Accounting for Pharmacokinetic and Pharmacodynamic Variability
Ten Factors to Consider Before Prescribing

PATRICIA O’MALLEY, PhD, RN, CNS

Outcomes of pharmacological therapy are more than an accurate assessment and appropriate choice of an agent. Patient outcomes are the result of complex interactions of factors known and unknown. This study explores 10 of many factors that clinical nurse specialists should consider before writing the prescription and monitoring responses to therapy.

The time course of drug action in the body can be defined as pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the processes that begin immediately when a drug enters the body and include absorption, distribution, metabolism (biotransformation), and elimination. All of these processes require passage of drug across cell membranes as well as a relationship with a receptor to drive drug action. Pharmacodynamics describes the process of drug action in the body. Pharmacokinetic and pharmacodynamic variability can significantly influence risks associated with medication therapy as well as patient outcomes. Broadly viewed, variability may be a function of clinical findings, genetics, and concomitant drug therapies.

Before prescribing any therapy, it is important to consider some of the significant factors that may impact therapy outcomes.

**BODY COMPOSITION**

Body composition can be described as the amount of water per kilogram of body weight. Volume overload, fluid shifts, or dilution effects can significantly alter the distribution of many drugs. Water composition is particularly important when prescribing water-soluble agents such as aminoglycoside antibiotics. Use special caution with neonates that have a higher volume of water to kilogram of body weight compared with adults, which significantly influences drug distribution. Always consider correcting dehydration or hypovolemia before beginning highly water-soluble drug therapy, and use ideal or lean body weight for dosing.

For lipid/fat-soluble drugs like Valium, it may be more appropriate to use total body weight for appropriate dosing. However, in some cases, use of lean body weight may be more appropriate to avoid drug toxicity. Certainly, more research is needed to determine the best practice for weight dosing of lipid/fat-soluble drugs. Finally, it is wise to remember, in light of a heavier population, that body size is not correlated with increases in hepatic and renal function.

Available proteins for binding are another body composition characteristic. Membrane proteins imbedded in cell bilayer may serve as ion channels, receptors, or transporters or selective sites for drug action. The degree of drug binding significantly affects drug disposition and movement in the body as much as molecular size, shape, ionization, and lipid solubility.

Finally, body composition can be expressed as the number of available receptor sites. Receptor site failure, upregulation or downregulation, changes in number of receptor sites, and multidrug competition for receptor sites can significantly influence outcomes of therapy.

**AGE**

Exercise caution in prescribing for the very young and very old since drug clearance is significantly influenced by age. Renal function is very low at birth and gradually increases during the first 2 weeks of life. During aging, decreases in cardiac output, plasma volume, and albumin as well as increasing body fat influence drug metabolism and excretion. Normal functional decline in renal function also occurs with aging and is present even with a normal creatinine clearance.

**RENAL FUNCTION**

Deterioration in renal function is a primary reason for drug dose adjustment. Glomerular filtration, molecular weight and electrical charge, degree of protein binding, and blood
flow influence renal filtering processes. With renal impairment, the dose or dosing interval may need to be modified to account for elimination half-life of the chosen agent.

Hemodialysis can remove some drugs. However, considering the short dialysis time, only a small amount of the drug is usually removed. For dialysis patients receiving antibiotics or antifungal agents, consider administration after dialysis to ensure therapeutic concentrations are maintained. Renal replacement therapy, particularly with newer ultra filtration with higher flow rates, can significantly affect drug clearance, dosage requirements, and outcomes.

HEPATIC FUNCTION

Unlike renal factors, hepatic indices cannot be directly tied to drug dosing. Elevated liver enzymes, low serum albumin, and coagulation abnormalities are not strongly linked to drug clearance. At birth, most enzymes are present but with low activity, and there is minimal evidence to suggest that liver function declines with age.

However, exercise great caution prescribing therapy for the patient with hepatic cirrhosis. Declines in first pass metabolism due to structural and circulatory changes associated with cirrhosis reduce drug delivery to the hepatocyte and increase drug bioavailability. Therefore, lower drug doses are generally required to avoid toxicity.

GENDER AND GENETICS

Except for gender-specific drugs, drug metabolism is not significantly different for males and females after correction for weight. However, individual isoenzyme production significantly impacts drug metabolism and dosing requirements. For example, cytochrome PH502D6 isoenzyme (CYP2D6) catalyzes many antiarrhythmics, antidepressants, and antipsychotic drugs. In addition, the genetic variability of glycoproteins influences the distribution, absorption, and elimination of many drugs. In the future, genetic screening may be required to determine individual drug doses for some therapies and may be used to predict genetic variability in pharmacokinetics.

DRUG ABSORPTION

Absorption influences transfer of drug across membranes and bioavailability. Drug formulation, solubility, resistance to gastric acid, intestinal enzymes, motility, and interactions with other drugs and food affect enteral absorption. The rectal route provides a more stable absorption than the remainder of the gastrointestinal tract.

If blood flow to the gastrointestinal is low or there is low motility, drug can potentially accumulate, resulting in toxic or unpredictable effects when blood flow or motility improves. Although parenteral routes avoid many of the problems with enteral absorption, the risks for toxicity and unpredictable effects remain if blood flow to tissues is low such as in shock states.

Intravenous delivery offers a stable drug delivery alternative. However, the degree of protein binding, ability to diffuse across the endothelium, interstitial fluid, and cellular membranes as well as blood flow to organs influence intravenous delivery outcomes.

DRUG INTERACTIONS

Drug interactions may be related to induction or inhibition of metabolizing enzymes or transporter proteins. If the interacting drug has a long elimination half-life, the interaction effect may persist for a long period after discontinuation.

HYPOXIA

Oxygen influences pharmacokinetics. Hypoxia decreases cytochrome P450 expression, which negatively affects the metabolism of many drugs. Drugs that increase oxygen consumption such as vaspressors, when administered in hypoxia, can lead to ischemic hepatitis as well as drug toxicity.

STRESS

Increased catecholamines during stress decreases overall liver flow and can mediate hepatocyte hypoxia and decreased enzyme expression needed for drug metabolism.

PATIENT CHARACTERISTICS

Health and disease states have profound effects on pharmacokinetics. Pregnancy, cardiac or respiratory disease, and infection can significantly impact pharmacokinetics and pharmacodynamics related to the hormonal, mediator, and chemical processes associated with these states.

Nutrition may play a significant role in pharmacokinetics. Patients consuming high protein, high lipid, and low carbohydrate diets have elevated cytochrome P450 that increases clearance of many drug therapies.

Allergy expression can range from a mild rash to anaphylaxis. Careful screening and monitoring is necessary to detect allergic responses and to prevent diagnosis of a drug reaction as an illness.

Finally, variations in adherence, missed doses, and unequal dose intervals can significantly affect responses to therapy particularly if the half-life of the drug is short. The impact of patient health, allergy, and compliance can be controlled by careful screening, education, and monitoring by the CNS.

References