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Objectives

After completing this chapter, the reader should be able to

- Describe the impact of culture, environment, and genetic variations on drug responses between individuals.
- Identify known and possible factors that influence the cytochrome P-450 system.
- Relate basic genetic concepts to the nurse anesthetist's pharmacology practice.
- Summarize the effect of common genetic polymorphisms on drug target proteins, drug metabolizing enzymes, and other biochemical systems that influence pharmacotherapy.
- Devise a clinically relevant strategy for assessing factors that may affect an individual's response to drugs.

3
Cultural, Environmental, and Genetic Influences on Drug Therapy

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Introduction

Clinical pharmacology requires that healthcare providers make decisions about issues such as drug dosages, timing, and monitoring for intended and unintended effects. This need led to the development of standardized drug doses, dosing intervals, therapeutic blood concentrations, and lists of frequent adverse effects and complications. Using these standardized tools is helpful for all healthcare providers. It is well recognized, however, that responses to drugs vary between individuals.

Unpredictable differences in both pharmacodynamics and pharmacokinetics pose many challenges in clinical pharmacology decision making, particularly for anesthesia providers. Most medications administered during anesthesia are administered through inhalation or intravenous routes. These routes typically provide for a short time interval until both intended effects and adverse effects are observed. Opportunities for monitoring serum concentrations are limited because of time constraints. Additionally, many agents used to create and maintain an anesthetized state carry a high risk of a variety of life-threatening effects, such as apnea, bradycardia, vasodilation, and/or changes in intracranial pressure. The time intervals between onset, effect, observable physical manifestations of the effect, and deleterious outcomes can be very brief. Hence, there is a need for every anesthesia provider to be able to predict, evaluate, deduce, and react to individual drug responses with both speed and accuracy. Strategies to help better predict interindividual response differences to drugs should lead to safer anesthesia care, a primary objective for all anesthesia providers.

Historic Perspective

Understanding the basic principles of pharmacodynamics and pharmacokinetics is imperative for anesthesia providers. Because the science behind these concepts is evolutionary, practitioners must be dedicated to engaging in lifelong learning. Consider how the trial-and-error approach to drug therapy has been pervasive in the history of health care. Choosing a dose of medication and then being prepared to either administer additional doses or counteract the drug's effect has been a pervasive theme in numerous healthcare specialties. The recognition that the therapeutic window of many drugs is very small, especially those used in anesthesia, has supported the need to identify those indicators that may influence whether a drug dose is efficacious or toxic.

Reasons for variations in drug responses between people have been postulated for more than two centuries. Factors such as age, body weight, allergies, cigarette smoking, and the impact of concurrent medication use are examples of the many influences that have been assessed by practitioners from the mid-1800s through today (Table 3-1). During the past several decades research has supported the need to consider these cultural and environmental factors, as well as other possible determinants. The combined influence of these factors is sometimes referred to as "ethnic pharmacology" or "ethnopharmacology." The term ethnopharmacology more accurately refers to the study of a culture's traditional use of plants for medicinal purposes.

The idea that genetics may impact a person's response to a drug is also traced back to the 1800s though the works of scientists such as Francis Galton, Archibald E. Garrod,

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Table 3-1 Common Factors Attributed to Variable Drug Responses

Identified differences in anatomy and physiology
Existing pathologic conditions
Known or suspected allergies
Age
Gender
Body habitus/weight
Concurrent medication/herbal drug use (drug–drug interactions)
Exposure to environmental chemicals
Dietary habits, including alcohol intake
Cigarette smoking
Genetics
Ethnic and cultural practices

and J. B. S. Haldane.[1–3] This spirit of investigation continued through the 20th century and is ongoing today. For example, in the 1950s Kalow identified that some patients undergoing electroconvulsive therapy experienced a longer than expected effect from intravenously administered succinylcholine. This led to the idea that individual differences in the amount of plasma cholinesterase exist as a result of genetics.[4,5] Likewise, in 1960 Denborough and Lovell wrote of a family's experiences with anesthetic complications as a result of an unidentified inherited metabolic disorder.[6] This is now called malignant hyperthermia and further supports the understanding that genetics influences drug responses. Through the work of countless clinicians and scientists, a blending of two sciences—genetics and pharmacology—led to the development of the term "pharmacogenetics." The mapping of the human genome and further understanding of how people's gene variations affect how they respond to a drug resulted in the broader term "pharmacogenomics." These terms, however, are frequently used interchangeably in clinical practice today.

