Pharmacokinetics in the Infant

Rebecca L. Milsap and William J. Jusko

Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York

Processes controlling the absorption, distribution, metabolism, excretion, and pharmacologic effects of drugs are likely to be immature or altered in neonates and infants. Absorption may be affected by differences in gastric pH and stomach emptying rate. Low serum protein concentrations and higher body water composition can change drug distribution. Drug metabolism enzyme activity is typically reduced in the neonate, but rapidly develops over the first year of life. Renal excretion mechanisms are low at birth, but mature over a few months. Limited data are available on the pharmacodynamics of drugs; infants show greater sensitivity to d-tubocurarine. Developmental changes are rapid during the first weeks and months of life, thus requiring continual modification of drug dosage regimens designed for treating pediatric patients. — Environ Health Perspect 102(Suppl 11):107-1100 (1994)

Key words: pharmacokinetics, absorption, distribution, metabolism, excretion, pharmacodynamics

Introduction

The safe and effective exposure to therapeutic drugs and inadvertent chemicals during the first year of life presents unique challenges to the clinician, pharmacokineticist, and toxicologist because of the rapid changes in size, body composition, and organ function of infants during this period. Ignorance of the unique nature of drug disposition in the neonate led to such preventable tragedies as gray baby syndrome from chloramphenicol, congenital anomalies from thalidomide, and kericterus from sulfonamides. The area of pediatric pharmacokinetics has blossomed since the 1970s, when advances in the development of sensitive and specific drug assays began. Pharmacokinetic parameters such as clearance (CL), volume of distribution (V) and half-life (t1/2) have been described for many therapeutic agents used in the newborn and young infant (1-6) and numerous reviews are devoted to this subject (1-12). However, quantitation of clinical effects and pharmacodynamic response as modified by development and disease are areas that have lagged behind description of pharmacokinetics in this age group (10).

The information available on pediatric pharmacokinetics has demonstrated significant differences in absorption, distribution, metabolism, and excretion in premature neonates, full-term neonates, and older infants (Table 1). A summary of the major age-related physiologic changes that impact on drug disposition follows.

Absorption from the Gastrointestinal Tract

Drugs administered by the oral route must move to sites of absorption and then cross multiple gastrointestinal (GI) membranes before they pass into systemic circulation. Most drugs appear to be absorbed by passive diffusion, although some drugs and nutrients are absorbed by an active process (13). Two major factors affecting the absorption of drugs are pH-dependent passive diffusion and gastric emptying (14-17). Both processes demonstrate a variable but age-related trend from birth well into infancy and childhood (15,17). The neutral gastric pH (pH 6-8) at birth is related to the presence of amniotic fluid in the stomach (14). Postnatally, gastric acid secretory capacity appears after the first 24 to 48 hr of life and gastric acidity decreases during the first weeks to months of life (15). Adult values are approached by 3 months of age. In premature infants, gastric pH may remain elevated due to immature acid secretion (18). This higher gastric pH may explain the higher serum concentrations of acid-labile drugs such as ampicillin, penicillin, and nafcillin observed in neonates relative to older children and adults (19,20).

Delayed absorption of phenobarbital, phenytoin, acetaminophen, and riboflavin occurs (13,20,21). The rate of gastric emptying during the neonatal period is both variable and prolonged (17). Gestational age and postnatal age both affect gastric emptying time (17) with prolonged emptying times seen in premature infants. Calculated rates of absorption for phenobarbital, digoxin, xylose, and other substances have demonstrated that although prolonged gastric emptying is present in neonates, it does not completely account for the delays seen in gastric absorption of these compounds (13). Figure 1 demonstrates the relationship of enteral absorption of phenobarbital to age after a single weight-adjusted dose in children age 10 days to 1 year. The rate constant, ka, increases with the age of the child (13). Age-dependent differences in absorption rate remain even after stimulation of intestinal motility. However, they demonstrate a decreased capacity of enteral absorption in neonates; this decrease is attributable to factors other than decreased gastric emptying time, and GI motility. Additional physiologic activities that are diminished in the neonate are pancreatic enzyme function and bile acid secretion (22).

