REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children

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INFANTS AND CHILDREN ARE FAR DIFFERENT FROM ADULTS IN TERMS OF societal, psychosocial, behavioral, and medical perspectives. More than 100 years ago Dr. Abraham Jacobi, the father of American pediatrics, recognized the importance of and need for age-appropriate pharmacotherapy when he wrote, "Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but . . . has its own independent range and horizon."[1] As our knowledge of normal growth and development has increased in the past several decades, so has our recognition that developmental changes profoundly affect the responses to medications and produce a need for age-dependent adjustments in doses.

Before the integration of developmental pharmacology into clinical and therapeutic decision making, numerous approaches to determining pediatric drug doses were recommended (e.g., formulas such as Young's rule and Clark's rule). Some of these approaches use discrete age points, whereas others use allometric principles (i.e., those based on relative body size) that generally assume there are predictable, linear relations between mass (e.g., cell mass and body weight) and body-surface area among infants, children, adolescents, and adults.[2] However, human growth is not a linear process; age-associated changes in body composition and organ function are dynamic and can be discordant during the first decade of life. Thus, simplified dosing approaches are not adequate for individualizing drug doses across the span of childhood.[3] As a result, the use of dosing equations has largely been replaced by adjustment (or normalization) of the drug dose for either body weight or body-surface area. Although such guidelines are generally adequate for initiating therapy, they may fall short when it comes to continued or long-term treatment, since maintenance therapy must be individualized on the basis of developmental differences in pharmacokinetics, pharmacodynamics, or both. Thus, the provision of safe and effective drug therapy for children requires a fundamental understanding and integration of the role of ontogeny in the disposition and actions of drugs.

ABSORPTION OF DRUGS

A variety of methods are used to administer drugs to children, the most common of which involve extravascular routes. A therapeutic agent administered by means of any extravascular route must overcome chemical, physical, mechanical, and biologic barriers in order to be absorbed. Developmental changes in absorptive surfaces such as the gas-

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trointestinal tract, skin, and pulmonary tree can influence the rate and extent of the bioavailability of a drug.

Most drugs are administered orally to children. Changes in the intraluminal pH in different segments of the gastrointestinal tract can directly affect both the stability and the degree of ionization of a drug, thus influencing the relative amount of drug available for absorption. During the neonatal period, intragastric pH is relatively elevated (greater than 4) consequent to reductions in both basal acid output and the total volume of gastric secretions.[4,5] Thus, oral administration of acid-labile compounds such as penicillin G produces greater bioavailability in neonates than in older infants and children.[6] In contrast, drugs that are weak acids, such as phenobarbital, may require larger oral doses in the very young in order to achieve therapeutic plasma levels.[7] In addition, the ability to solubilize and subsequently absorb lipophilic drugs can be influenced by age-dependent changes in biliary function. Immature conjugation and transport of bile salts into the intestinal lumen result in low intraduodenal levels despite the presence of blood levels that exceed those of adults.[8,9]

Gastric emptying and intestinal motility are the primary determinants of the rate at which drugs are presented to and dispersed along the mucosal surface of the small intestine. At birth, the coordination of antral contractions improves, resulting in a marked increase in gastric emptying during the first week of life.[10,11] Similarly, intestinal motor activity matures throughout early infancy, with consequent increases in the frequency, amplitude, and duration of propagating contractions.[12] Unfortunately, few studies have systematically evaluated the effect of these developmental changes on drug absorption in infants and children. The few bioavailability studies that have examined the absorption of drugs (e.g., phenobarbital, sulfonamides, and digoxin) and nutrient macromolecules (e.g., arabinose and xylose) suggest that the processes of both passive and active transport are fully mature in infants by approximately four months of age.[13] Generally, the rate at which most drugs are absorbed is slower in neonates and young infants than in older children; thus, the time required to achieve maximal plasma levels is prolonged in the very young.