Today's practitioners recognize that differences between an individual's responses to an administered drug are both complex and multifactorial. A growing body of evidence is adding to the list of modifiers that lead to the interindividual variations to a given dose of a drug. Researchers continue to uncover the impact of cultural, environmental, and genetic influences on drug choice, dose requirements, and outcomes.

Cultural and Environmental Influences

Consider an individual's exposure to things like air, water, and food as exogenous substances. A person's geographic environment, food and beverage preferences, and other habits and behaviors may result in exposure to some substances more or less than others. When these nonindigenous chemical substances, referred to as xenobiotics, make contact with and enter the body, they are viewed as foreign materials. The body subsequently initiates strategies to modify, degrade, and eventually eliminate these foreign substances, calling on many of the enzymatic systems that have been developed over human evolution. In fact, these systems developed as a result of exogenous substance exposure. Repeated exposure to some substances over time may result in a variety of anatomic and physiologic changes. This includes changes to the drug targets, or the biochemical systems that absorb, distribute, metabolize, or eliminate the drugs. In some cases the body evolves to tolerate these non-naturally occurring substances.

Several biochemical systems, commonly divided into phase I and phase II reactions (see Chapter 1), are known to react with drugs in an attempt to eliminate them from the body. Examples include the cytochrome P-450 monooxygenase system, the flavin-containing monooxygenase system, the sulfotransferase system, alcohol and aldehyde dehydrogenase systems, the esterases and amidases for hydrolysis, the amino acid *N*-acyl transferases for acetylation, and the monoamine oxidase systems.

The cytochrome P-450 system is one of the most recognized and important metabolizing pathways. This collection of metabolizing microsomal enzymes act upon chemicals that enter the body through food, environment, or medications. In humans there are currently 50 known functionally active enzymes. These enzymes are labeled with the abbreviation "CYP." Based on their amino acid sequence, they are then identified by family using an Arabic numeral, followed by a subfamily classification using a letter, followed by another Arabic number to distinguish different isoforms within the subfamily.[7] For example, CYP1A2 is involved in the metabolism of caffeine, ondansetron, and theophylline. Another common enzyme, CYP3A4, is involved in the metabolism of dexamethasone, fentanyl, and oxycodone. It is supposed that the vast majority of drug oxidation involves six CYP enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[8] A gene encodes the instruction for the construction of each of the CYP enzymes. The gene that correlates with the enzyme carries the same label but is identified by italics, for example, *CYP1A2* or *CYP3A4*.

The CYP enzymes are influenced by a variety of factors, including exposure to some of the chemicals they metabolize. Some chemical substances stimulate this enzymatic system to metabolize quicker; others inhibit it. A drug therefore may undergo an enzymatic process more quickly

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or more slowly. If the originally ingested parent drug compound is responsible for exerting its effect on a target, midazolam for example, and that parent drug compound is more rapidly metabolized, less drug will be available to exert an effect. A higher dosage of that drug will be required for the intended effect. What if the ingested drug is a prodrug—that is, a compound that is inactive (or minimally active) but is metabolized into active metabolites that exert its intended pharmacologic effects? If the parent compound is metabolized more rapidly into the active metabolite, codeine for example, more of the active drug metabolite will be available quickly and could lead to a toxic effect. Among other factors, diet and nutrition are both implicated as modulators of this enzymatic system.

Dietary Influences

Until recently foods were rarely considered ingested "chemicals" that could affect the body. One exception recognized by nurses for several decades are those foods rich in vitamin K, such as green leafy vegetables, like spinach or kale. It is common knowledge that this particular food–drug interaction has the potential to alter the effectiveness of the drug Coumadin. More recently, however, the rise in popularity of various herbal remedies to prevent, influence, or treat diseases has increased awareness of the impact food can have on physiologic processes. Drawing along this line of thought, food intake could influence enzymatic activity and therefore influence the body's reactions to a drug, as suggested by the work of Parke and Ioannides.[9,10]

One food substance that has received attention for possible health effects is the phytochemical. Phytochemicals, or phytonutrients, are naturally occurring chemicals in plants that are consumed as food. Long used for medicinal purposes, it has been suggested that some phytochemicals may contribute to health by acting as antioxidants or exhibiting anti-inflammatory effects. Some examples of phytochemicals include lutein, found in leafy green vegetables, beta-carotene found in carrots and pumpkins, and lycopene found in tomatoes. An example of a phytochemical from the Pacific yew tree used in the manufacturing of a medication is the antineoplastic agent paclitaxel (Taxol).

