and Congressional passage of the Food and Drug Administration Modernization Act in 1997 validated the medical significance of differences between children and adults. These regulatory actions prompted increased initiatives for well-designed...
studies to test the efficacy and/or toxicity of specific substrates using the knowledge guideposts derived from developmental biology and physiology, adult pharmacology, and, on occasion, animal modeling.

Similar to adults, a relationship between what the body does with a drug (pharmacokinetics) and what the drug does to the body (pharmacodynamics) is present in children. For environmental toxicants, the terms “toxicokinetics” and “toxicodynamics” are similarly defined as they are identical processes. An understanding of differential susceptibility between children and adults requires an understanding of the impact of the dynamic process of growth, development, and maturation on both processes and their interface. Description of pharmacokinetic differences alone may either incompletely describe risk or may totally miss adverse reactions present only in children. Nevertheless, a number of quantitative and qualitative differences in the anatomy and physiology of developing infants and children significantly affect the pharmacokinetics of xenobiotics.

The ontogeny of basic physiologic processes provides guideposts for understanding the mechanisms underlying differences between adults and children and assist with a priori study design for specific agents. For example, body composition changes have an impact on drug distribution and metabolism. Total body water falls from approximately 80% to 60% of body weight by 5 months of age. Simultaneously, the contribution of fat to body composition doubles. Extracellular body water progressively decreases across childhood. Knowledge of these changes in conjunction with the characteristics of a xenobiotic provide insight into distribution volumes that partially determine concentration/dose relationships. The liver and kidney, the predominant organs of xenobiotic metabolism and excretion, are several-fold greater relative to body weight in children compared with adults. The process of physical growth may have both direct and indirect impacts on the disposition of xenobiotics. Growth hormone levels are increased greatly during the newborn period and during the growth spurs of puberty. Among growth hormone–deficient prepubertal children, physiologic growth hormone replacement was associated with a 2-fold increase in the half-life of amobarbital. Consistent with this and the known pubertal growth hormone surge, caffeine metabolism decreases at puberty, representing downregulation of CYP1A2. Mechanistically, growth hormone has an impact on many pathways involved in the xenobiotic response, stimulating early response genes such as c-fos and c-jun, as well as inducing HNF-6, a hepatic transcription factor that activates a network of liver transcription factors that control cytochromes P450 and plasma protein transcription (reviewed in 16).

Pharmacokinetics classically encompasses 4 processes: absorption, distribution, metabolism, and excretion. Developmental variation in absorption is attributable to differences in gastric pH, gastric emptying, pancreatic enzymes, and first-pass metabolism of drugs in the stomach, small intestine, or liver. Oral absorption differences are most notable in early infancy as demonstrated by the absorption rate constants of phenobarbital, phenytoin, and digoxin. Significant absorption of topical agents, such as hexachlorophene and theophylline, has been shown to occur and is likely attributable to developmental differences in skin thickness, vascularization, and hydration. Distribution of drugs may differ because of changes in body composition, protein, or tissue binding. For example, p-tubocurarine, a drug with limited tissue uptake that distributes largely into body water, has approximately a 2-fold greater volume of distribution in neonates compared with adults, and these distribution changes mirror the pattern of ontogeny of extracellular fluid. The free fraction of total drug available for diffusion into tissues is substantially higher among newborns for drugs such as lidocaine and phenytoin because of qualitative and quantitative differences in protein binding. Tissue drug binding, which is a more direct marker of the pharmacokinetic-pharmacodynamic interface than plasma values, may also be age dependent. The binding of the cardiac glycoside digoxin to myocardium is approximately 6-fold greater in infants when either normalized to the amount of cardiac tissue studied or evaluated using the myocardial/plasma ratio. Although the distribution of drugs across membranes recently has been shown to be influenced by a growing number of drug transporters, little is known about their ontogeny. P-glycoprotein, for example, plays an obstructive role at the blood-brain barrier, as well as across the brush border of the small intestine. When present, ontogenetic differences in transporter expression in a tissue-specific manner may explain the increased likelihood of central nervous system transfer of the endogenous neurotoxicant unconjugated bilirubin among increasingly premature infants.