Additional developmental factors have a role in altered drug absorption in infants and children. Although it is generally assumed that intestinal surface area is reduced in early life, the average intestinal length as a percentage of adult values exceeds other anthropometric measurements throughout development.[14] Villous formation begins at eight weeks of gestation and matures by week 20,[15] rendering it unlikely that reductions in the surface area of the small intestine contribute to reduced absorption. Furthermore, age-associated changes in splanchnic blood flow during the first two to three weeks of life[16-18] may influence absorption rates by altering the concentration gradient across the intestinal mucosa.

Developmental differences in the activity of intestinal drug-metabolizing enzymes and efflux transporters that can markedly alter the bioavailability of drugs are incompletely characterized.[19] Examination of duodenal- and jejunal-biopsy specimens from infants and children suggests that epoxide hydrolase and glutathione peroxidase activities demonstrate little age dependence, whereas the intestinal activity of cytochrome P-450 1A1 (CYP1A1) appears to increase with age.[20] In contrast, biopsy of the distal duodenum suggests that glutathione-S-transferase activity decreases from infancy through early adolescence, as reflected by reduced apparent oral clearance of busulfan, a substrate for this enzyme.[21] There are no data concerning developmental expression of the efflux transporter P-glycoprotein (also known as MDR1) in the human intestine. Finally, changes in the intestinal microflora during infancy are suggested by the finding that the urinary excretion of metabolites such as digoxin reduction products produced by bacterial (enzyme) degradation is age dependent.[22]

Developmental changes also can alter the absorption of drugs by other extravascular routes. Enhanced percutaneous absorption during infancy may be accounted for, in part, by the presence of a thinner stratum corneum in the preterm neonate[23] and by the greater extent of cutaneous perfusion and hydration of the epidermis (relative to adults) throughout childhood.[24,25] The ratio of total body-surface area to body mass in infants and young children far exceeds that in adults. Thus, the relative systemic exposure of infants and children to topically applied drugs (e.g., corticosteroids, antihistamines, and antiseptics) may exceed that in adults, with consequent toxic effects in some instances.[26,27]

Reduced skeletal-muscle blood flow and inefficient muscular contractions (responsible for drug dispersion) may reduce the rate of intramuscular absorption of drugs in neonates.[28] However, the influence of these factors on bioavailability may be off-

set by the relatively higher density of skeletal-muscle capillaries in infants than in older children.[29] Accordingly, evidence supports the concept that intramuscular absorption of specific agents (e.g., amikacin and cephalothin) is more efficient in neonates and infants than in older children.[30,31]

The bioavailability of extensively metabolized compounds administered rectally may be enhanced in neonates and very young infants, most likely owing to the developmental immaturity of hepatic metabolism rather than to enhanced mucosal translocation. However, infants have a greater number of high-amplitude pulsatile contractions in the rectum than do adults, which can enhance the expulsion of solid forms of drugs,[32] effectively decreasing the absorption of drugs such as erythromycin and acetaminophen.[33-35]

Intrapulmonary administration of drugs (inhalation) is increasingly being used in infants and children. Although the principal goal of this route of administration is to achieve a predominantly local effect, systemic exposure does occur, as evidenced by the suppression of cortisol that occurs in association with inhaled corticosteroid therapy.[36] Developmental changes in the architecture of the lung and its ventilatory capacity (e.g., minute ventilation, vital capacity, and the respiratory rate) most likely alter the patterns of drug deposition and consequent systemic absorption after the intrapulmonary administration of a drug. Unfortunately, current investigations have focused on the effects that either the device or the formulation has on the delivery and deposition of inhaled drugs rather than on the rate and extent of their pulmonary absorption.[37]

DISTRIBUTION OF DRUGS

Age-dependent changes in body composition (Fig. 1)[38] alter the physiologic spaces into which a drug may be distributed. The relatively larger extracellular and total-body water spaces in neonates and young infants as compared with adults, coupled with adipose stores that have a higher ratio of water to lipid, result in lower plasma levels of drugs in these compartments when the drugs are administered in a weight-based fashion.[49] The influence of age on the apparent volume of distribution is not as readily apparent for lipophilic drugs that are primarily distributed in tissue.