Evidence has emerged that phytochemicals influence the cytochrome P-450 metabolic processes. Cruciferous vegetables, such as broccoli, Brussels sprouts, and cauliflower, have been shown to induce or stimulate the cytochrome P-450 enzyme CYP1A2, thereby increasing the rate of phase I biochemical processes (Table 3-2).[11–13] In vitro studies suggest that cruciferous vegetables also contain other classes of chemicals that both stimulate and inhibit various cytochrome P-450 enzymes.[14,15] The effects of vegetables in the Apiaceae family, like carrots and celery, have been shown to decrease cytochrome P-450 enzyme activity.[11]

Grapefruit juice has long been identified as a beverage that interferes with the first-pass metabolism and transportation of many drugs, including felodipine, saquinavir, midazolam, and erythromycin.[16–19] It is theorized that the compounds in grapefruit juice inhibit the intestinal cytochrome P-450 enzyme activity but facilitate drug absorption. Combined, these actions lead to an increased plasma drug level. Several studies have demonstrated prolongation of this effect lasting several days.[20–22]

Other common foods like potatoes, tomatoes, and eggplants—all high in solanaceous glycoalkaloids—may pose problems for certain drugs, including those used during an anesthetic.[23] Solanaceous glycoalkaloids reportedly inhibit both acetylcholinesterase and butyrylcholinesterase (plasma cholinesterase). As little as one serving of mashed potatoes increases serum solanaceous glycoalkaloid levels. This impacts the metabolism of many chemicals, including cocaine, ester-type local anesthetics, neuromuscular blocking agents, and esmolol. Ethnic groups who traditionally consume high quantities of these foods (e.g., those from Turkey, Morocco, and Middle Eastern regions where eggplant is a dietary staple) may very well be at risk for altered responses to these drugs. Again, additional research is needed.

Alcohol Consumption

Much has been written about the effect that drinking alcoholic beverages has on various medications and health in general. Alcohol consumption is fairly common, and the frequency of alcohol ingestion appears to vary between groups. In 2006 the Centers for Disease Control and Prevention, an agency of the U.S. Department of Health and Human Services, reported that more than 60% of adults in households surveyed consumed alcohol in the past year; 20% of current drinkers report having five or more drinks

Table 3-2 Examples of Cruciferous Vegetables

Bok choy
Broccoli
Cabbage
Cauliflower
Collard greens
Kale
Radish
Wasabi
Watercress

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on at least 1 day in the past year.[24] Some groups contain a higher percentage of alcohol consumers, although outliers certainly exist on both ends of the spectrum, making generalizations difficult at best. Non-Hispanic whites and males between the ages of 18 and 44 are reported to be the heaviest users. Adult males are two times more likely to binge drink than adult women. Evidence that the impact of alcohol consumption poses a particularly concerning public health impact on Native Americans and Alaska Native populations exists.[25,26] From an international perspective, the prevalence of alcohol abuse and dependence among Europeans is even higher than in the United States.[27]

Acute alcohol intoxication poses a different set of problems than chronic alcohol use. Changes in sensorium create psychomotor impairments and can lead to a higher risk of injury, vomiting, delayed gastric emptying, and decisional incapacity. An elevated blood alcohol level is known to cause an increased sensitivity to other drugs because of its additive depressant effects.

Chronic alcohol consumption, associated with alcohol use disorder, is frequently accompanied by concurrent illnesses.[28,29] These may include pathology of the nervous, cardiovascular, gastrointestinal, and renal systems. Alcohol-associated hepatic disease raises additional concerns for the anesthesia provider. Long-term alcohol abuse has also been linked to an altered immune response, resulting in a significantly increased risk of postoperative infection, prolonged stays in the intensive care unit, and prolonged stays in the hospital.[30]

