

## REVIEW ARTICLE

## DRUG THERAPY

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

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

Gregory L. Kearns, Pharm.D., Ph.D., Susan M. Abdel-Rahman, Pharm.D.,  
Sarah W. Alander, M.D., Douglas L. Blowey, M.D.,  
J. Steven Leeder, Pharm.D., Ph.D., and Ralph E. Kauffman, M.D.

**I**NFANTS 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.”<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> As a result, the use of dosing equations has largely been replaced by adjustment (or normalization) of the drug dose for either body weight or body-surface area.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-

From the Departments of Pediatrics (G.L.K., S.M.A.-R., S.W.A., D.L.B., J.S.L., R.E.K.), Pharmacology (G.L.K., D.L.B., J.S.L., R.E.K.), and Pharmacy Practice (S.M.A.-R.), University of Missouri at Kansas City; and the Divisions of Pediatric Pharmacology and Medical Toxicology (G.L.K., S.M.A.-R., S.W.A., D.L.B., J.S.L., R.E.K.), Emergency Medicine (S.W.A.), and Nephrology (D.L.B.), Children’s Mercy Hospitals and Clinics — both in Kansas City, Mo. Address reprint requests to Dr. Kearns at the Division of Pediatric Pharmacology and Medical Toxicology, Department of Pediatrics, Children’s Mercy Hospitals and Clinics, 2401 Gillham Rd., Kansas City, MO 64108, or at gkearns@cmh.edu.

N Engl J Med 2003;349:1157-67.

Copyright © 2003 Massachusetts Medical Society.

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.<sup>4,5</sup> Thus, oral administration of acid-labile compounds such as penicillin G produces greater bioavailability in neonates than in older infants and children.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup>

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.<sup>10,11</sup> Similarly, intestinal motor activity matures throughout early infancy, with consequent increases in the frequency, amplitude, and duration of propagating contractions.<sup>12</sup> 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.<sup>13</sup> 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 intes-

tinal length as a percentage of adult values exceeds other anthropometric measurements throughout development.<sup>14</sup> Villous formation begins at eight weeks of gestation and matures by week 20,<sup>15</sup> 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<sup>16-18</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup>

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<sup>23</sup> and by the greater extent of cutaneous perfusion and hydration of the epidermis (relative to adults) throughout childhood.<sup>24,25</sup> 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.<sup>26,27</sup>

Reduced skeletal-muscle blood flow and inefficient muscular contractions (responsible for drug dispersion) may reduce the rate of intramuscular absorption of drugs in neonates.<sup>28</sup> 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.<sup>29</sup> 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.<sup>30,31</sup>

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,<sup>32</sup> effectively decreasing the absorption of drugs such as erythromycin and acetaminophen.<sup>33-35</sup>

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.<sup>36</sup> 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.<sup>37</sup>