Changes in the composition and amount of circulating plasma proteins such as albumin and α_1-acid glycoprotein can also influence the distribution of highly bound drugs. A reduction in the quantity of total plasma proteins (including albumin) in the neonate and young infant increases the free fraction of drug, thereby influencing the availability of the active moiety.[50,51] The presence of fetal albumin (which has reduced binding affinity for weak acids) and an increase in endogenous substances (e.g., bilirubin and free fatty acids) capable of displacing a drug from albumin binding sites during the neonatal period may also contribute to the higher free fractions of highly protein-bound drugs in neonates.[50-52] Other factors associated with development or disease, such as variability in regional blood flow, organ perfusion, permeability of cell membranes, changes in acid–base balance, and cardiac output, can also influence drug binding and distribution.

Although much of the distribution of a drug is the result of simple passive diffusion along concentration gradients and associated binding of the drug to tissue components, the expression by tissue of transporters capable of producing a biologic barrier also contributes. P-glycoprotein, a member of the ATP-binding cassette family of transporters that functions as an efflux transporter capable of extruding selected toxins and xenobiotics from cells, is one such example. The expression and localization of P-glycoprotein in specific tissues facilitate its ability to limit cellular uptake of xenobiotic substrates to these sites (e.g., the blood–brain barrier, hepatocytes, renal tubular cells, and enterocytes).[53]

There are limited data on the ontogeny of the expression of P-glycoprotein in humans. A single study of the expression of P-glycoprotein in the central nervous system in tissue obtained post mortem from neonates born at 23 to 42 weeks of gestational age suggests a pattern of localization similar to that in adults late in gestation and at term. However, the level of expression of P-glycoprotein appeared to be lower than that in adults.[54] Limited data in neonates suggest that the passive diffusion of drugs into the central nervous system is age dependent, as reflected by the progressive increase in the ratios of brain phenobarbital to plasma phenobarbital from 28 to 39 weeks of gestational age, demonstrating the increased transport of phenobarbital into the brain.[55] Although studies in animals suggested that the observed changes in blood flow and pore density (rather than pore size) are responsible for the increased permeability of the central nervous system to drugs in neonates and young infants, this possibility has not been systematically studied in humans.