Drinking alcohol is known to induce a number of anatomic and physiologic consequences. For example, if the patient is hypoalbuminemic and/or has impaired hepatic blood flow, drug distribution and metabolism will be impaired. As a result, the duration of neuromuscular blocking agents may be prolonged. Additionally, drinking alcohol may modulate synaptic and extrasynaptic γ-aminobutyric acid (GABA) receptors in the thalamus.[31] Chronic alcohol consumption is known to proliferate the membranes of the endoplasmic reticulum, accelerate ethanol metabolism, and boost the production of acetaldehyde.[32] Table 3-3 provides a description of the effects of alcohol consumption on some frequently prescribed medications. Because chronic alcohol use is known to induce the CYP enzymes, particularly CYP2E1, dose requirements for many of the drugs used during an anesthetic may need to be increased, including propofol, barbiturates, opioids, and the minimum alveolar concentration (MAC) of inhalation agents. Ironically, just as alcohol and liver disease affect the CYP enzymes, the CYP enzymes appear to have a role in the origin of several liver diseases. CYP metabolism of some parent compounds to their toxic metabolites, like acetaminophen and halothane, provokes hepatotoxicity.[33]

Smoking

The Centers for Disease Control and Prevention tracks and provides statistics on tobacco use in the United States. It is estimated that more than 20% of Americans are current cigarette smokers. Some ethnic and geographic groups engage in smoking more than others. The rate of tobacco product use among Native American and Alaska Native tribes is significantly higher than in the general U.S. population. Some Native American and Alaska Native tribes have use rates as high as 40%. Likewise, age is also a factor: The prevalence of smoking among U.S. teenagers is higher than adults.[34]

There are clinical anesthesia implications of engaging in cigarette smoking that extend beyond the usual known health risks. These effects are influenced by the length of time an individual has smoked, the makeup of the cigarettes smoked, and how the smoker inhales. The compounds associated with both the particulate and gaseous components of cigarette smoke, including benzene, polyphenols, arsenic, carbon monoxide, and polycyclic aromatic hydrocarbons (PAHs), influence the activities of the enzymes in the CYP system. PAHs are also derived from some environmental pollutants and charbroiled meats. Many of these substances, particularly the PAHs, induce certain enzymes, specifically CYP1A1, CYP1A2, and CYP2E1.[35] As a result the drugs or substrates that are metabolized by those affected enzymes are metabolized more quickly in smokers.[36] Smokers therefore require higher doses of some drugs, for example, theophylline and morphine. Table 3-3 describes the effects of cigarette smoking on many commonly prescribed medications.

It is commonly known among anesthesia providers that smoking is a risk reducer for postoperative nausea and vomiting.[37] The benefit hardly extends beyond this example. PAHs and their metabolites are unfortunately also known to induce DNA mutations, contributing to the potential development of cancer.

Several drugs germane to the practice of anesthesiology are impacted by the effects of cigarette smoke, including neuromuscular blocking agents (increased dose needed), opioids (increased dose needed), and some sedatives (increased dose needed).[38] Some of the evidence, however, remains conflicting; differing conclusions point to the need for continued inquiry into this clinically relevant topic.

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Table 3-3 Potential Interactions Between Cigarette Smoking, Alcohol Consumption, and Frequently Prescribed Medications

Product	Effects of Cigarette Smoking	Effects of Alcohol Consumption
Lipitor		Possible liver damage
Hydrocodone/APAP	Decreased analgesic effect	Increased CNS depression
Toprol-XL	Decreased drug effect	Increased drowsiness/dizziness
Norvasc		Increased drowsiness/dizziness and decreased BP
Amoxicillin		
Synthroid		
Nexium		
Lexapro		Not recommended
Albuterol		
Singular		
Lisinopril		Decreased BP and increased adverse effects
Ambien	Decreased sedation	Increased drowsiness
Zyrtec	Theoretical	Increased drowsiness/dizziness
Prevacid		Decreased medication effect and increased acid production
Zoloft		Not recommended
Warfarin	Increased clearance	Increased anticlotting effect
Advair	Decreased drug effect	Not recommended
Furosemide		Increased adverse effects of alcohol
Fosamax	Not recommended	Not recommended
Protonix		
Azithromax		
Effexor XR		Increased adverse effects
Zocor		Possible liver damage
Plavix	Theoretical	Increased bleeding possibility
Oxycodone/APAP	Decreased analgesic effect	Increased CNS depression
Vytorin		Possible liver damage
Cephalexin		
Diovan		Decreased BP and increased adverse effects
Metformin		Inhibits alcohol metabolism
Atenolol	Decreased drug effect	Increased drowsiness/dizziness
Prednisone		Can damage stomach
Levaquin		
Lotrel		Decreased BP and increased adverse effects
Zetia		Increased dizziness
Seroquel		Increased drowsiness and adverse effects
Wellbutrin XL	Theoretical	Increased risk of seizures
Celebrex		Increased risk of GI bleed
Avandia		Increased risk of hypoglycemia
Hydrochlorothiazide		Increased adverse effects
Actos		Increased risk of hypoglycemia
Diovan HCT		Decreased BP and increased adverse effects
Premarin	Anti-estrogen effects	

