6 Drug Metabolism and Disposition in Pediatric and Gerontological Stages of Life

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The clinical responses to drug administration can be greatly influenced both by the chronological age of the patient and by the relative maturity of the particular organ system that is being targeted. Human development follows a continuum of time-related events. There are unique therapeutic differences and concerns associated with the treatment of the very young and the elderly patient. Age-dependent changes in body function are known to alter the pharmacokinetic parameters that determine each compound's duration of action, extent of drug–receptor interaction, and the drug's rates of absorption, distribution, metabolism, and excretion. This chapter discusses some of these principles and the cautions that must be considered when treating these particular patient populations.

DRUG DISPOSITION IN PEDIATRIC PATIENTS

In spite of recent advances in this area, knowledge of the disposition and actions of drugs in children is limited. This lack of information has made drug therapy for them difficult and dangerous. There are two major obstacles to clinical drug studies in children. One is an ethical issue, the inability to obtain true informed consent. The second obstacle is inherent to children; they grow and change rapidly. Drug studies must be performed on children at each stage of their development to determine appropriate usage for all patients.

To study drug disposition in children it is most informative to divide them into five age groups: preterm infants, term infants from birth through the first month of life, children 1 month to 2 years of age, children 2 to 12 years of age, and children 12 to 18 years of age. Tanner staging of sexual maturation may more appropriately break down this latter group. Children that are Tanner stages I, II, and III are appropriately considered children; those who are Tanner stages IV and V are considered adults.

Preterm infants, especially those near the limits of viability (24 weeks' gestation), have glomerular filtration rates approximately one-tenth that of a term newborn. Because of limitations on tubular reabsorption, they have increased urinary loss of filtered substances. Glucuronidation pathways appear after 20 weeks of gestation and so are limited in extremely premature infants.

Recent advances have made it possible for drug therapy to begin prior to birth. Many mothers and therefore their infants are receiving corticosteroids to induce maturation of the lungs. Some fetal cardiac arrhythmias, such as supraventricular tachycardia, are successfully managed by treating the mother during pregnancy. Since most drugs cross the placenta, the infant has the potential to be affected by drugs that the mother takes. Metabolism and excretion are not the responsibility of the fetus, as the placenta and the maternal liver and kidneys contribute significantly to drug elimination.

At birth, term infants can metabolize and eliminate drugs. For most patients these systems did not function during fetal life and therefore even at birth are not very efficient. Table 6.1 outlines the time required for maturation of some of the systems used in drug absorption and elimination. Table 6.2 lists other factors that alter drug disposition in newborns. The ability to absorb and eliminate drugs increases slowly over the first month of life.

TABLE 6.1 Age-related Maturation of Selected Systems

System	Age Adult Level Attained
Gastric acid production	3 mo
Gastric emptying	6–8 mo
Hepatic metabolism	
Phase I enzyme reactions	5 mo–5 yr
Phase II enzyme reactions	3–6 mo
Excretion	
Glomerular filtration	3–5 mo
Tubular secretion	6–9 mo
Renal blood flow	5–12 mo

Maternally administered drugs also may affect infants who are breast-fed. Most drugs are present in breast milk in small quantities. However, several drugs can reach concentrations sufficient to adversely affect the newborn. Drugs that are contraindicated during breast-feeding include cocaine, ergotamine, and cimetidine. Unfortunately, for many drugs the information regarding risks to the infant from drug in breast milk is not available.

The period from 1 month to 2 years of age is a time of rapid growth and maturation. By the end of this period, most systems function at adult levels. Paradoxically, between 2 and 12 years of age drug clearance greatly increases and often exceeds adult levels. Half-lives are shorter and dosing requirements are frequently greater than for adults (Table 6.3).

From 12 to 18 years of age sex differences start to appear. These differences are often associated with a decreased drug absorption and elimination in the female as opposed to the male. Females have less gastric acidity and an increased gastric emptying time. Estrogens decrease hepatic cytochrome P450 content and therefore may decrease metabolism of some drugs via phase I pathways. Cyclic changes in glomerular filtration are noted during the menstrual cycle.

Absorption

Oral absorption of drugs is influenced by gastric acidity and emptying time. Gastric acid is rarely found in the stomach of infants at less than 32 weeks' gestation. Acid initially is secreted within the first few hours after birth, reaching peak levels within the first 10 days of life. It decreases during the next 20 days of extrauterine life. Gastric acid secretion approaches the lower limits of adult values by 3 months of age. The initiation of acid secretion is often delayed in infants with delayed initiation of oral feedings, such as extreme preemies and those with anomalies of the gastrointestinal tract.

