CHAPTER 6

DRUG DOSING IN PEDIATRIC PATIENTS

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Pediatric patients have been labeled *therapeutic orphans* because of the lack of pharmacokinetic, pharmacodynamic, efficacy, and safety data necessary to provide safe and effective drug therapy to this population. Efficacy and safety trials of new drugs are initially conducted in adult patients, most often excluding infants, children, and pregnant women. Many drugs routinely used in pediatric patients do not have pediatric labeling. Rather, safety and efficacy data may come from trial and error approaches with use of these drugs.

Children of all ages should not be considered miniature adults; adult doses scaled down based on body weight may not be as safe or effective in the pediatric population as in adults. Further, as neonates develop into toddlers and then young adolescents, physiologic events occur that change the body composition and organ function. Changes in body water, body fat, plasma proteins, hormonal composition, and renal and hepatic function all occur and influence drug disposition.

Table 6-1 shows the classification of the pediatric population into distinct age groups and provides selected birth age terminology.[1,2] However, physiological changes resulting in growth and development of a human body do not strictly occur within these age-related boundaries and are often not linearly related to age. Drug disposition in pediatric patients may change due to certain intrinsic factors such as sex, race, heredity, inherited diseases, and certain extrinsic factors such as acquired diseases, diet, and prior exposure to drug therapy. To provide safe and effective drug therapy to pediatric patients, it is important to gain knowledge of the pharmacokinetic and pharmacodynamic properties of each drug and the effect of development on its disposition. Within the pediatric population, neonates (especially premature neonates) exhibit marked differences in body composition and organ function when compared to each other and to the rest of the pediatric population. This chapter focuses on the influence of growth and maturation on drug disposition and pharmacodynamic response to drugs in the pediatric population, ranging from neonates to adolescents.

TABLE 6-1. AGE GROUPINGS OF CHILDREN AND BIRTH AGE

Terminology	Age Grouping
Neonates	Birth to 4 weeks of age
Premature neonate	Gestational age <37 weeks at birth
Full-term neonate	Gestational age 39–40 weeks at birth
Post-term neonate	Gestational age ≥38 weeks at birth
Infant	1 to <12 months of age
Child	1–12 years of age
Adolescent	13–18 years of age
Pediatric	Birth to 18 years of age
Birth Age Terminology	
Gestational age (GA)	Number of weeks from the first day of the last normal menstrual period to birth
Postnatal age or chronological age	Age since birth
Postconceptional age or postmenstrual age	Gestational age + postnatal age, in weeks

GENERAL PHARMACOKINETIC INFORMATION

Table 6-2 lists physiologic changes that occur with aging in children and some examples of the pharmacokinetic consequences that can result from the changes.

TABLE 6-2. AGE-DEPENDENT DIFFERENCES IN PHYSIOLOGIC FUNCTIONS AND DRUG DISPOSITION

Physiologic Variability	Neonate	Infant	Child	Adolescent	Pharmacokinetic Consequence
Absorption					
Gastric pH	(>5)	(2–4)	(2–3)	↔	Increase in bioavailability of acid-labile drugs, e.g., penicillin G in neonates and infants compared to children and adults; decreased bioavailability of weak organic acids, e.g., phenobarbital[3,4]
Gastric and intestinal emptying time	↑	↑	↔	↔	Specific examples influencing drug pharmacokinetics not available.
Biliary function	↓	~ ↔	↔	↔	Reduced absorption of fat and fat-soluble vitamins D and E in neonates compared to infants and children.[5]
Pancreatic function	↓	~ ↔	↔	↔	Reduced hydrolysis and bioavailability of oral liquid ester formulations of clindamycin and chloramphenicol in neonates compared to infants and children.[6]
Gut microbial colonization	↓	~ ↔	↔	↔	Increased bioavailability of digoxin in neonates and infants compared to adults due to lack of microbial gut colonization with an oral digoxin-reducing anaerobic bacteria.[7]
Intramuscular absorption (rate and extent)	↓	↑	↑ to ~ ↔	↔	Benzathine penicillin G more rapidly absorbed in children compared to adults since no measurable activity was detected in children 18 days after the injection.[8]
Skin permeability and percutaneous absorption	↑	↑ (extent)	~ ↔	↔	EMLA should be used with caution in patients <3 months of age due to risk of methemoglobinemia from increased percutaneous absorption of prilocaine and decreased methemoglobin reductase, especially in combination with other methemoglobinemia-inducing agents.[9]
Distribution					
Total body water and extracellular water	↑	↑	↓ ~ ↔	↔	Increase in mean apparent volume of distribution (V) for hydrophilic drugs, e.g., gentamicin in neonates and infants.[10,11]
Total body fat	↓	↓	Increases by ages 5–10 yr	↔	Mean apparent V for lipophilic drugs increases from infants to adults, e.g., diazepam. 1.3–2.6 L/kg in infants vs. 1.6–3.2 L/kg in adults.[12]
Total plasma proteins	↓	↓ or ~ ↔	↔	↔	Increase in V and unbound phenytoin fraction in infants and children.[13]
Renal Elimination					
Glomerular filtration	↓	↔	↔	↔	Famotidine—renal clearance reduced in neonates but equivalent to adults by 1 yr of age.[14]