(continues)

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Table 3-3 Potential Interactions Between Cigarette Smoking, Alcohol Consumption, and Frequently Prescribed Medications *(continued)*

Product	Effects of Cigarette Smoking	Effects of Alcohol Consumption
Altace		Decreased BP and increased adverse effects
Crestor		Possible liver damage
Coreg	Decreased drug effect	Increased drowsiness/dizziness
Flomax		Increased dizziness
Actonel	Not recommended	Not recommended
Nasonex	Decreased drug effect	
Risperdal		Increased drowsiness and adverse effects
Yasmin 28	Increased adverse effects	Slow alcohol elimination
Lantus	Decreased absorption	Increased risk of hypoglycemia
Viagra		
Tricor		Possible liver damage
Alprazolam	Decreased sedation	Increased CNS depression
Cozaar		Decreased BP and increased adverse effects
Digitek		
Ibuprofen		Increased risk of GI bleed
Trazodone		Increased CNS depression
Cymbalta	Theoretical	Possible liver damage
Codeine/APAP	Decreased analgesic effect	Increased CNS depression
Triamterene and hydrochlorothiazide	Theoretical	Increased adverse effects
Paroxetine	Theoretical	Increased CNS depression
Adderall XR		Not recommended
Clonazepam	Decreased sedation	Increased CNS depression
Omnicef		
Aricept		Increased drowsiness/dizziness
Fluoxetine		Increased CNS depression
Propoxyphene/APAP	Increased doses needed	Increased CNS depression
Gabapentin		Increased adverse effects
Fexofenadine		
Valtrex		
Concerta		Not recommended
Ortho-Tri-Cyclen Lo	Increased adverse effects	Slow alcohol elimination
Aciphex		
Clonidine		
Topamax		Increased drowsiness/sedation
Xalatan		Increased adverse effects
Lorazepam	Decreased sedation	Increased CNS depression

BP, blood pressure; CNS, central nervous system; GI, gastrointestinal.

Source: Smith RG. An appraisal of potential drug interactions in cigarette smokers and alcohol drinkers. *J Am Podiatr Med Assoc.* 2009;99:81-88. Reprinted with permission from American Podiatric Medical Association.

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Herbal Preparations

Much has been written about the interaction between prescribed medications and consumed herbal preparations. These interactions are significant because it is estimated that more than 46% of the U.S. population uses at least one prescription medication per month, and more than 20% uses three or more prescription medications per month.[39] Because many of the herbal preparations marketed as preventive or therapeutic agents contain phytochemicals, they have potential impact on many of the cytochrome P-450 enzymes. St. John's wort, for example, has been implicated in causing a decrease in the therapeutic plasma levels of the immunosuppressant cyclosporine, the protease inhibitor indinavir, the antiretroviral drug nevirapine, and oral contraceptives, to name a few.[40–44]

Clearly, science supports the existence of a relationship between variations in drug responses and such cultural practices as food preferences and intake, use of herbal preparations, alcohol use, and cigarette smoking. In fact, exposure to any number of environmental chemical compounds over time has the potential to influence the biochemical processes of the body. Fortunately, researchers are continuously identifying inhibitors and inducers so the challenge of optimizing drug doses for therapy is becoming less reliant on probability and chance.

Genetic Influences

Technologic advancements in genomics have enhanced our understanding of many areas of health care. The answers to many important clinical questions have been expanded to include the genetic basis of disease etiology and treatment. A basic understanding of genetics is now expected of those pursuing a study of healthcare sciences. Although a thorough explanation of genetics is beyond the scope of this text, it is important to provide an overview of some key definitions to understand the basis of some interindividual differences to drug responses.