TABLE 6.2 Other Factors Affecting Newborn Drug Disposition

Increased body water
Decreased body fat
Decreased exocrine pancreatic function
Decreased albumin concentration and binding
Decreased total plasma protein

TABLE 6.3 Age-dependent $t_{1/2}$ of Trimethoprim

Age	$t_{1/2}$ (hr)
Newborn	10.8
1–3 yr	3.7
8–10 yr	5.4
Young adult	11.2

Gastric emptying time in infants is related to their age and to the type of formula they receive. Formulas containing long-chain fatty acids will delay gastric emptying. Both gastric emptying time and small-intestine peristalsis tend to be slow until the later part of the first year of life. In children aged 2 to 12 years gastric emptying time dramatically increases, as does splanchnic blood flow. These physiological changes result in faster drug absorption and increased peak blood concentrations of drug. The decreased small intestine transit time during this period may result in decreased absorption of some drugs. Because of low blood flow through muscles in the neonatal period, drugs administered intramuscularly are absorbed erratically.

Percutaneous drug absorption can present special problems in newborns, especially in preterm infants. While the skin of a newborn term infant may have the same protective capacity as the skin of an adult, a preterm infant will not have this protective barrier until after 2 to 3 weeks of life. Excessive percutaneous absorption has caused significant toxicity to preterm babies. Absorption of hexachlorophene soap used to bathe newborns has resulted in brain damage and death. Aniline dyes on hospital linen have caused cyanosis secondary to methemoglobinemia, and EMLA (lidocaine/prilocaine) cream may cause methemoglobinemia when administered to infants less than 3 months of age.

Distribution

The total body water of prematures, newborns, and infants is significantly greater than it is for older children and adults. This increased total body water increases the volume of drug distribution for water-soluble compounds. As a consequence, there is a need to administer

loading doses of some drugs. Differences in total body water are basically insignificant after the first year of life. Newborns have decreased body fat and therefore less storage ability for fat-soluble drugs.

Newborns, especially prematures, have decreased plasma albumin and total plasma protein concentrations. In addition, albumin from these patients shows a decreased drug-binding affinity. This may result in increased plasma levels of free drug and the potential for toxicity. In the past, concerns were raised that certain drugs, such as sulfonamides, could displace endogenous substances, like bilirubin, from albumin-binding sites. Theoretically, such an interaction would increase the risk for kernicterus. Although this belief has been challenged recently, reluctance to treat newborns with sulfonamides persists.

Metabolism

As with adults, the primary organ responsible for drug metabolism in children is the liver. Although the cytochrome P450 system is fully developed at birth, it functions more slowly than in adults. Phase I oxidation reactions and demethylation enzyme systems are significantly reduced at birth. However, the reductive enzyme systems approach adult levels and the methylation pathways are enhanced at birth. This often contributes to the production of different metabolites in newborns from those in adults. For example, newborns metabolize approximately 30% of theophylline to caffeine rather than to uric acid derivatives, as occurs in adults. While most phase I enzymes have reached adult levels by 6 months of age, alcohol dehydrogenase activity appears around 2 months of age and approaches adult levels only by age 5 years.

Phase II synthetic enzyme reactions are responsible for the elimination of endogenous compounds, such as bilirubin, and many exogenous substances. The immaturity of the glucuronidation pathway was responsible for the development of gray baby syndrome (see Chapter 47) in newborns receiving chloramphenicol. Preterm and newborn infants dying of this syndrome developed anemia and cardiovascular collapse because of high blood concentrations of unconjugated chloramphenicol. The plasma half-life was found to be 26 hours in these patients compared with 4 hours in older children.

Infants and children have a greater capacity to carry out sulfate conjugation than do adults. For example, acetaminophen is excreted predominantly as a sulfate conjugate in children as opposed to a glucuronide conjugate in adults. This enhanced sulfation of acetaminophen, along with decreased metabolism via cytochrome P450 pathways and increased glutathione turnover, are thought to explain the decreased hepatotoxicity caused by this analgesic in children under 6 years of age. Phase II enzyme systems reach adult levels between 3 and 6 months of age.