#### DISTRIBUTION OF DRUGS

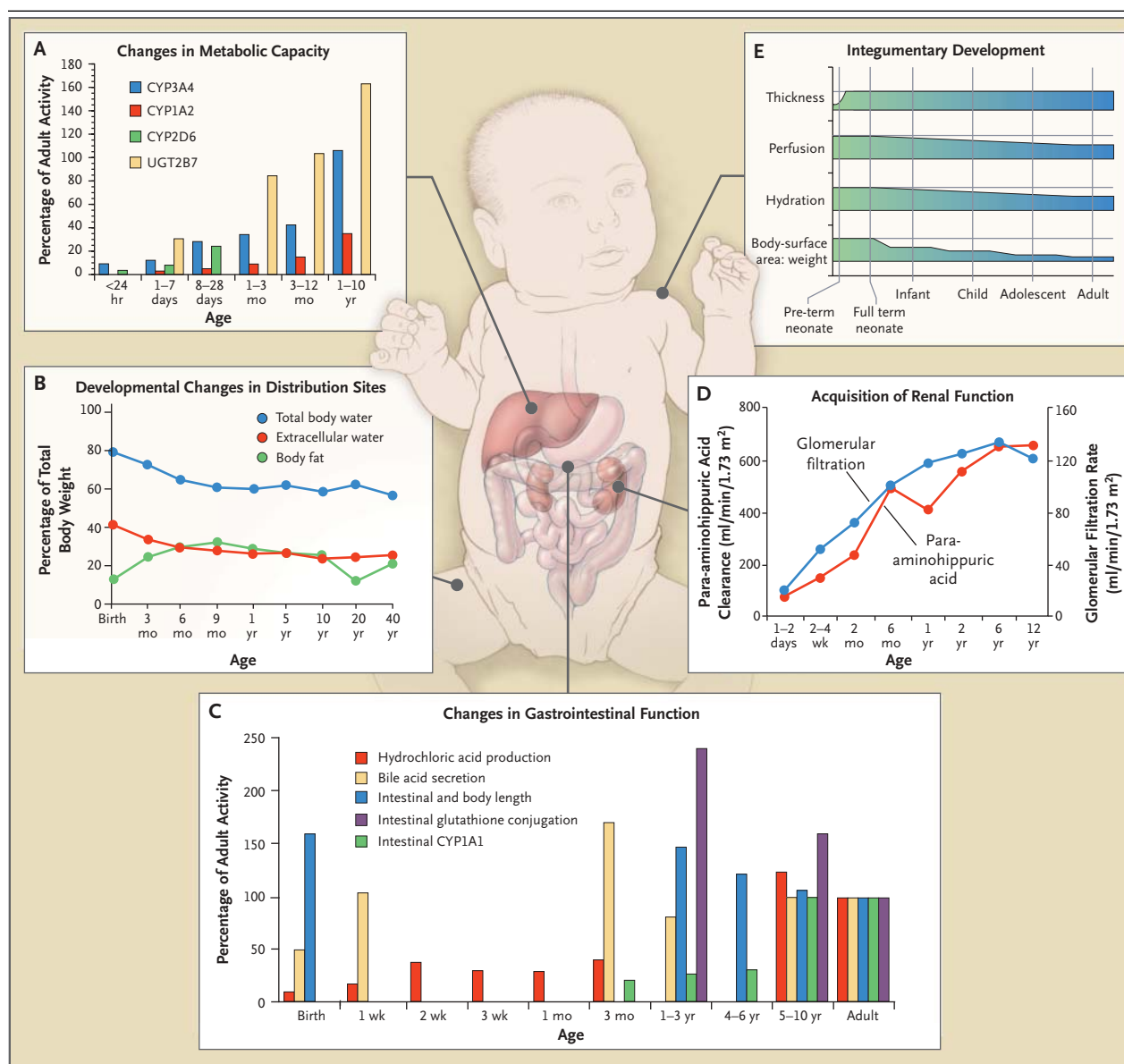
Age-dependent changes in body composition (Fig. 1)<sup>38</sup> alter the physiologic spaces into which a drug may be distributed. The relatively larger extracellular and total-body water spaces in neonates and young infants as compared with adults, coupled with adipose stores that have a higher ratio of water to lipid, result in lower plasma levels of drugs in these compartments when the drugs are administered in a weight-based fashion.<sup>49</sup> 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  $\alpha_1$ -acid glycoprotein can also influence the distri-

bution 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.<sup>50,51</sup> 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.<sup>50-52</sup> 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).<sup>53</sup>

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.<sup>54</sup> 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.<sup>55</sup> 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.,<sup>4</sup> Rodbro et al.,<sup>5</sup> Poley et al.,<sup>9</sup> Gibbs et al.,<sup>21</sup> Okah et al.,<sup>24</sup> West et al.,<sup>27</sup> Friis-Hansen,<sup>38</sup> Young and Lietman,<sup>39</sup> Hines and McCarver,<sup>40</sup> Treluyer et al.,<sup>41</sup> Kinirons et al.,<sup>42</sup> Pynnönen et al.,<sup>43</sup> Aranda et al.,<sup>44</sup> Miller et al.,<sup>45</sup> Barrett et al.,<sup>46</sup> Murry et al.,<sup>47</sup> and Robillard et al.<sup>48</sup>