Absorption from Skin and Muscle

Percutaneous absorption may be drastically increased in neonates owning to an immature epidermis and increased skin hydration. Toxicity because of topical application of
hexachlorophene (23) and isopropanol (24), among other agents, has been documented. Conversely, therapeutic serum theophylline concentrations can be obtained in premature infants by applying theophylline gel to the skin (25). Drug absorption from an intramuscular site may be unpredictable and decreased due to insufficient blood flow, poor muscle tone, and compromised muscle oxygenation (3). Variable intramuscular absorption has been demonstrated for digoxin, gentamicin, phenobarbital, and diazepam in neonates (3,26).

**Distribution**

The distribution of drugs within the body is influenced most notably by the amount and character of plasma proteins, and the relative size of the fluid, fat, and tissue compartments of the body. Total body water, expressed as a percentage of total body weight, is as much as 85% in preterm and 78% in full-term neonates (27). The effect of an increased fraction of total body water is apparent when assessing the pharmacokinetic parameter-volume of distribution—which relates drug concentration in plasma to the remaining portions of the body. Table 2 presents calculated Vₜ for various drugs. Drugs which distribute in parallel with body water content have higher V values for infants than adults. Conversely, a lipophilic drug such as diazepam would have a smaller V in infants.

The binding of drugs to plasma proteins is dependent on multiple factors, all of which may be immature in the neonate (4). During this period, plasma albumin, total protein concentrations, and α₁-acid glycoprotein are decreased and do not approach adult values until about 1 year of age (28,29). In addition, acid-base disturbances, competition for binding sites by increased circulatory concentrations of endogenous bilirubin and free fatty acids, and the qualitatively different albumin seen during the neonatal period, alone or in concert, may all affect drug protein binding (1,4).

**Metabolism**

Hepatic enzyme activity and plasma/tissue esterase activity are both reduced during the neonatal period (3). Most enzymatic microsomal systems responsible for drug metabolism are present at birth and their activities increase with advancing gestational and postnatal age (3,12,30–32). Hepatic phase I reactions (i.e., oxidation, reduction, hydroxylation) develop rapidly during infancy, with adult capacities attained by 6 months of life (30–32). These changes have been documented for phenobarbital, phenytoin, diazepam, meperidine and numerous other agents (3,33). Drugs subject to a low hepatic extraction undergo an even further reduction in metabolism by neonates (4,12).

Phase II conjugation reactions are generally reduced at birth, although exceptions have been demonstrated. The conjugation with glucuronic acid is significantly depressed at birth, although a well-developed capability for sulfate conjugation exists (20). Glycine conjugations are present in neonates at levels comparable to those of adults (31). Enzymatic systems responsible for theophylline oxidation and methylation to caffeine are active in premature neonates; whereas, the development of enzymes for oxidative demethylation do not develop for several months of life (34,35). The variation of theophylline metabolism observed during the first year of life is presented in Figure 2. Data compiled from multiple clinical studies conducted in premature neonates, full-term neonates, and infants during the first year of life, shows the interindividual variation of theophylline clearance and its increase with age. The effect of exogenous growth hormone administration to deficient children was associated with a decrease in theophylline half-life in small number of patients (36).

Esterase activity is depressed to a greater extent in premature infants than term infants and does not achieve even term infant activity for 10 to 12 months postnataally. Low esterase activity coupled with a diminished volume of distribution in the newborn may account for the prolonged effect of local anesthetics seen during delivery (37).

A factor also to be considered is in utero exposure to enzyme inducing agents such as barbiturates, glucocorticoids, caffeine, and tobacco (12). Prenatal exposure to these agents may significantly alter the disposition of such drugs as diazepam, phenobarbital, and phenytoin after birth (12). Recently, caffeine has been identified as a sensitive biomarker for development of the P450 monoxygenase system activity (38) and maturation of this system during critical phases of growth and development could be mapped. Slower biotransformations in premature neonates, compared to older infants and adults, have been documented for theophylline, meperidine, and promazine in premature infants (9,10). These slowing of drug metabolism, together with other factors such as impaired drug absorption, have significant impact on the pharmacokinetics of drugs in the neonate.