Excretion

Renal blood flow, glomerular filtration rate, and tubular function are reduced in both preterm and term neonates. Therefore, newborns, especially those less than 34 weeks' gestation, require less frequent dosing intervals for many drugs. Aminoglycosides are administered every 8 hours in older children, every 12 hours in newborns, and every 24 hours in extremely premature infants. The glomerular filtration rate of the term newborn is approximately 50% less than the adult level but reaches adult values by 1 year of age. Renal blood flow approaches adult values between ages 5 and 12 months. Tubular secretory functions mature at a slower rate than does glomerular filtration. Renal excretion of organic anions, such as penicillin, furosemide, and indomethacin, is very low in the newborn. Tubular secretion and reabsorption reach adult levels by 7 months of age. Renal elimination of drugs appears to play a greater role than does metabolism in newborns. Over the first year of life the infant develops a more adult-type excretory pattern.

Drug Action

Most drugs are administered to infants and children for the same therapeutic indications as for adults. However, a few drugs have found unique uses in children. Among these are theophylline and caffeine, which are used to treat apnea of prematurity; indomethacin, which closes a patent ductus arteriosus; and prostaglandin E_1, which maintains the patency of the ductus arteriosus. Paradoxically, drugs such as phenobarbital, which have a sedating action on adults, may produce hyperactivity in children, and some adult stimulant drugs, such as methylphenidate, are used to treat children with hyperactivity.

Adverse Reactions

Children may display adverse reactions different from those noted in adult patients. Table 6.4 lists a number of drugs that demonstrate unique actions in children.

Special Considerations

Several problems unique to pediatric drug therapy deserve special mention. For example, most medications are commercially available only in adult dose forms. Preparing pediatric doses from adult tablets or capsules can be very difficult and may require special skill on the part of the pharmacist. For some drugs it is simpler to administer the intravenous (IV) preparation orally than to develop a preparation from the oral medication.

IV drug administration is most effective in children when given via a pump infusion system close to the site of IV insertion. Because of the small size of many pediatric doses and the fact that some drugs adhere to IV tubing, a significant percentage of the drug can be lost if

TABLE 6.4 Pediatric Specific Adverse Drug Reactions

Drug	Reaction
Furosemide (*Lasix*)	Nephrocalcinosis
Indomethacin (*Indocin*)	Renal Failure, bowel perforation
Adrenocorticoids	Delayed development, growth suppression
Tetracyclines	Discolored teeth
Phenobarbital	Hyperactivity, impaired intellectual development
Phenytoin (*Dilantin*)	Thickened skull, coarse features
Chloramphenicol	Gray baby syndrome
Phenothiazines	Extrapyramidal reaction
Valproic acid (*Depakene*)	Hepatotoxicity (<2 yr)
Aspirin	Reye's syndrome in patients with chickenpox or influenza

Compiled from Outslander JG. Drug therapy in the Elderly. Ann Intern Med 1981;95:711; and Richey DP and Bender AD. Pharmacokinetic consequences of aging. Annu Rev Pharmacol Toxicol 1977;17:49; and references therein.

it is given using techniques usually reserved for adults. For many prematures and newborns, the volume of administration is also critical and therefore much more easily managed by IV infusion pumps.

Most adult drugs must be diluted to achieve appropriate pediatric dosages. Some drugs must be diluted several times. This introduces the potential for significant error in dilution. Some drugs such as NPH (Neutral Protamine Hagedorn) insulin may lose their effectiveness if diluted.

Children with chronic illnesses require special consideration. For example, patients with cystic fibrosis have increased hepatic metabolism and therefore increased drug clearance. This may necessitate the administration of increased drug dosages.

Calculation of pediatric dosages is usually done on the basis of weight (e.g., milligrams per kilogram) for infants and toddlers and on the basis of weight or body surface area (milligrams per square meter) for older children. Repeated increases in drug dosage are required to accommodate for growth in children receiving chronic drug therapy.

In summary, children, especially those in the first year of life, present significant pharmacological challenges. Drug administration must be tailored to meet the unique needs of children at their varied stages of development. Special attention must be given to unexpected drug actions and adverse reactions in these patients, who are maturing at variable rates. When planning drug therapy for children, it is important to remember:

- Children are not small adults.
- Infants are not small children.
- Newborns are not small infants.
- Preemies are not small newborns.