## 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.<sup>39,56</sup> 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.<sup>40,57</sup> 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<sup>58</sup> and potentially teratogenic derivatives of retinoic acid.<sup>59</sup> The expression of CYP3A7 peaks shortly after birth and then declines rapidly to levels that are undetectable in most adults.<sup>60</sup> Distinct patterns of isoform-specific developmental expression of CYPs have been observed postnatally. Within hours after birth, CYP2E1 activity surges,<sup>61</sup> and CYP2D6 becomes detectable soon thereafter.<sup>62</sup> CYP3A4 and CYP2C (CYP2C9 and CYP2C19) appear during the first week of life,<sup>41,60</sup> whereas CYP1A2 is the last hepatic CYP to appear, at one to three months of life.<sup>63</sup>

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,<sup>42</sup> 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.<sup>64</sup> The clearance of carbamazepine from plasma, which is also largely dependent on CYP3A4,<sup>65</sup> is greater in children than in adults,<sup>43,66</sup> 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 pri-

marily responsible for the biotransformation of phenytoin.<sup>67</sup> 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.<sup>68</sup> 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.<sup>69</sup> 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,<sup>70</sup> 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<sup>44</sup>; by the time infants are six months of age (as reflected by theophylline plasma clearance), the rate may exceed that in adults.<sup>71,72</sup> 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,<sup>73</sup> 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.<sup>45</sup> Glucuronidation of morphine (a UGT2B7 substrate) can be detected in premature infants as young as 24 weeks of gestational age.<sup>46</sup> The clearance of morphine from plasma is positively correlated with post-conceptual age and quadruples between 27 and 40 weeks postconceptual age, thereby necessitating corresponding increases in the dose of morphine to maintain effective analgesia.<sup>74</sup>



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.<sup>75</sup> However, a detailed study of the CYP2C9 substrate S-warfarin<sup>76</sup> 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,<sup>77,78</sup> correlates significantly with age, even after correction for liver weight.<sup>47</sup> 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.<sup>48</sup> The glomerular filtration rate is approximately 2 to 4 ml per minute per 1.73 m<sup>2</sup> in term neonates, but it may be as low as 0.6 to 0.8 ml per minute per 1.73 m<sup>2</sup> 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.<sup>79,80</sup> Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life.

