Pharmacology for Infants and Children

Peter J. Davis, MD

As growth and maturation occur, there are inevitable changes that occur with drug kinetics and drug pharmacology. Adults are not big "little people" nor are children small "big people." Knowing the physiologic and anatomic changes that occur with age helps in understanding some of the principles involved in pediatric anesthesia and pediatric pharmacology.

The one constant in childhood development is change. With age, large changes in total body water, body water distribution, and body composition occur. Infants have a much larger proportion of body weight in the form of water than do adults. The fetus has high total body water that at birth accounts for approximately 75% of the body weight in the full-term newborn infant and 80% in the pre-term newborn. The total body water decreases during the first year of life to approximately 60% of body weight and stays at that level until puberty (1). In addition, the distribution of body water is also different. In term infants, 45% and 35% of body water is extracellular and intracellular respectively, whereas in adults, it is 20% and 40% respectively. Muscle and fat content also change dramatically with age.

Albumin and α_1 acid glycoprotein (AAG) are the two major binding proteins for opioids. These two binding proteins undergo quantitative as well as qualitative changes. With age, protein binding increases. In neonates, the reduced amount of total plasma protein (including the albumin), the presence of fetal albumin (that has reduced binding affinity for weak acids), and the increased concentrations of endogenous substances (i.e., bilirubin, and free fatty acids that reduce binding capacity of albumin) all contribute to a higher free-unbound fraction of highly protein-bound drugs (phenytoin, valporic acid, salycilates) (2–5).

Basic drugs bind with high affinity to α_1 acid glycoprotein. The concentrations of AAG are low at birth but reach the adult levels over the first year of life. Its seems that the lower AAG levels in neonates and infants are responsible for the decrease in protein binding of sufentanil in these age groups compared with adults.

The more a drug is protein bound to plasma proteins, the less is its free drug fraction and the smaller its volume of distribution. Distribution of drugs is the process by which a drug leaves the bloodstream and enters the extracellular fluids and tissues. The distribution of a drug is determined by body composition, permeability of tissue membranes, cardiac output, regional blood flow, blood and tissues, the lipid solubility, ionizable drugs, and plasma and tissue binding (6–8). Therefore, the developmental changes that occur with protein binding and body composition affect changes in drug distribution.

In addition to developmental changes in body composition and protein binding, developmental changes in drug clearance also occur. The liver is the major site of drug metabolism. Drugs that undergo hepatic metabolism have either a high or low hepatic extraction coefficient. Drugs with a high hepatic extraction coefficient (e.g., fentanyl, morphine) are dependent on hepatic blood flow and independent of protein binding for drug clearance, whereas drugs with low hepatic extraction coefficients (alfentanil) depend on free drug fraction and on hepatic enzyme kinetics as the rate-limiting step in drug elimination. As the infant matures, hepatic blood flow increases. For drugs with high extraction coefficients, changes in hepatic blood flow can markedly influence drug clearance. Factors known to decrease hepatic blood flow include increased intraabdominal pressure, positive pressure ventilation, hypoxemia, hypercarbia, increased catecholamines, β-adrenergic blockade, general anesthesia, regional anesthesia, and patency of the ductus venous. In infants, the ductus venous has been reported to be patent for as long as 6 to 11 days after birth. Protein binding also affects drug clearance. In contrast to highly extracted drugs in which protein binding does not influence clearance, for drugs with low extraction ratios, protein binding inversely affects the clearance. That is, increased protein binding results in reduced clearance, whereas decreased protein binding and subsequent increase in free-unbound fraction augments the hepatic clearance of the drug.

Drug Metabolism

Hepatic biotransformation is a main route of elimination for many drugs. In general, hepatic metabolism

increases the hydrophilicity of drugs and allows their renal elimination.

Enzyme reactions involved with drug metabolism are classified into two groups. Phase I reactions involve oxidation, reduction, and/or hydrolysis. The second phase of metabolism generally consists of conjugation reactions that involve coupling the drug or its metabolite to a substrate (e.g., glucuronidation, sulfonation) to ensure excretion of the drug. For most of the opioids, enzyme metabolism is through the P_{450} isoenzymes. Changes in enzyme maturation and activity occur with age. At birth, the cytochrome P_{450} enzymes are reduced to 50% of adult values. In addition to intrinsic reduction in enzyme activity some drugs can compete with the P_{450} isoenzymes and thereby further alter drug metabolism. In animal *in vitro* studies, inhalational anesthetics (i.e., halothane) decrease the metabolic capacity of the P_{450} isoenzymes. The expression of phase I enzymes such as the P_{450} cytochromes (CYPs) changes markedly during development. Distinct patterns of isoform-specific developmental expression of CYPs have been observed postnatally. Within hours after birth, CYP2E1 activity increases and CYP2D6 becomes detectable soon thereafter. CYP3A4 and CYP2C (CYP2C and CYP2C19) appear during the first week of life, whereas CYP1A2 is the last hepatic CYP to appear, at 1 to 3 mo of life (9–13).

The clearance of IV administered midazolam from plasma is primarily a function of hepatic CYP3A4 and CYP3A5 activity, and the level of activity increases from 1.2 to 9 mL/min per kilogram of body weight during the first 3 mo of life. The activity of the CYPs can affect clearance in a computer simulation model of the context-sensitive half-time. Alfentanil can behave as a long-acting or as a rapid-acting opioid (14).