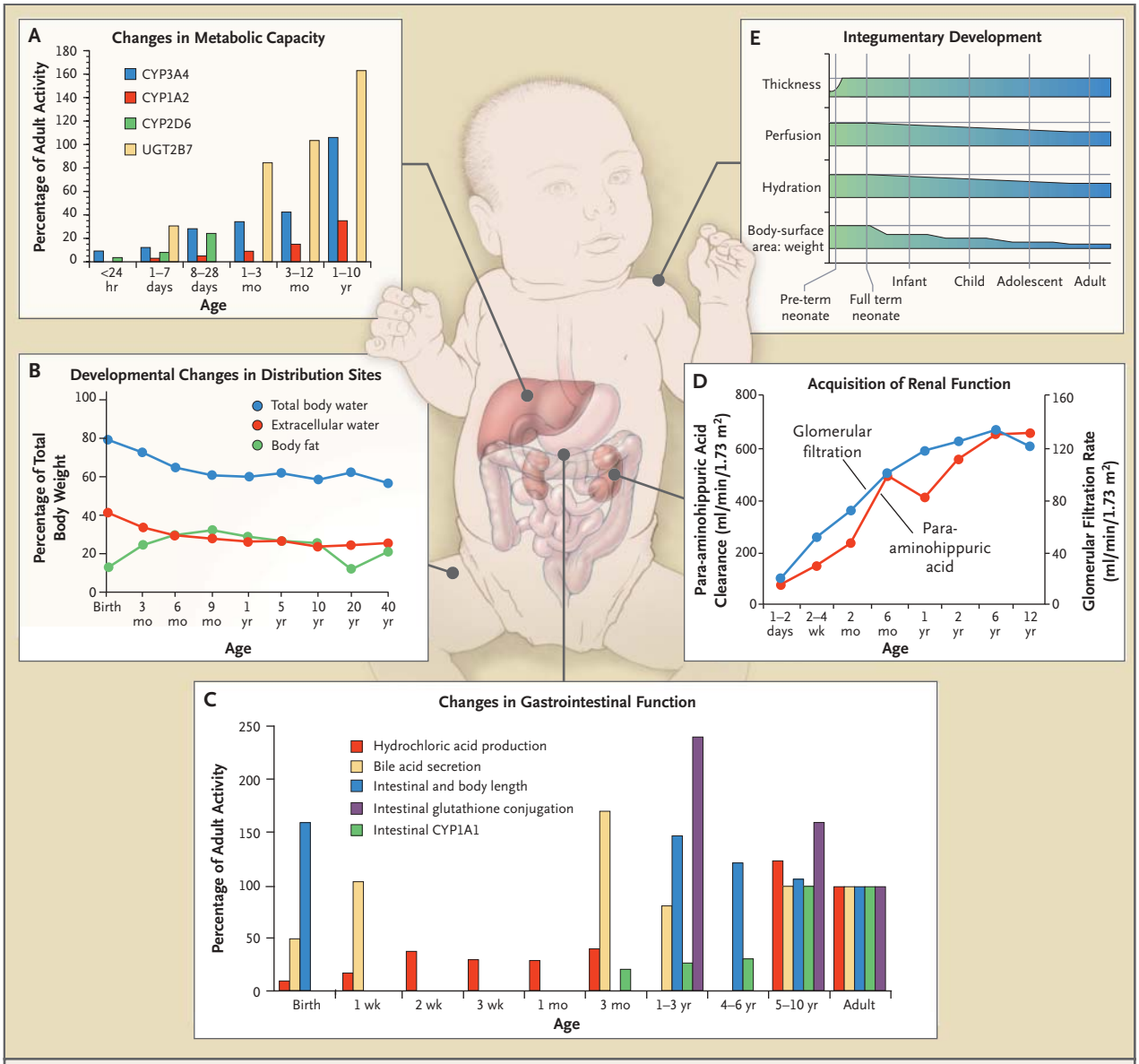

Figure 1. Developmental Changes in Physiologic Factors That Influence Drug Disposition in Infants, Children, and Adolescents.

Physiologic changes in multiple organs and organ systems during development are responsible for age-related differences in drug disposition. As reflected by Panel A, the activity of many cytochrome P-450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the first two months of life. In addition, the acquisition of adult activity over time is enzyme- and isoform-specific. Panel B shows age-dependent changes in body composition, which influence the apparent volume of distribution for drugs. Infants in the first six months of life have markedly expanded total-body water and extracellular water, expressed as a percentage of total body weight, as compared with older infants and adults. Panel C shows the age-dependent changes in both the structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes (Panel A), the activity of cytochrome P-450 1A1 (CYP1A1) in the intestine is low during early life. Panel D summarizes the effect of postnatal development on the processes of active tubular secretion — represented by the clearance of para-aminohippuric acid and the glomerular filtration rate, both of which approximate adult activity by 6 to 12 months of age. Panel E shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body-surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. Data were adapted from Agunod et al.,[4] Rodbro et al.,[5] Poley et al.,[9] Gibbs et al.,[21] Okah et al.,[24] West et al.,[27] Friis-Hansen,[38] Young and Lietman,[39] Hines and McCarver,[40] Treluyer et al.,[41] Kinirons et al.,[42] Pynnönen et al.,[43] Aranda et al.,[44] Miller et al.,[45] Barrett et al.,[46] Murry et al.,[47] and Robillard et al.[48]

DRUG METABOLISM

Delayed maturation of drug-metabolizing enzyme activity may account for the marked toxicity of drugs in the very young, as exemplified by the cardiovascular collapse associated with the gray syndrome in newborns treated with chloramphenicol.[39,56] Important developmental changes in the biotransformation of drugs prompt the need for age-appropriate dose regimens for many drugs commonly used in neonates and young infants, such as the methylxanthines, nafcillin, third-generation cephalosporins, captopril, and morphine. Distinct patterns of isoform-specific developmental changes in the biotransformation of drugs are apparent for many phase I (primarily oxidation) and phase II (conjugation) drug-metabolizing enzymes.[40,57] Selected examples are summarized below.