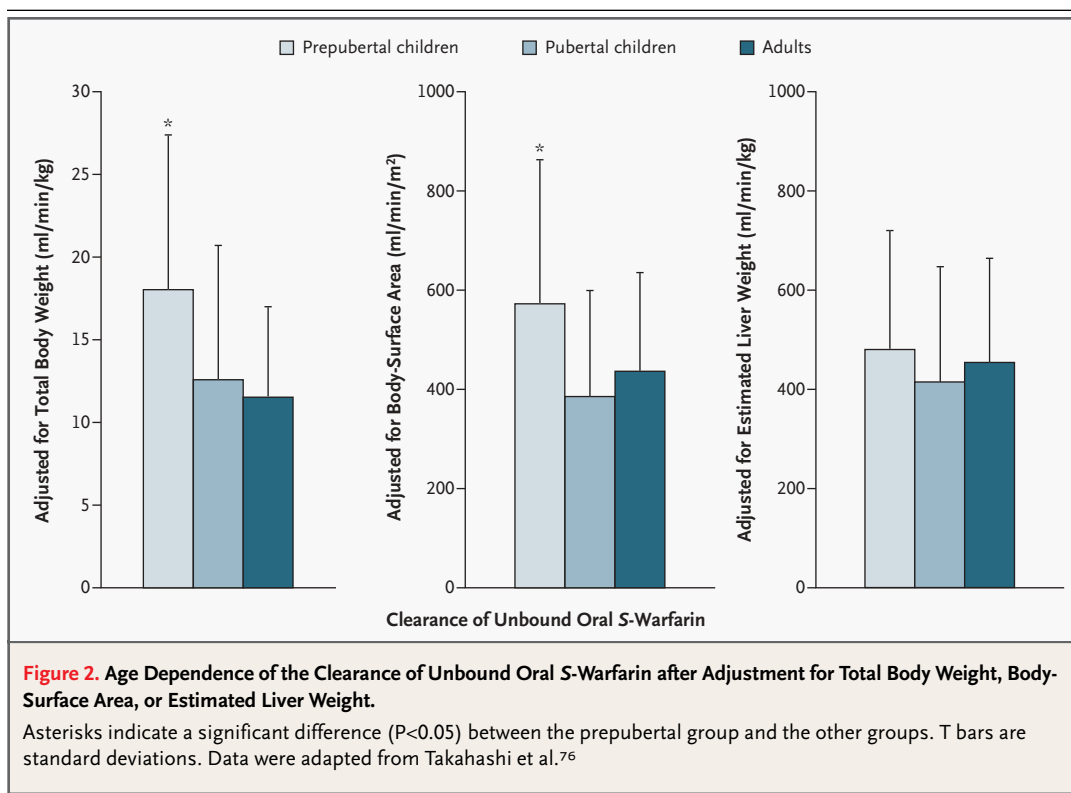
Collectively, developmental changes in renal function can dramatically alter the plasma clearance of compounds with extensive renal elimination and

thus constitute a major determinant of the age-appropriate selection of a dose regimen. Pharmacokinetic studies of drugs such as ceftazidime<sup>80</sup> and famotidine,<sup>81</sup> 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.<sup>82</sup> 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.<sup>83</sup> Furthermore, concomitant administration of medications such as betamethasone and indomethacin may alter the normal pattern of renal maturation in neonates.<sup>84</sup> 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<sup>81</sup> 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<sup>76</sup> and cyclosporine<sup>85</sup>) or in the relation between the plasma level and the pharmacologic effect of a given drug (e.g., sedation associated with midazolam<sup>86,87</sup>).

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)<sup>88,89</sup> and to the likelihood of severe adverse events (e.g., the hepatotoxicity of valproic acid is increased in young infants).<sup>90</sup> Recent evidence of the age-dependent expression of intestinal motilin receptors and the modulation of antral



contractions appears to have implications with respect to the prokinetic effects of erythromycin in preterm infants.<sup>91</sup> 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.<sup>3</sup> 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.<sup>92</sup> 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,<sup>93</sup> 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.<sup>94</sup> 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.<sup>93</sup> 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<sup>2</sup>) × 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 un-

derstanding 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<sup>95</sup> and an ethical construct for conducting drug research in children that is viewed as permissive (as opposed to restrictive)<sup>96</sup> 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.<sup>97</sup> 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.



Supported by grants from the National Institutes of Health (5 U01 HD31313-10, R01 GM58883-04, R01 ES10855-04, and U01 HD044239-01).

We are indebted to Dr. John N. van den Anker for skillful editorial assistance.