**Table 2. Comparative distribution parameters of drugs in neonates and adults.**

| Drug        | Volume of distribution, l/kg | Protein binding, % | References |
|-------------|------------------------------|--------------------|------------|
| Gentamicin  | 0.77–1.52                    | 2.5 X T            | N/A        |
| Theophylline| 0.20–2.80                    | 3 X T              | 32–48, 53–65, 1/3 X ↓ |
| Diazepam    | 1.40–1.82                    | 1/3 X ↓            | 64, 94–98, 1/6 X ↓ |
| Phenytoin   | 1.20–1.40                    | 2 X T              | 75–64, 89–92, 1/10 X ↓ |

*Approximate mean % change compared to adult value.
tion of metronidazole, a drug metabolized by P450 enzyme system, has been demonstrated in severely malnourished infants and children as compared to the nonmalnourished state (39).

Renal Excretion
Significant age-dependent changes in renal function affect the elimination of drugs and their metabolites. At birth, glomerular function is more advanced than tubular function and this persists until 6 months of age (40–42). The processes of glomerular filtration, tubular secretion, and tubular reabsorption all define the efficiency with which the kidney eliminates such drugs as tobramycin (43), netilmicin (44), mezlocillin (45), gentamicin (46), and such other agents as glucose, phosphate, and bicarbonate (11,40). All of these clearances may be reduced during infancy. At birth, glomerular filtration rate (GFR) is 2 to 4 ml/min in term neonates and as low as 0.6 to 0.8 ml/min in premature infants (40–42). Dramatic increases occur during the first 72 hr of life where GFR may increase 4-fold (40–42). In general, the renal clearance of drugs that parallel GFR, such as the aminoglycosides, will exhibit pharmacokinetic changes consistent with maturation of renal function, an age dependent process. A strong relationship has been demonstrated between mezlocillin CL and body weight (45) (Figure 3). Further investigation has revealed that nonrenal clearance of the antibiotic also occurs (47).

Pharmacodynamics and Receptor Sensitivity
Recent technological developments have enabled the characterization of cholinergic, adrenergic, glucocorticoid, opiate, and histamine receptors (11,48–51). Age-related alterations in β-receptor affinity for adrenergic agonists has been demonstrated in the elderly (49). The different sensitivity of the neuromuscular junction to d-tubocurarine (d-TC) among neonates, infants, and children and adults has been determined (52). In addition to the pharmacodynamic response, the pharmacokinetics were also assessed. Figure 4 presents a summary of the age-dependent variables of CL, V, t½, and d-tubocurarine plasma concentration required to produce 50% paralysis. Although plasma clearance appeared not to change with age, half-life was prolonged due to the larger V. The distribution of d-TC parallels that of a molecule that distributes to extracellular fluid. The plasma concentration d-TC that correlates with 50% response was significantly lower in neonates and infants than children and adults. Receptor sensitivity at the neuromuscular blockade appears then to be increased with paralysis occurring at a lower concentration in this age group.

Data available on receptor sensitivity during the neonatal period is limited. Extrapolation from in vitro data may not be reflective of the true pharmacodynamic response, although data from isolated tissue preparations provide relevant information regarding developmental and maturational changes in receptor binding characteristics.

Drug Monitoring
Pharmacokinetic and toxicologic assessment during the neonatal period and throughout infancy should appreciate not only the serum drug concentration as an index of xenobiotic exposure, but also the stage of development of organ function and body composition (53–55). Neonates represent the most fragile group due to their physiologic instabilities and their increased potential for toxic effects.

In conclusion, it is readily apparent that most of the physiologic variables influencing drug disposition are unique in the neonate and infant as compared to children and adults. This age group should remain an active population for concern in future pharmacokinetic, pharmacodynamic, and toxicologic research.

REFERENCES

1. Morselli PL. Clinical pharmacokinetics in neonates. Clin Pharmacokinet 1:81–98 (1976).
2. Rane A, Wilson JT. Clinical pharmacokinetics in infants and children. Clin Pharmacokinet 1:2–24 (1976).
3. Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants; age-related differences and therapeutic implications. Clin Pharmacokinet 5:485–527 (1980).
4. Besunder JB, Reed MD, Blumer JL. Principles of drug disposition in the neonate; a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part I). Clin Pharmacokinet 14:189–216 (1988).
5. Besunder JB, Reed MD, Blumer JL. Principles of drug disposition in the neonate; a critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part II). Clin Pharmacokinet 14:261–286 (1988).
6. Kearns GL, Reed MD. Clinical pharmacokinetics in infants and children: a reappraisal. Clin Pharmacokinet 17:29–67 (1989).
7. Mirkin BL. Perinatal pharmacology: placental transfer, fetal localization, and neonatal disposition of drugs. Anesthesiology

Figure 3. Mezlocillin clearance in relation to gestational age in infants less than 1 week of age. Clearance values for adults are shown for comparison. From Janicke et al. (45).