DEVELOPMENT OF PHASE I ENZYMES

The expression of phase I enzymes such as the P-450 cytochromes (CYPs) changes markedly during development. CYP3A7, the predominant CYP isoform expressed in fetal liver, may protect the fetus by detoxifying dehydroepiandrosterone sulfate[58] and potentially teratogenic derivatives of retinoic acid.[59] The expression of CYP3A7 peaks shortly after birth and then declines rapidly to levels that are undetectable in most adults.[60] Distinct patterns of isoform-specific developmental expression of CYPs have been observed postnatally. Within hours after birth, CYP2E1 activity surges,[61] and CYP2D6 becomes detectable soon thereafter.[62] CYP3A4 and CYP2C (CYP2C9 and CYP2C19) appear during the first week of life,[41,60] whereas CYP1A2 is the last hepatic CYP to appear, at one to three months of life.[63]

Insight into the ontogeny of drug metabolism can also be derived from pharmacokinetic studies of drugs metabolized by specific CYP isoforms. The clearance of intravenously administered midazolam from plasma is primarily a function of hepatic CYP3A4 and CYP3A5 activity,[42] and the level of activity increases from 1.2 to 9 ml per minute per kilogram of body weight during the first three months of life.[64] The clearance of carbamazepine from plasma, which is also largely dependent on CYP3A4,[65] is greater in children than in adults,[43,66] thereby necessitating higher weight-adjusted doses (i.e., milligrams per kilogram of body weight) of the drug to achieve therapeutic plasma levels.

CYP2C9 and, to a lesser extent, CYP2C19 are primarily responsible for the biotransformation of phenytoin.[67] The apparent half-life of phenytoin is prolonged (to approximately 75 hours) in preterm infants, but it decreases to approximately 20 hours in term infants during the first week of life and to approximately 8 hours after the second week of life.[68] Concentration-dependent metabolism (i.e., that accounted for by Michaelis–Menten kinetics) does not appear until approximately 10 days of age, demonstrating the developmental acquisition of CYP2C9 activity.[69] The maximal velocity of phenytoin (which reflects the extent of CYP2C9 activity) declines from an average value of 14 mg per kilogram per day in infants to 8 mg per kilogram per day in adolescents,[70] producing a profound corresponding age-related difference in the daily therapeutic dose requirement.

Caffeine and theophylline, both substrates for CYP1A2, are commonly prescribed for neonates and young infants. In infants older than four months of age, the clearance of caffeine from plasma primarily reflects demethylation activity mediated by CYP1A2 and approaches adult values[44]; by the time infants are six months of age (as reflected by theophylline plasma clearance), the rate may exceed that in adults.[71,72] Furthermore, the rate of demethylation of caffeine in adolescent girls appears to decline to levels seen in adults once girls reach Tanner stage 2, whereas it occurs at Tanner stage 4 or 5 in adolescent boys,[73] thus demonstrating an apparent sex-based difference in the ontogeny of CYP1A2.

DEVELOPMENT OF PHASE II ENZYMES

The ontogeny of conjugation reactions (i.e., those involving phase II enzymes) is less well established than the ontogeny of reactions involving phase I enzymes. Available data indicate that the individual isoforms of glucuronosyltransferase (UGT) have unique maturational profiles with pharmacokinetic consequences. For example, the glucuronidation of acetaminophen (a substrate for UGT1A6 and, to a lesser extent, UGT1A9) is decreased in newborns and young children as compared with adolescents and adults.[45] Glucuronidation of morphine (a UGT2B7 substrate) can be detected in premature infants as young as 24 weeks of gestational age.[46] The clearance of morphine from plasma is positively correlated with post-conceptional age and quadruples between 27 and 40 weeks postconceptual age, thereby necessitating corresponding increases in the dose of morphine to maintain effective analgesia.[74]