# REFERENCES

1. Halpern SA. American pediatrics: the social dynamic of professionalism, 1880–1980. Berkeley: University of California Press, 1988:52.
2. Drug dosage in children. In: Ritschel WA. Handbook of basic pharmacokinetics. 2nd ed. Hamilton, Ill.: Drug Intelligence, 1980:296–310.
3. Kearns GL. Impact of developmental pharmacology on pediatric study design: overcoming the challenges. *J Allergy Clin Immunol* 2000;106:Suppl:S128–S138.
4. Agunod M, Yamaguchi N, Lopez R, Luhby AL, Glass GB. Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. *Am J Dig Dis* 1969;14:400–14.
5. Rodbro P, Krasilnikoff PA, Christiansen PM. Parietal cell secretory function in early childhood. *Scand J Gastroenterol* 1967;2:209–13.
6. Huang NN, High RH. Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. *J Pediatr* 1953;42:657–68.
7. Morselli PL. Antiepileptic drugs. In: Morselli PL, ed. Drug disposition during development. New York: Spectrum, 1977:311–60.
8. Suchy FJ, Balistreri WF, Heubi JE, Searcy JE, Levin RS. Physiologic cholestasis: elevation of the primary serum bile acid concentrations in normal infants. *Gastroenterology* 1981;80:1037–41.
9. Poley JR, Dower JC, Owen CA Jr, Stickler GB. Bile acids in infants and children. *J Lab Clin Med* 1964;63:838–46.
10. Gupta M, Brans YW. Gastric retention in neonates. *Pediatrics* 1978;62:26–9.
11. Ittmann PI, Amarnath RA, Berseth CL. Maturation of antroduodenal motor activity in preterm and term infants. *Dig Dis Sci* 1992;37:14–9.
12. Berseth CL. Gestational evolution of small intestine motility in preterm and term infants. *J Pediatr* 1989;115:646–51.
13. Heimann G. Enteral absorption and bioavailability in children in relation to age. *Eur J Clin Pharmacol* 1980;18:43–50.
14. Weaver LT, Austin S, Cole TJ. Small intestinal length: a factor essential for gut adaptation. *Gut* 1991;32:1321–3.
15. Grand RJ, Watkins JB, Torti FM. Development of the human gastrointestinal tract: a review. *Gastroenterology* 1976;70:790–810.
16. Yanowitz TD, Yao AC, Pettigrew KD, Werner JC, Oh W, Stonestreet BS. Postnatal hemodynamic changes in very-low-birth-weight infants. *J Appl Physiol* 1999;87:370–80.
17. Martinussen M, Brubakk AM, Vik T, Yao AC. Mesenteric blood flow velocity and its relation to transitional circulatory adaptation in appropriate for gestational age preterm infants. *Pediatr Res* 1996;39:275–80.
18. Martinussen M, Brubakk AM, Linker DT, Vik T, Yao AC. Mesenteric blood flow velocity and its relation to circulatory adaptation during the first week of life in healthy term infants. *Pediatr Res* 1994;36:334–9.
19. Hall SD, Thummel KE, Watkins PB, et al. Molecular and physical mechanisms of first-pass extraction. *Drug Metab Dispos* 1999;27:161–6.
20. Stahlberg MR, Hietanen E, Maki M. Mucosal biotransformation rates in the small intestine of children. *Gut* 1988;29:1058–63.
21. Gibbs JP, Liacouras CA, Baldassano RN, Slattery JT. Up-regulation of glutathione S-transferase activity in enterocytes of young children. *Drug Metab Dispos* 1999;27:1466–9.
22. Linday L, Dobkin JF, Wang TC, Butler VP Jr, Saha JR, Lindenbaum J. Digoxin inactivation by the gut flora in infancy and childhood. *Pediatrics* 1987;79:544–8.
23. Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. *Clin Perinatol* 1987;14:911–30.