Figure 4. Pharmacokinetic and pharmacodynamic data from neonates, infants, children, and adults following d-tubocurarine infusion. From Fisher et al. (52).
43:156–170 (1975).
8. Assael BM. Pharmacokinetics and drug distribution during postnatal development. Pharmacol Ther 18:159–197 (1982).
9. Aranda JV, Stern L. Clinical aspects of developmental pharmacology and toxicology. Pharmacol Ther 20:1–51 (1983).
10. Barrels H. Drug therapy in childhood: what has been done and what has to be done? Pediatr Pharmacol 3:131–143 (1983).
11. Milsap RL, Hill MR, Szefler SJ. Special pharmacokinetic considerations in children. In: Applied Pharmacokinetics, 3rd (Evans WE, Schentag JJ, Jusko WJ, eds). Applied Therapeutics (1992).
12. Morrelli PL. Clinical pharmacology of the perinatal period and early infancy. Clin Pharmacokinet 17:13–28 (1989).
13. Heimann G. Enteral absorption and bioavailability in children in relation to age. Eur J Clin Pharmacol 18:43–50 (1980).
14. Avery GB, Randolph JG, Weaver T. Gastric acidity on the first day of life. Pediatrics 37:1005–1007 (1966).
15. Miller RA. Observations on the gastric acidity during the first month of life. Arch Dis Child 16:22–30 (1941).
16. Siegel M, Lebenthal E, Krantz B. Effect of caloric density on gastric emptying in premature infants. J Pediatr 118:122–126 (1986).
17. Siegner E, Friedrich R. Gastric emptying in newborns and young infants. Acta Paediatr Scand 64:525–530 (1975).
18. Agnssod M, Yamaguchi N, Lopez R, Luby AL, Glass GBJ. Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. Am J Dig Dis 14:400–414 (1969).
19. Silverio J, and Poole JW. Serum concentrations of ampicillin in newborn infants after oral administration. Pediatrics 51:578–580 (1973).
20. Levy G, Khanna NN, soda DM, Tsuzuki O, Stern L. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and d-Glucuronic acid excretion. Pediatrics 55:818–825 (1975).
21. Jusko WJ, Khanna N, Levy G, Stern L, Yaffe SJ. Riboflavin absorption and excretion in the neonate. Pediatrics 45:945–949 (1970).
22. Murphy GM, Signer E. Progress report: bile acid metabolism in infants and children. Gut 15:151–163 (1974).
23. Tyrrea EA, Hillman LS, Hillman RE, Dodson WE. Clinical pharmacology of hexachlorophene in newborn infants. J Pediatr 91:481–486 (1977).
24. McFadden SW, Haddow JE. Coma produced by topical application of isopropanol. J Pediatr 43:622–623 (1969).
25. Evans NJ, Rutter N, Hadgraft J, Parr G. Percutaneous administration of theophylline in the preterm infant. Pediatrics 70:307–311 (1982).
26. Szefler SJ, Koup JR, Giaoco GP. Pardoxical behavior of serum digoxin concentrations in an anuric neonate. J Pediatr 91:487–489 (1977).
27. Friis-Hansen B. Body composition during growth: biochemical data and in vivo measurements. Pediatrics 47:264–274 (1971).
28. Henngren L, Ehnebo M, Borells LO. Drug binding to plasma proteins during human pregnancy and in the perinatal period. Dev Pharmacol Ther 6:110–124 (1983).
29. Brodersen R, Friis-Hansen B, Stern L. Drug-induced displacement of bilirubin from albumin in the newborn. Dev Pharmacol Ther 6:217–229 (1983).
30. Neims AH, Warner M, Loughnan PM, Aranda JV, Developmental aspects of the hepatic cytochrome P450 monoxygenase system. Annu Rev Pharmacol Toxicol 16:427–445 (1976).
31. Dutton GJ. Developmental aspects of drug conjugation, with special reference to glucuronidation. Annu Rev Pharmacol Toxicol 18:17–35 (1978).