A consistent observation in clinical studies of drugs metabolized in the liver is an age-dependent increase in plasma clearance in children younger than 10 years of age, as compared with adults, which necessitates relatively higher weight-based dose requirements. The mechanisms underlying these age-related increases in plasma drug clearance are largely unknown. A single small in vitro study failed to identify developmental differences in hepatic expression of CYPs.[75] However, a detailed study of the CYP2C9 substrate S-warfarin[76] confirmed that the clearance of unbound oral S-warfarin was significantly greater among prepubertal children than among pubertal children or adults after adjustment for total body weight or body-surface area but not estimated liver weight (Fig. 2). However, the clearance of antipyrine, which is dependent on several CYPs,[77,78] correlates significantly with age, even after correction for liver weight.[47] Therefore, it is unlikely that the greater drug clearance in infants and young children can be attributed solely to a disproportionate increase in liver mass, given that the weight of the liver as a percentage of total body mass reaches a maximum between one and three years of age and declines to adult values during adolescence. This assertion would appear to be particularly true for drugs metabolized by enzymes with substantial extrahepatic expression (e.g., CYP3A4, CYP3A5, and isoforms of UGT).

RENAL ELIMINATION OF DRUGS

Maturation of renal function is a dynamic process that begins during fetal organogenesis and is complete by early childhood. The developmental increase in the glomerular filtration rate relies on the existence of normal nephrogenesis, a process that begins at 9 weeks of gestation and is complete by 36 weeks of gestation, followed by postnatal changes in renal and intrarenal blood flow.[48] The glomerular filtration rate is approximately 2 to 4 ml per minute per 1.73 m^2 in term neonates, but it may be as low as 0.6 to 0.8 ml per minute per 1.73 m^2 in preterm neonates. The glomerular filtration rate increases rapidly during the first two weeks of life and then rises steadily until adult values are reached at 8 to 12 months of age.[79,80] Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life.

Collectively, developmental changes in renal function can dramatically alter the plasma clearance of compounds with extensive renal elimination and thus constitute a major determinant of the age-appropriate selection of a dose regimen. Pharmacokinetic studies of drugs such as ceftazidime[80] and famotidine,[81] which are excreted primarily by the glomeruli, have shown correlations between plasma drug clearance and normal maturational changes in renal function. For example, tobramycin is eliminated predominantly by glomerular filtration, necessitating dosing intervals of 36 to 48 hours in preterm newborns and of 24 hours in term newborns.[82] Failure to account for the ontogeny of renal function and to adjust aminoglycoside dosing regimens accordingly can result in the exposure of infants to potentially toxic serum levels of these drugs.[83] Furthermore, concomitant administration of medications such as betamethasone and indomethacin may alter the normal pattern of renal maturation in neonates.[84] Thus, for drugs that are primarily eliminated by the kidney, clinicians must individualize treatment regimens in an age-appropriate fashion that reflects both maturational and treatment-associated changes in kidney function.

PHARMACODYNAMICS

Although it is generally accepted that development can alter the action of and response to a drug, little information exists about the effect of human ontogeny on interactions between drugs and receptors and the consequence of these interactions (i.e., the pharmacodynamics). For example, the apparent developmental differences in the pharmacodynamics of famotidine in neonates[81] are directly associated with the reduced plasma clearance of the drug owing to the developmentally dependent reductions in the glomerular filtration rate. However, data on certain other drugs appear to support the existence of true age-dependent differences either in the interaction between a drug and its specific receptor (e.g., warfarin[76] and cyclosporine[85]) or in the relation between the plasma level and the pharmacologic effect of a given drug (e.g., sedation associated with midazolam[86,87]).

Apparent pharmacogenetic determinants of the action of a drug may contribute to the age-dependent differences in the response to treatment of children with certain well-defined diseases (e.g., asthma and leukemia)[88,89] and to the likelihood of severe adverse events (e.g., the hepatotoxicity of valproic acid is increased in young infants).[90] Recent evidence of the age-dependent expression of intestinal motilin receptors and the modulation of antral