24. Okah FA, Wickett RR, Pickens WL, Hoath SB. Surface electrical capacitance as a noninvasive bedside measure of epidermal barrier maturation in the newborn infant. *Pediatrics* 1995;96:688–92.
25. Fluhr JW, Pfisterer S, Gloor M. Direct comparison of skin physiology in children and adults with bioengineering methods. *Pediatr Dermatol* 2000;17:436–9.
26. Amato M, Huppi P, Isenschmid M, Schneider H. Developmental aspects of percutaneous caffeine absorption in premature infants. *Am J Perinatol* 1992;9:431–4.
27. West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol* 1981;76:147–50.
28. Greenblatt DJ, Koch-Weser J. Intramuscular injection of drugs. *N Engl J Med* 1976;295:542–6.
29. Carry MR, Ringel SP, Starcevic JM. Distribution of capillaries in normal and diseased human skeletal muscle. *Muscle Nerve* 1986;9:445–54.
30. Kafetzis DA, Sinaniotis CA, Papadatos CJ, Kosmidis J. Pharmacokinetics of amikacin in infants and pre-school children. *Acta Paediatr Scand* 1979;68:419–22.
31. Sheng KT, Huang NN, Promadhattavedi V. Serum concentrations of cephalothin in infants and children and placental transmission of the antibiotic. *Antimicrob Agents Chemother* 1964:200–6.
32. Di Lorenzo C, Flores AF, Hyman PE. Age-related changes in colon motility. *J Pediatr* 1995;127:593–6.
33. Stratchunsky LS, Nazarov AD, Firsov AA, Petrachenkova NA. Age dependence of erythromycin rectal bioavailability in children. *Eur J Drug Metab Pharmacokinet* 1991;3:321–3.
34. van Lingen RA, Deinum JT, Quak JM, et al. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F59–F63.
35. Coulthard KP, Nielson HW, Schroder M, et al. Relative bioavailability and plasma paracetamol profiles of Panadol suppositories in children. *J Paediatr Child Health* 1998;34:425–31.
36. Thorsson L, Edsbacker S, Kallen A, Lofdahl CG. Pharmacokinetics and systemic activity of fluticasone via Diskus and pMDI, and of budesonide via Turbuhaler. *Br J Clin Pharmacol* 2001;52:529–38.
37. Schiller-Scotland CF, Hlawa R, Gebhart J. Experimental data for total deposition in the respiratory tract of children. *Toxicol Lett* 1994;72:137–44.
38. Friis-Hansen B. Water distribution in the foetus and newborn infant. *Acta Paediatr Scand Suppl* 1983;305:7–11.
39. Young WS, Lietman PS. Chloramphenicol glucuronyl transferase: assay, ontogeny and inducibility. *J Pharmacol Exp Ther* 1978;204:203–11.
40. Hines RN, McCarver DG. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther* 2002;300:355–60.
41. Treluyer J-M, Gueret G, Cheron G, Sonnier M, Cresteil T. Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility. *Pharmacogenetics* 1997;7:441–52.
42. Kinirons MT, O'Shea D, Kim RB, et al. Failure of erythromycin breath test to correlate with midazolam clearance as a probe of cytochrome P4503A. *Clin Pharmacol Ther* 1999;66:224–31.
43. Pynnönen S, Sillanpää M, Frey H, Iisalo E. Carbamazepine and its 10,11-epoxide in children and adults with epilepsy. *Eur J Clin Pharmacol* 1977;11:129–33.
44. Aranda JV, Collinge JM, Zinman R, Waters G. Maturation of caffeine elimination in infancy. *Arch Dis Child* 1979;54:946–9.
45. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. *Clin Pharmacol Ther* 1976;19:284–94.
46. Barrett DA, Barker DP, Rutter N, Pawula M, Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996;41:531–7.