The *in vitro* CYP2D6 activity has been evaluated in fetal, neonatal, infant, pediatric, and adult liver tissue to study the ontogeny of CYP2D6. Treluyer et al. (15) detected limited CYP2D6 protein and activity in 30% of fetal livers. In the first month of life, CYP2D6 protein and activity increased further, and between 1 mo and 5 yr of age protein levels were reported to be approximately two thirds of adult levels. Another study reported no additional significant differences in protein levels of CYP2D6 in infants older and younger than 1 yr, suggesting that CYP2D6 ontogeny is complete by age 1 yr.

Phase II reactions catalyze the conjugation (glucuronidation, sulfation, glutathione conjugation) of a water-soluble endogenous molecule to the drug compound and further enhance the water solubility of drugs and their renal or biliary excretion. Glucuronidation, glutathione conjugation, and acetylation are deficient in the neonate, whereas sulfate conjugation is an effective pathway at birth. 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. Glucuronidation of morphine (a UGT2B7 substrate) can be detected in premature infants as young as 24 wk of gestational age. The clearance of morphine from plasma is positively correlated with postconceptional age and quadruples between 27 and 40 wk postconceptual age, thereby necessitating corresponding increases in the dose of morphine to maintain effective analgesia (16).

Along with changes in hepatic maturation, developmental changes occur with renal function. The nephrogenesis that begins in the eighth week of gestation is completed by 36 wk of age. At that time, for the full complement of nephrons, glomerular filtration rate (GFR) is only 5% of the adult values (17–19). Measurements of renal plasma flow (PAH) and GFR (inulin or mannitol) that are normalized for the body surface area indicate that adult values are reached between 6 and 12 mo of age.

Both anatomical and functional immaturity of renal tubules is present at birth, and both passive reabsorption and active secretion are diminished. The maturation of renal tubular function reaches the adult renal tubular function values by 12–18 mo of age. If the constant of pediatric physiology is change, then variability in the rate of change must occur. Variability in drug pharmacology is an inevitable consequence of growth and development.

Developmental changes in renal function can dramatically alter the plasma clearance of compounds with extensive renal elimination and thereby affect the age-appropriate selection of a dose regimen. Pharmacokinetic studies of drugs, which are excreted primarily by the glomeruli, have shown correlations between plasma drug clearance and normal maturational changes in renal function. Concomitant administration of medications such as betamethasone and indomethacin may alter the normal pattern of renal maturation in neonates. 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.

In addition to changes in kinetics, differences in drug transporter proteins as well as drug receptors occur. These changes lead to variability of the drug response and analgesic effects of most opioids procedures, their intended effects, and side effects as to mu-opioid receptors. Polymorphism of the OPRM1 receptor, specifically single nucleotide polymorphisms SRPs, has been shown to have different effects for analgesic and respiratory effects (20).

This lecture will focus on how these developmental changes affect opioid clearance in children and how

the pharmacokinetic changes coupled with underlying genetic differences can create pharmacodynamic variability in drug effect.

References

1. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. Pediatrics 1961;28:169–81.
2. Ehrnebo M, Agurell S, Jalling B, Boreus LO. Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults. J Eur Clin Pharmacol 1971;3:189–93.
3. Kurz H, Michels H, Stickel HH. Differences in the binding of drugs to plasma proteins from newborn to adult man. Eur J Clin Pharmacol 1977;11:469–72.
4. Wallace S. Altered plasma albumin in the newborn infant. Br J Clin Pharmacol 1977;4:83–5.
5. Meistelman C, Benhamou D, Barre J, et al. Effects of age on plasma protein binding of sufentanil. Anesthesiology 1990;72: 470–3.
6. Benedetti SM Baltes EL. Drug metabolism and disposition in children. Fundam Clin Pharmacol 2003;17:281–99.
7. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Drug therapy: developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349:1157–67.
8. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Part I. Clin Pharmacokinet 2002; 41:959–98.
9. Lacroix D, Sonnier M, Moncion A, et al. 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.
10. Sonnier M, Cresteil T. Delayed ontogenesis of CYP1A2 in the human liver. Eur J Biochem 1998;251:893–8.
11. Tateishi T, Nakura H, Asoh M, et al. A comparison of hepatic cytochrome P450 protein expression between infancy and postinfancy. Life Sci 1997;61:2567–74.
12. 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.
13. Treluyer J-M, Gueret G, Cheron G, et al. Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: In-vivo-in-vitro correlation and inducibility. Pharmacogenetics 1997;7:441–52.
14. Kharasch ED, Russell M, Mautz D, et al. The role of cytochrome P450 3A4 in alfentanil clearance. Implications for interindividual variability in disposition and perioperative drug interactions. Anesthesiology 1997;87:36–50.
15. Treluyer J-M, Jacqz-Aigrain E, Alvarez F, Cresteil T. Expression of CYP2D6 in developing human liver. Eur J Biochem 1991;202: 583–8.
16. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999;135: 423–9.
17. Heilbron DC, Holliday MA, al-Dahwi A, et al. Expressing glomerular filtration rate in children. Pediatr Nephrol 1991;5:5–11.
18. Haycock GB Development of glomerular filtration and tubular sodium reabsorption in the human fetus and newborn. Br J Urol 1998;81 Suppl 2:33–8.
19. Rubin M, Bruck E, Rapoport M. Maturation of renal function in childhood: clearance studies. J Clin Invest 1949;28:1144–62.
20. Romberg RR, Olofsen E, Bijl H, et al. Polymorphism of μ-opioid receptor gene (OPRM1:c. 118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology 2005;102:522–30.