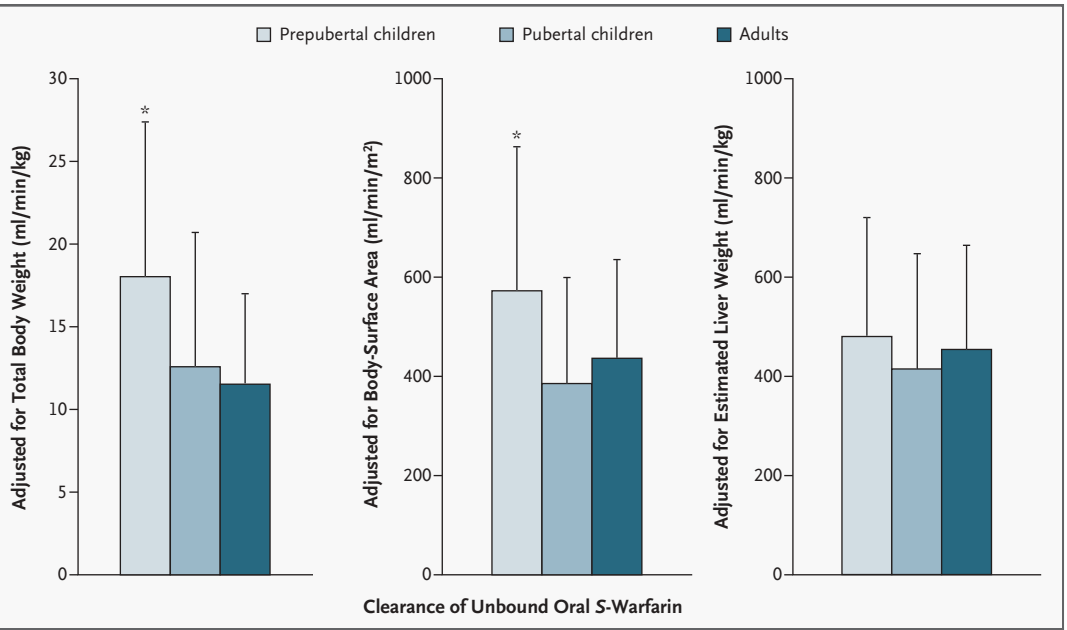

Figure 2. Age Dependence of the Clearance of Unbound Oral *S*-Warfarin after Adjustment for Total Body Weight, Body-Surface Area, or Estimated Liver Weight.

Asterisks indicate a significant difference ($P<0.05$) between the prepubertal group and the other groups. T bars are standard deviations. Data were adapted from Takahashi et al.[76]

contractions appears to have implications with respect to the prokinetic effects of erythromycin in preterm infants.[91] Clearly, any assessment of pharmacodynamics in children must take into consideration the influence of ontogeny on the efficacy or safety of a given drug with respect to age-dependent differences.

AGE-SPECIFIC DOSING REGIMENS

Most current age-specific dosing requirements are based on the known influence of ontogeny on the disposition of drugs.[3] As summarized in Figure 1, developmental changes in physiology produce many of the age-associated changes in the absorption, distribution, metabolism, and excretion of drugs that culminate in altered pharmacokinetics and thus serve as the determinants of age-specific dose requirements. Current gaps in our knowledge (e.g., the lack of complete developmental profiles of hepatic and extrahepatic drug-metabolizing enzymes and questions about the expression of drug transporters that may influence the clearance or bioavailability of a drug) preclude the use of simple dosage formulas and allometric scaling.[92] Such approaches may have potential clinical utility in children older than eight years of age and in adolescents, whose organ function and body composition approximate that of young adults, but these approaches have limited value in very young infants and children, who have dramatic age-related differences in drug disposition.

Examples of age-specific dosing regimens commonly used for selected drugs that are based on age-dependent differences in drug disposition are given in Table 1. For specific drugs, there are dramatic differences in the dose and the dosing interval used in children and those used in adults. The particular dosing regimens chosen as examples were obtained from a widely used handbook,[93] which along with other recognized compendiums, represents the state-of-the-art approaches to pediatric dosing. In the absence of complete pharmacokinetic data or established dosing guidelines, a method to approximate the initial dose for an infant on the basis of the established dose for adults has been proposed that uses descriptors of body size, such as ideal body weight adjusted for height, body-surface area, and the apparent volume of distribution.[94] This method is illustrated by the following equations:

Table 1. Examples of Age-Specific Usual Doses of Drugs Commonly Used in Pediatric Medicine.*