47. Murry DJ, Crom WR, Reddick WE, Bhargava R, Evans WE. Liver volume as a determinant of drug clearance in children and adolescents. *Drug Metab Dispos* 1995;23:1110-6.
48. Robillard JE, Guillery EN, Petershank JA. Renal function during fetal life. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric nephrology*. 4th ed. Baltimore: Lippincott Williams & Wilkins, 1999:21-37.
49. Siber GR, Echeverria P, Smith AL, Paisley JW, Smith DH. Pharmacokinetics of gentamicin in children and adults. *J Infect Dis* 1975;132:637-51.
50. Windorfer A, Kuenzer W, Urbanek R. The influence of age on the activity of acetylsalicylic acid-esterase and protein-salicylate binding. *Eur J Clin Pharmacol* 1974;7:227-31.
51. Ehrnebo M, Agurell S, Jalling B, Boreus LO. Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults. *Eur J Clin Pharmacol* 1971;3:189-93.
52. Fredholm BB, Rane A, Persson B. Diphenylhydantoin binding to proteins in plasma and its dependence on free fatty acid and bilirubin concentration in dogs and newborn infants. *Pediatr Res* 1975;9:26-30.
53. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet* 2003;42:59-98.
54. Tsai C, Ahdab-Barmada M, Daood MJ, Watchko JE. P-glycoprotein expression in the developing human central nervous system: cellular and tissue localization. *Pediatr Res* 2001;47:Suppl:436A. abstract.
55. Painter MJ, Pippenger C, Wasterlain C, et al. Phenobarbital and phenytoin in neonatal seizures: metabolism and tissue distribution. *Neurology* 1981;31:1107-12.
56. Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant: a physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med* 1960;262:787-94.
57. McCarver DG, Hines RN. The ontogeny of human drug metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J Pharmacol Exp Ther* 2002;300:361-6.
58. Kitada M, Kamataki T, Itahashi K, Rikihisa T, Kanakubo Y. P-450 HFLa, a form of cytochrome P-450 purified from human fetal livers, is the 16 $\alpha$ -hydroxylase of dehydroepiandrosterone 3-sulfate. *J Biol Chem* 1987;262:13534-7.
59. Chen H, Fantel AG, Juchau MR. Catalysis of the 4-hydroxylation of retinoic acids by CYP3A7 in human fetal hepatic tissues. *Drug Metab Dispos* 2000;28:1051-7.
60. Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T. Expression of CYP3A in the human liver: evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. *Eur J Biochem* 1997;247:625-34.
61. Vieira I, Sonnier M, Cresteil T. Developmental expression of CYP2E1 in the human liver: hypermethylation control of gene expression during the neonatal period. *Eur J Biochem* 1996;238:476-83.
62. Treluyer J-M, Jacqz-Aigrain E, Alvarez F, Cresteil T. Expression of CYP2D6 in developing human liver. *Eur J Biochem* 1991;202:583-8.
63. Sonnier M, Cresteil T. Delayed ontogenesis of CYP1A2 in the human liver. *Eur J Biochem* 1998;251:893-8.
64. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. *Clin Pharmacokinet* 1999;37:485-505.
65. Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism: role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol* 1994;47:1969-79.
66. Riva R, Contin M, Albani F, Perucca E, Procaccianti G, Baruzzi A. Free concentration of carbamazepine and carbamazepine-10,11-epoxide in children and adults: influence of age and phenobarbital co-medication. *Clin Pharmacokinet* 1985;10:524-31.
67. Bajpai M, Roskos LK, Shen DD, Levy RH. Rules of cytochrome P4502C9 and cytochrome P4502C19 in the stereoselective metabolism of phenytoin to its major metabolite. *Drug Metab Dispos* 1996;24:1401-3.
68. Loughnan PM, Greenwald A, Purton WW, Aranda JV, Watters G, Neims AH. Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977;52:302-9.
69. Bourgeois BFD, Dodson WE. Phenytoin elimination in newborns. *Neurology* 1983;33:173-8.
70. Chiba K, Ishizaki T, Miura H, Minigawa K. Michaelis-Menten pharmacokinetics of diphenylhydantoin and application in the pediatric age patient. *J Pediatr* 1980;96:479-84.