DRUG DISPOSITION IN GERIATRIC PATIENTS

The elderly (individuals over 65 years of age) constitute more than 13% of the population. This figure is increasing steadily and is expected to reach 50 million by the year 2020. This segment of our society is the most highly drug-treated and accounts for about 25% of prescription drugs dispensed. The average Medicare patient in an acute-care hospital receives approximately 10 different drugs daily, and this translates into a higher incidence of adverse drug reactions in geriatric patients than in the general population.

Chronological aging may not necessarily be an accurate index of biological aging, which is the result of many genetic and environmental factors. While most 20-year-olds have a similar response to a given drug, it is difficult to predict the response among 80-year-olds. A clear relationship between the appearance of untoward effects to drugs and aging has been demonstrated only for about 10 drugs. For some 90 other drugs in common clinical use, age alone was not a major determinant of clinical toxicity. It is apparent that an increase in life span is accompanied by an increase in chronic illnesses such as hypertension, congestive heart failure, arthritis, and diabetes. The pharmacological management of these conditions, especially when the same person has several diseases, becomes increasingly complex.

Age-related alterations in pharmacokinetics (absorption, distribution, metabolism, and excretion) have received considerable attention. Thus, physiological changes in elderly patients, when taken together, may contribute to impairments in drug clearance in this segment of the population (Table 6.5).

Absorption

Elderly patients may absorb drugs less completely or more slowly because of decreased splanchnic blood flow or delayed gastric emptying. Reduced gastric acidity may decrease the absorption of drugs that require high acidity.

Distribution

Drug distribution in elderly patients may be altered by hypoalbuminemia, qualitative changes in drug-binding sites, reductions in relative muscle mass, increases in the proportion of body fat, and decreases in total body water. The plasma level of free, active drug is often a direct function of the extent of drug binding to plasma proteins. There is a well-documented age-dependent decline (about 20%) in plasma albumin concentration in humans due to a reduced rate of hepatic albumin

TABLE 6.5 Plasma Half-lives of Several Drugs in Young Adult and Elderly Patients

Drug	Plasma or serum $t_{1/2}$	
	Young (20–30 yr)	Elderly (65–80 yr)
Penicillin G	20.7 min	39.1 min
Dihydrostreptomycin	5.2 hr	8.4 hr
Tetracycline	3.5 hr	4.5 hr
Kanamycin	107.0 min	282.0 min
Digoxin	52.0 hr	73.0 hr
Aminopyrine	3.0 hr	10.0 hr
Phenobarbital	71.0 hr	107.0 hr
Diazepam	20.0 hr	80.0 hr
Lidocaine	80.6 min	139.6 min
Chlordiazepoxide	8.9 hr	16.7 hr
Antipyrine	12.0 hr	17.4 hr
Phenylbutazone	81.2 hr	104.6 hr
Isoniazid	1.4 hr	1.5 hr
Warfarin	37.0 hr	44.0 hr

Source: Compiled from J.G. Ouslander, Drug therapy in the elderly. *Ann. Intern. Med.* 95:711, 1981; and D.P. Richey and A.D. Bender, Pharmacokinetic consequences of aging. *Annu. Rev. Pharmacol. Toxicol.* 17:49, 1977, and references therein.

synthesis. These changes in serum albumin may affect the free drug concentration for a number of highly bound drugs, such as phenytoin, warfarin, and meperidine.

Metabolism

In addition to changes in metabolism that occur as a result of reduced hepatic enzyme activity, metabolism may be impaired by a reduction in hepatic mass, volume, and blood flow (Fig. 6.1). Phase I oxidative pathways are decreased with age, while phase II conjugation pathways are unchanged.

In a carefully controlled clinical study, the plasma half-life of diazepam (Valium), a widely used antianxiety agent, exhibited a striking age dependency. In patients aged 20 years, the $t_{1/2}$was about 20 hours, and this increased linearly with age to about 90 hours at 80 years. Half-lives of other drugs in young and old patients are presented in Table 6.5. These data demonstrate changes in drug half-life with increasing age, suggesting that at least for some drugs, elderly patients have reduced metabolism, drug clearance, or both.

Excretion

Renal elimination of foreign compounds may change dramatically with increasing age by factors such as reduced renal blood flow, reduced glomerular filtration rate, reduced tubular secretory activity, and a reduction in the number of functional nephrons. It has been estimated that in humans, beginning at age 20 years, renal function declines by about 10% for each decade of life. This decline in renal excretion is particularly important for drugs such as penicillin and digoxin, which are eliminated primarily by the kidney.