Drug	Average Dose				Primary Determinants of Difference in Age-Related Doses
	Neonates	Infants	Children	Adults	
Gentamicin	2.5 mg/kg every 12 hr	2.5 mg/kg every 6–8 hr	2.5 mg/kg every 8 hr	1–2 mg/kg every 8 hr	Pharmacokinetic: apparent renal clearance and apparent volume of distribution
Ceftazidime	50 mg/kg every 12 hr	50 mg/kg every 8 hr	50 mg/kg every 8 hr	14–28 mg/kg every 8–12 hr	Pharmacokinetic: apparent renal clearance and apparent volume of distribution
Clindamycin	15 mg/kg every 8 hr	10 mg/kg every 6–8 hr	10 mg/kg every 6–8 hr	8–12 mg/kg every 8–12 hr	Pharmacokinetic: apparent hepatic clearance
Carbamazepine	Not established	3–10 mg/kg every 8 hr	3–10 mg/kg every 8 hr	5–8 mg/kg every 12 hr	Pharmacokinetic: apparent hepatic clearance
Phenytoin	2.5–4.0 mg/kg every 12 hr	2–3 mg/kg every 8 hr	2.3–2.6 mg/kg every 8 hr	2 mg/kg every 12 hr	Pharmacokinetic: apparent hepatic clearance
Phenobarbital	3–4 mg/kg every 24 hr	2.5–3.0 mg/kg every 12 hr	2–4 mg/kg every 12 hr	0.5–1.0 mg/kg every 12 hr	Pharmacokinetic: apparent hepatic clearance, followed by apparent volume of distribution
Theophylline	0.5 mg/kg/hr	0.6–0.7 mg/kg/hr	1.0–1.2 mg/kg/hr	0.5–0.7 mg/kg/hr	Pharmacokinetic: apparent hepatic clearance
Digoxin	4–8 μg/kg every 24 hr	7.5–12.0 μg/kg every 24 hr	3–8 μg/kg every 24 hr	1.4–4.0 μg/kg every 24 hr	Pharmacokinetic (apparent renal clearance followed by apparent volume of distribution) and pharmacodynamic
Captopril†	0.01–0.05 mg/kg every 8–12 hr	0.15–0.3 mg/kg every 8–12 hr	0.2–0.4 mg/kg every 12–24 hr	0.2–0.4 mg/kg every 8–12 hr	Pharmacokinetic: apparent hepatic clearance
Ranitidine	0.75–1.0 mg/kg every 12 hr	0.75–1.0 mg/kg every 12 hr	1 mg/kg every 6–12 hr	0.7 mg/kg every 6–8 hr	Pharmacokinetic: apparent renal clearance, followed by apparent volume of distribution

* The usual doses in adults were adjusted for an average ideal adult body weight of 70 kg. All other doses reflected average ranges recommended in a widely used pediatric handbook.[93] Unless otherwise noted, all drugs are given intravenously. The information contained in this table is intended only to illustrate the influence of developmental differences in drug disposition and action on average dose requirements among the age groups and is not meant to convey specific dose recommendations.
† The initial oral doses of captopril are given.

Infant dose if volume of distribution is <0.3 liter per kilogram = infant's body-surface area (in square meters ÷ 1.73 m^2) × the adult dose

and

Infant dose if volume of distribution (determined from the literature) is ≥0.3 liter per kilogram = infant's body weight (in kilograms ÷ 70 kg) × the adult dose.

This approach is useful only in determining the dose as opposed to the dosing interval, in that the equations contain no specific variable that describes potential age-associated differences in drug clearance.

CONCLUSIONS

The advances in pediatric clinical pharmacology during the past decade stem from an enhanced understanding of the influence of growth and development on the disposition and actions of drugs. The expanded scope of clinical trials involving children afforded by the provisions of the Best Pharmaceuticals for Children Act of 2002[95] and an ethical construct for conducting drug research in children that is viewed as permissive (as opposed to restrictive)[96] will facilitate improvements in drug therapy for this age group. Ensuing research into the ontogeny and pharmacogenomics of transporters, receptor systems, and cell signaling will also elucidate the developmental events that affect the treatment of childhood diseases and their response to drug treatment.[97] The ultimate goal of providing infants and children with safe and effective drug therapy must be kept clearly in sight and will be made possible by specifically including them in clinical trials.

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