71. Kraus DM, Fischer JH, Reitz SJ, et al. Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993;54:351-9.
72. Milavetz G, Vaughan LM, Weinberger MM, Hendeles L. Evaluation of a scheme for establishing and maintaining dosage of theophylline in ambulatory patients with chronic asthma. *J Pediatr* 1986;109:351-4.
73. Lambert GH, Schoeller DA, Kotake AN, Flores C, Hay D. The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther* 1986;9:375-88.
74. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr* 1999;135:423-9.
75. Blanco JG, Harrison PL, Evans WE, Relling MV. Human cytochrome P450 maximal activities in pediatric versus adult liver. *Drug Metab Dispos* 2000;28:379-82.
76. Takahashi H, Ishikawa S, Nomoto S, et al. Developmental changes in pharmacokinetics and pharmacodynamics of warfarin enantiomers in Japanese children. *Clin Pharmacol Ther* 2000;68:541-55.
77. Sharer JE, Wrighton SA. Identification of the human hepatic cytochromes P450 involved in the in vitro oxidation of antipyrine. *Drug Metab Dispos* 1996;24:487-94.
78. Engel G, Hofmann U, Heidemann H, Cosme J, Eichelbaum M. Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. *Clin Pharmacol Ther* 1996;59:613-23.
79. Arant BS Jr. Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr* 1978;92:705-12.
80. van den Anker JN, Schoemaker RC, Hop WC, et al. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 1995;58:650-9.
81. James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998;38:1089-95. [Erratum, *J Clin Pharmacol* 2000;40:1298.]
82. Brion LP, Fleischman AR, Schwartz GJ. Gentamicin interval in newborn infants as determined by renal function and postconceptional age. *Pediatr Nephrol* 1991;5:675-9.
83. Szefer SJ, Wynn RJ, Clarke DF, Buckwald S, Shen D, Schentag JJ. Relationship of gentamicin serum concentrations to gestational age in preterm and term neonates. *J Pediatr* 1980;97:312-5.
84. van den Anker JN, Hop WC, de Groot R, et al. Effects of prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in the preterm infant. *Pediatr Res* 1994;36:578-81.
85. Marshall JD, Kearns GL. Developmental pharmacodynamics of cyclosporine. *Clin Pharmacol Ther* 1999;66:66-75.
86. Marshall J, Rodarte A, Blumer J, Khoo K-C, Akbari B, Kearns GL. Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol* 2000;40:578-89.
87. deWildt SN, Kearns GL, Sie SD, Hop WCJ, van den Anker JN. Pharmacodynamics of intravenous and oral midazolam in preterm infants. *Clin Drug Invest* 2003;23:27-38.
88. Silverman ES, Liggett SB, Gelfand EW, et al. The pharmacogenetics of asthma: a candidate gene approach. *Pharmacogenomics* 2001;1:27-37.
89. Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukaemia — current status and future perspectives. *Lancet Oncol* 2001;2:597-607.
90. Leeder JS. Ontogeny of drug-metabolizing enzymes and its influence on the pathogenesis of adverse drug reactions in children. *Curr Ther Res* 2001;62:900-12.
91. Jadcherla SR, Berseth CL. Effect of

erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr* 2002;34:16-22.

92. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. *Clin Pharmacokinet* 2002;41:1077-94.

93. Taketomo CK, Hodding JH, Kraus DM.

*Pediatric dosage handbook*. 6th ed. Hudson, Ohio: Lexi-Comp, 2000.

94. Ritschel WA, Kearns GL, eds. *Handbook of basic pharmacokinetics — including clinical applications*. 5th ed. Washington, D.C.: American Pharmaceutical, 1999:318-9.

95. Steinbrook R. Testing medications in children. *N Engl J Med* 2002;347:1462-70.

96. Kauffman RE. Clinical trials in children: problems and pitfalls. *Paediatr Drugs* 2000;2:411-8.

97. Leeder JS, Kearns GL. The challenges of delivering pharmacogenomics into clinical pediatrics. *Pharmacogenomics J* 2002;2:141-3.

Copyright © 2003 Massachusetts Medical Society.



Jennifer R. Bellon, M.D.