32. Aranda JV, MacLeod SM, Renton KW, Eade NR. Hepatic microsomal drug oxidation and electron transport in newborn infants. J Pediatr 85:534–542 (1974).
33. Hornig MG, Butler CM, Nowlin J, Hill RM. Drug metabolism in the human neonate. Life Sciences 16:651–672 (1975).
34. Bonati M, Latini R, Marra G, Assael BM, Parini R. Theophylline metabolism during the first month of life and development. Pediatr Res 15:304–308 (1981).
35. Tseng KY, King KC, Takieddieen FN. Theophylline metabolism in premature infants. Clin Pharmacol Ther 29:594–600 (1981).
36. Redmond GP, Bell JJ, Nicholls PS, Perel JM. Effect of growth hormone on human drug metabolism: time course and substrate specificity. Pediatr Pharmacol 1:63–70 (1980).
37. Ecobichon DJ, Stephens DS. Perinatal development of human blood esterases. Clin Pharmacol Ther 14:111–114 (1973).
38. Phelps SJ, Evans WE, Chesney RW. Advances in pediatric pharmacokinetics and therapeutics. J Pediatr 117:996–1001 (1990).
39. Lares-Asseff I, Cariotti J, Santiago P, Perez-Ortiz B. Pharmacokinetics of metronidazole in severely malnourished and nutritionally rehabilitated children. Clin Pharmacol Ther 51:42–50 (1992).
40. Guignard JP, Torrado A, DaCunha O, Gautier E. Glomerular filtration rate in the first three weeks of life. Pediatrics 92:268–272 (1975).
41. Arant BS Jr. Developmental patterns of renal functional maturation compared in the human neonate. J Pediatr 92:705–712 (1978).
42. Hook JB, Hewitt WR. Development of mechanisms for drug excretion. Am J Med 62:497–506 (1982).
43. Nakata MC, Powell DA, Durrell DE, Miller MC, Glazer JP. Effect of gestational age and birth weight on tobramycin kinetics in newborn infants. J Antimicrob Chemother 14:59–65 (1984).
44. Kuhn RJ, Nakata MC, Powell DA, Bickers RG. Pharmacokinetics of netilmicin in premature infants. Eur J Clin Pharmacol 29:635–637 (1986).
45. Janicke DM, Rubio TJ, Wirth FW Jr, Karotkin EH, Jusko WJ. Developmental pharmacokinetics of mezlocillin in newborn infants. J Pediatr 104:773–781 (1984).
46. Szefler SJ, Wynn RJ, Clarke DF, Buckwald S, Shen D, Schentag JJ. Relationship of gentamicin serum concentrations to gestational age in pre-term and term neonates. J Pediatr 92:705–712 (1978).
47. Jungbluth GL, Wirth FH Jr, Rubio TT, Janicke DM, Jusko WJ. Developmental pharmacokinetics of mezlocillin in 4 newborn infants. Dev Pharmacol Ther 11:317–321 (1988).
48. Birnbaum LS. Pharmacokinetic basis of age-related changes in sensitivity to toxicants. Annu Rev Pharmacol Toxicol 31:101–128 (1991).
49. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJL. Alterations in leukocyte β-receptor affinity with aging. N Engl J Med 310:815–819 (1984).
50. Ballard PL. Glucocorticoid receptors in the lung. Fed Proc 36:2660–2665 (1977).
51. Mirkin BL. Ontogenesis of the adrenergic nervous system: functional and pharmacologic implications. Fed Proc 31:65–73 (1972).
52. Fisher DM, O’Keeffe C, Stanski DR, Cronnelly R, Miller RD, Gregory G. Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children and adults. Anesthesiology 57:203–208 (1982).
53. Walson PD, Edwards R, Cox S. Neonatal therapeutic drug monitoring—its clinical relevance. Ther Drug Monit 11:425–430 (1989).
54. Giaoco GP. The future of neonatal therapeutic drug monitoring. Ther Drug Monit 12:311–315 (1990).
55. Gilman JT. Therapeutic drug monitoring in the neonate and paediatric age group. Clin Pharmacokinetic 19:1–10 (1990).