Basic Genetic Concepts

A gene is the basic unit of inheritance that is responsible for a trait or characteristic. In essence, genes behave as the "instruction manuals" for an organism's body, encoding the directives that define its unique features and characteristics. The complete set of these instructions for making an organism—a "master instruction manual"—is called its genome. Found in the nucleus of every cell, there is estimated to be somewhere around 30,000 genes in every human being.

Genes are made of molecules of DNA. DNA is known for its twisted ladder shape, called the double helix. This double helix is built with a sugar–phosphate backbone along which are arranged pairs of four nitrogenous bases, or nucleotides: adenine, which pairs with thymine, and cytosine, which pairs with guanine (A, T, C, and G). Human genomes contain more than 3 billion DNA base pairs. The base pairs combine in various combinations, known as the DNA sequence, which serve as the directives for the cell to synthesize proteins. Proteins are produced from amino acids. It is these proteins that provide for the structure of cells and enzymes for biochemical processes. The proteins enable each cell in the body to perform a specific function.

DNA is packaged in storage units known as chromosomes. A chromosome is a physically separate molecule of DNA. Each human cell is organized into two sets of 23 chromosomes, for a total of 46 chromosomes. Of these 46 chromosomes, 44 are autosomes and 2 are sex chromosomes. One set of chromosomes is provided by the maternal side and one set of the chromosomes is provided by the paternal side of the offspring. It is this passing of chromosomes from parent to child, which eventually yields traits, that is the basis of heredity. Our genes, therefore, encode the instructions that delineate our unique identity.

Genetic Variations

Humans possess obvious and not so obvious genetic variations, from hair color to blood type. The unique genetic makeup of a cell or individual is its genotype. The outward appearance or physical expression of a genotype is known as a phenotype. These genotypic variations are the consequence of the small mutations in DNA sequence that occur in all organisms. These mutations may occur during the process of DNA replication and are spontaneous.

Mutations provide the human species—in fact, all species—with an opportunity for adaptation to new environments ("survival of the fittest" concept). If a variation exists in greater than 1% of the population, it is labeled a polymorphism. Variations that exist in less than 1% of the population are termed mutations. An allelomorph—commonly known as an allele—is the word for any one of the alternative forms of a gene. The normal expression of a gene is known as the wild-type allele. Mutant alleles occur because of an alteration of the wild-type allele.

A DNA polymorphism that is caused by a single nucleotide alteration—such as A (adenine) replacing one of the other three nucleotide letters (C, G, or T)—is called a

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single nucleotide polymorphism, or SNP. SNPs occur in the human population more than 1% of the time and help identify a person's predisposition to a variety of diseases. They also are the basis for the interindividual differences in drug responses because they may alter the drug's pharmacodynamics or pharmacokinetics. Categorizing SNPs, their impact on drug responses, and then being able to identify an individual's SNPs would allow healthcare providers to better predict a person's responses to a drug.

Making the Clinical Connection

Is it possible to correlate a phenotype with a person's underlying genotype in hopes of identifying variant drug responses or diseases? The answer is complex and remains not fully answerable. Genotyping is certainly more accurate than using race, ethnic groups, or other phenotypes to project a drug response. Some genetic polymorphisms, however, are more frequently expressed within a group of people with a commonality, like gender or geographic origin. Identifying gender is fairly easy; geographic origin is not so easy. Commonly, we refer to a group of people with a shared origin as a "race" or "ethnic group." Race and ethnicity, however, are challenging labels to apply, especially given our heterogeneous and mobile society. Therefore self-identified race or ethnicity is not consistently predictive. As a result, phenotypic expressions may provide clues but not certainty regarding underlying genetic variations. Nonetheless, some polymorphisms are more common in some groups of people than in others.

Polymorphisms occur in drug target proteins and target pathways, in drug-metabolizing enzymes, and in unrelated physiologic variances that coincidentally influence pharmacodynamics and/or pharmacokinetics. Polymorphisms in the genes specifically for drug-metabolizing enzymes have been identified and are somewhat common. Some polymorphisms result in greater enzyme activity, whereas others result in greatly reduced or no enzyme activity. Also, some enzyme activity appears to be "polymorphically distributed." Depending on their genes, a percentage of the population demonstrates reduced enzyme activity and is categorized as poor metabolizers. Another percentage of the population with normal enzyme activity is categorized as extensive metabolizers. And yet another percentage of the population with increased enzyme activity is termed ultra-extensive or ultra-rapid metabolizers.