Adverse Drug Effects

The incidence of iatrogenic complications is three to five times greater in the elderly than in the general population. Adverse drug reactions account for 20 to 40% of these complications. Inappropriate drug use has been noted in almost half of hospitalized elderly patients. One-fourth of these patients were receiving contraindicated drugs, and three-fourths were receiving unneces-

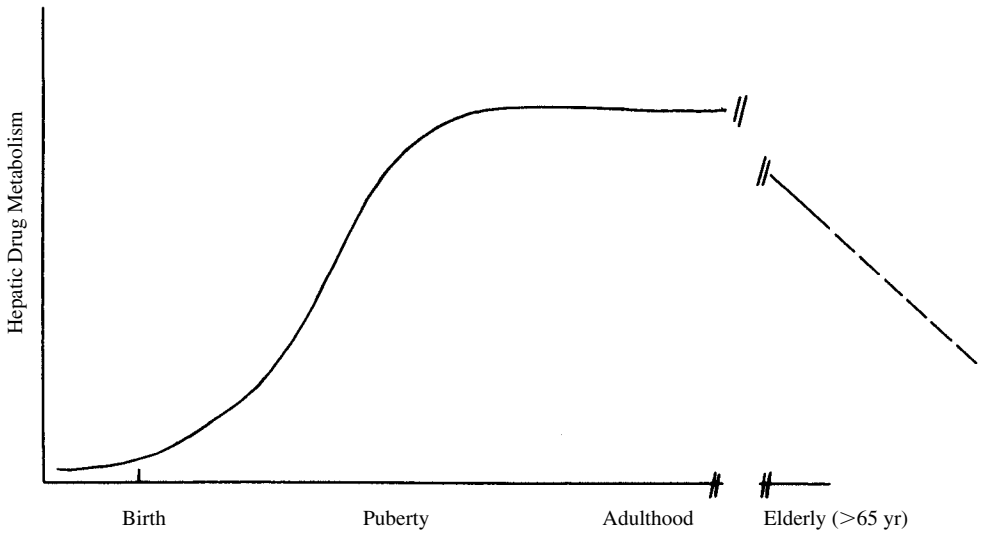

FIGURE 6.1
The ontogeny of hepatic drug metabolic activity.

sary drugs. Half of adverse drug reactions occur in patients receiving inappropriate drugs.

Delirium and cognitive impairment are common adverse reactions in the elderly. While almost every class of drugs has the potential to produce delirium in the elderly, it is most frequent with psychoactive drugs. The risk increases with the number of drugs the patient is receiving, reaching a 14-fold increase in risk for patients taking more than 6 drugs.

Special Considerations

The following should be considered when prescribing drugs for elderly patients.

Drugs should be prescribed only if nonpharmacological techniques are ineffective, such as for problems like sleeplessness and anxiety. When drugs are prescribed for these conditions, they should be given for a limited time and the patient closely monitored for adverse effects. Dosage should start at or below the lowest recommended levels.

Keep it simple. Prescribe drugs only if you have available extensive experience and prescribing information for that drug in elderly patients. Use the least number of drugs and doses per day.

Reevaluate the continued use of all medications the patient is receiving, including over-the-counter medications, on a regular basis.

Noncompliance is a significant problem, with almost 50% of elderly patients failing to take their medications as prescribed. Some of the reasons for noncompliance are inability to pay for the drug, side effects, mental impairment, and inability to understand complex instructions.

SUMMARY

Physicians should exercise caution when prescribing drugs for pediatric and geriatric patients. This is virtually axiomatic in premature infants, whose severely restricted ability to metabolize drugs is well documented. Caution also must be exerted in prescribing for the elderly population, since these individuals may be taking 10 to 15 different drugs daily. Problems associated with drug interaction and declining physiological function are very real. It is simply inadequate to administer drugs to very young and very old patients strictly on a body mass basis. Dose adjustments often must be made empirically, depending upon the changing pharmacokinetic characteristics of the drug in question, the nature of the disease, and the physiological status of the major organs and tissues involved in drug absorption, distribution, metabolism, and excretion.