Of the multiple processes involved in xenobiologic disposition, metabolism is the most complicated. In part, this complexity relates to the wide variety of enzymes that participate in drug metabolism and the great degree of variance in tissue-specific expression. For example, the major family of drug-metabolizing phase I enzymes, the cytochromes P450, are expressed in >17 isofoms, but expression varies by tissue and by developmental status (reviewed in 28). In contrast to rodent models, human CYP expression occurs relatively early, generally before birth or within the first several months of life. For example, CYP2E1, an enzyme responsible for the oxidation of drugs, protoxicants, and procarcinogens, is expressed by 8 weeks in human cephalic tissue at greater levels than that of hepatic tissue. Hepatic expression is seen as early as the second trimester and rapidly increases after birth with adult expression levels being reached by 3 months. In contrast to the fetal expression of CYP2E1, CYP1A2, an enzyme also involved in the metabolism of many drugs and toxicants, is not expressed until several months of postnatal age (reviewed in 28). This developmental lag and the progression of CYP1A2 expression with age partially explain the long caffeine half-life in neonates and the need for age-dependent increases in theophylline dosing. For drugs exclu-
sively metabolized by a single hepatic enzyme, such as S-warfarin, simultaneous consideration of both liver size and genotype may limit the pharmacokinetic differences between adults and children.\textsuperscript{34} Thus, assessment of drug or toxicant age-dependent disposition should consider specific enzyme expression and its ontogenetic determinants, genetic variation, and tissue specificity. Studies of specific agent total disposition using measures such as total parent drug clearance or half-life document significant pharmacokinetic differences between children and adults. However, if only the kinetics of the parent drug are assessed, then important age-dependent differences in the underlying metabolic pathways may be missed. These differences result in differential shunting of the parent drug into pathways that may be more or less toxic, such as developmental differences in acetaminophen and carbamazepine disposition.\textsuperscript{35,36} Finally, urinary excretion is determined by water-soluble compounds being filtered by the glomerulus and/or secreted by the tubule. Tubular secretion matures more slowly than glomerular filtration, and peak renal capacity is reached at approximately 2 to 3 years of age.\textsuperscript{37,38} Compounds, such as most penicillins, that are excreted primarily by glomerular filtration and/or secreted by the tubule. Tubu-
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strained by secretion commonly exhibit significant age-dependent differences that necessitate a change in dosing.\textsuperscript{39}

In summary, growth and development add complexity to pharmacokinetics and pharmacodynamics and their interface. Children may experience altered efficacy and may be more or less vulnerable to adverse reactions. Pondering questions about the differing susceptibility of children requires consideration of the specific substrate, the ontogeny of the specific processes involved, and division of childhood into physiologically relevant age groups. Because of the known differences across species, animal data must be modeled appropriately and mechanistically relevant. Although much progress has been made in improving dosing for children, many challenges persist, including better understanding of multixenobiotic exposures; the role of tissue-specific ontogeny; the question of age-dependent xenobiotic transporters; the predictive value of surrogate endpoints in predicting long-term efficacy and toxicity, particularly with chronic exposures; and additional study of the impact of disease states that are unique to children. As knowledge gaps are filled, efficacy and safety of therapeutic agents will continue to improve for pediatric patients. To some degree, information about therapeutic agents in children will continue to be more complete than that about environmental toxicants because intentional toxicant dosing studies are unethical. However, additional observational studies of many toxicants are both possible and necessary to determine whether children metabolize these xenobiotics differently from adults. Furthermore, when present, developmental toxicokinetic differences ultimately must be linked to clinically relevant disease endpoints. Developmental pharmacology data provide a plethora of physiologic information that can be used to better design such studies of many ubiquitous toxicants, including heavy metals, pesticides, and solvents.

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