These distributions have been found to vary between ethnic groups and are enzyme dependent (Table 3-4). For example, several variants of the CYP2C19 enzyme have been identified. This particular enzyme is involved with the metabolism of many drugs, including the proton pump inhibitor omeprazole. One variant, CYP2C19*17, which is associated with ultra-extensive metabolizers, appears relatively common in three ethnic groups: Swedes, Ethiopians, and Chinese (at 18%, 18%, and 4% frequencies, respectively). This is believed to result in 40% lower omeprazole concentrations for people in these groups.[45]

Another example is the CYP2D6 enzyme, which is involved in the metabolism of approximately 25% of all drugs, including beta-blockers, amide local anesthetics, antiemetics, and opioids. It is estimated that approximately 10% of European whites have the variant allele associated with being a poor metabolizer. For the clinician managing pain, this translates into a percentage of that population who fail to adequately convert codeine to morphine. Thus these individuals receive inadequate analgesia from the standard dose of codeine.[46,47]

The possible genetic factors influencing drug responses are limitless. In 2004 Liem and colleagues[48] provided empirical support for something most anesthesia practitioners suspected: Individuals with natural red hair, an expression of a mutation of the melanocortin-1 receptor gene, required a statistically significant higher minimum alveolar concentration of inhalation anesthetic compared with individuals with dark hair. Some studies even suggest that gender is a factor: Gan and his associates[49] found that

Table 3-4 Outcome of Genetic Disposition on Enzyme Activity and Drug Response

Genetic Disposition	Rate of Metabolism	Outcome of Standard Dose of an *Active* Drug	Outcome of Standard Dose of a *Pro*-Drug
Poor metabolizer (PM)	Slower than "normal"	Slower metabolism increases risk of overdose, side effects	Insufficient active metabolites to create an effect; underdose; pro-drug accumulates and may cause side effects
Extensive metabolizer (EM)	"Normal"	Expected drug effect	Expected drug effect
Ultra-extensive/ rapid metabolizer (UM)	Faster than "normal"	Rapid metabolism of drug necessitates higher than standard dose to achieve intended effect	Active metabolites produced quickly; rapid effect could increase risk of side effects

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men had significantly longer recovery times than women after general anesthesia with propofol.

Conclusion

Clearly, current science supports a wide array of factors that clinicians must consider in making decisions that involve clinical pharmacology. The traditional approach of simply basing doses and expected outcomes on limited variables like age, weight, hepatic function, and renal function are no longer defendable. A growing body of evidence substantiates the influences of variable factors like culture and environmental issues as well as genes, which remain constant throughout life. Pharmacogenetic information will continue to expand. Healthcare providers, particularly CRNAs, must possess a working knowledge of genetics and be able to apply it to clinical practice. This expanding and evolving area also underscores the importance for every CRNA to establish an evidence-based practice, engaging in continued self-development and lifelong learning. This will help to reduce the risk involved with medication administration and enhance patient safety initiatives. It is a professional imperative that every patient deserves.

Key Points

- Many factors contribute to interindividual variations in drug responses observed, including culture, environment, and genetics.
- Exposure to xenobiotics may result in changes to drug targets or the biochemical systems that absorb, distribute, metabolize, or eliminate the drugs.
- The CYP enzymes are influenced by a variety of factors, including exposure to some of the chemicals that they metabolize.
- Humans possess obvious and not so obvious genetic variations. These genotypic variations are the consequence of the small mutations in the DNA sequence that occur in all organisms. Mutations provide the human species with an opportunity for adaptation to new environments.
- Some genetic polymorphisms are more frequently expressed within a group of people who share a commonality. Polymorphisms occur in drug target proteins and target pathways, in drug-metabolizing enzymes, and in unrelated physiologic variances that coincidentally influence pharmacodynamics and/or pharmacokinetics.

Chapter Questions

1. What factors are currently believed to contribute to interindividual variations to a given dose of a drug?
2. How do cultural practices and behaviors, such as dietary preferences or cigarette smoking, influence drug pathways and drug-metabolizing enzymes?
3. What association exists between an individual's genotype and phenotype?
4. Which genetic polymorphisms are associated with a specific ethnic or racial group?
5. How do interindividual variations to drug responses affect the practice of anesthesiology?

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