Study Questions

1. It is well established that most drugs taken by pregnant women are capable of crossing the placenta and reaching the developing fetus. The placenta itself can aid in the protection of the fetus from excessive exposure to drugs in the maternal circulation by
(A) Impairing diffusion of lipid soluble drugs
(B) Preventing the passage of drugs having a molecular weight under 250
(C) Playing a role as a site of drug metabolism
(D) Secreting drugs from the fetal circulation to the maternal circulation

2. Neonates having a patent ductus arteriosus can be treated with which agent to induce a relatively rapid closure and thus often avoid surgical intervention?
(A) Phenobarbital
(B) Indomethacin
(C) Hydrochlorothiazide
(D) Prostaglandin E_1
(E) Epinephrine

3. Which of the following is an accurate description of changes taking place in elderly individuals compared to younger adults?
(A) Increased lean body mass
(B) Diminished body fat as a relative percentage of total body mass
(C) Increase in the levels of plasma proteins
(D) General increase in hepatic drug metabolizing capacity
(E) Decrease in renal clearance of many drugs

4. A neonate is given drug A, a compound with a high affinity for plasma proteins, in a dose that does not exceed the binding capacity of albumin. Later, a second drug, B, that also binds strongly to albumin, is given in amounts that greatly exceed albumin's binding capacity. Which of the following statements is most likely to be true?
(A) The free plasma concentration of drug A is decreased.
(B) The relative free drug concentration of both compounds is unchanged.
(C) The concentration of drug A in tissues is likely to be increased.
(D) The concentration of drug A in tissues is likely to be decreased.
(E) The free plasma concentration of drug B would likely be markedly increased if drug A were given second rather than first.

5. Mr. Johnson, a 70-year-old, has come into a physician's office complaining of not being able to sleep well at night because of residual pain associated

with a recent hip replacement. He is taking a thiazide diuretic (A) for mild hypertension, digitalis (B) for congestive heart failure, and an oral hypoglycemic agent (C) for mild type 2 diabetes. An opioid analgesic (D) that gave him considerable pain relief when he broke his arm 30 years ago is prescribed. About a week later Mr. Johnson is seen in the emergency department complaining of shortness of breath and a feeling of suffocation. Which of the drugs he is receiving is a likely possible cause of this particular symptom?

ANSWERS

1. **C.** The placenta can serve as a site of metabolism for some drugs passing through it. The placenta can carry out a number of drug metabolizing reactions, including dealkylation and hydroxylation. Lipophilic drugs readily diffuse across the placenta and enter the fetal circulation; drugs with a molecular weight of under 500 generally can easily cross the placenta; and no known active transport systems play any important role in drug secretion in the placenta.
2. **B.** Indomethacin's action as a potent nonselective COX inhibitor appears to be important in speeding up ductus closure. The other drugs do not have such an action, and prostaglandin E_1 given by infusion would cause the ductus to remain open.
3. **E.** The kidney, the most important organ involved in drug clearance, especially of highly water-soluble drugs, shows an age-related decline in function. Lean body mass decreases, percentage of body fat increases, production of plasma proteins decrease, and drug metabolism decreases for most drugs as patients reach their seventh and eighth decade.
4. **C.** The large amounts of drug B that are given can displace the almost completely bound drug A from its albumin binding site and lead to an increase in free drug. The latter is then available to be distributed outside the blood compartment and reach tissues where its concentrations will increase.
5. **D.** The elderly are frequently sensitive to the pulmonary depressing actions of opioid analgesics. These agents should be used with caution in the elderly until an adequate dosage has been determined for a particular patient. This does not mean that the older patient should not be given opioid analgesics for pain, however, since appropriate pain management should always be part of any total clinical treatment plan.

SUPPLEMENTAL READING

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CASE Study A Choice of Sedative

Mrs. Jones celebrated her 71st birthday by taking her grandchildren to the park. She fell while pushing the merry-go-round and broke her wrist. She has no pain now but is too uncomfortable with the cast to sleep well. She has tried soothing music, reading, and relaxing techniques but is still unable to sleep. She has requested a sleeping pill. Based on knowledge of psychotropic drugs in elderly patients, what medication would be an appropriate choice?

ANSWER: Benzodiazepines are effective for short-term use as sedative–hypnotics. Long-acting types with active metabolites, such as diazepam, would normally be expected to have a prolonged half-life. The half-life would be even more prolonged in Mrs. Jones because of the increase in body fat and decreased renal excretion that are typical for persons of her age. After several weeks of administration, daytime confusion may occur in this patient and may put her at risk for a fall and another serious injury. A short-acting benzodiazepine with inactive metabolites, such as oxazepam, could provide the desired effect with minimal adverse effects.