CHAPTER 4

The Pharmacogenetics of Drug Metabolism

Ali Roberts, PharmD, BCPS; Landry K. Kamdem, PharmD, PhD; and G. Scott Weston, RPh, PhD

LEARNING OBJECTIVES

After completing this chapter, the reader should be able to

- Briefly explain the potential health impacts of pharmacogenetic differences influencing drug-metabolizing enzymes on the rate of adverse drug reactions or events that occur in patients receiving drug therapy.
- List and discuss several commonly used therapeutic agents whose safe and effective usage is impacted by pharmacogenetic differences affecting drug-metabolizing enzymes.
- Identify the primary phenotypes, or metabolizer status, resulting from common pharmacogenetic differences that affect drug-metabolizing enzymes.
- Give examples of common medication dosing adjustments or therapeutic changes that may be needed due to pharmacogenetic differences impacting drug-metabolizing enzymes.

KEY DEFINITIONS

ADVERSE DRUG EVENT OR REACTION (ADE OR ADR)—a response to a medicine that is noxious, unintended, and occurs at doses normally used in man.[1]

CYTOCHROME P450S (CYP450S OR CYPS, MICROSOMAL MIXED FUNCTION OXIDASES)—a family of heme-containing monooxygenase enzymes, many polymorphic, that are major players in drug metabolism.

ISOFORM—a protein having a similar function and sequence as another protein but arising from a different gene (or from a splice variant of the same gene).

NARROW THERAPEUTIC INDEX (OR RATIO) (NTI) AGENT—an agent for which there is less than a twofold difference in median lethal dose (LD50) and median effective dose (ED50) values, or there is less than a twofold difference in the minimum toxic concentration and minimum effective concentration in the blood, and for which the safe and effective use of the drug products require careful titration and patient monitoring.[2]

STAR ALLELE—a standardized annotation nomenclature for denoting genetic polymorphisms (e.g., CYP2D6*4C).

XENOBIOTIC—a substance foreign to the human body.

INTRODUCTION

A patient's safe and effective use of therapeutic agents is the goal of every healthcare professional. The advent of *precision, or personalized, medicine* allows this goal to be made even more specific—namely, to determine which patients are most likely to *benefit* from a given therapy, which patients may have *inappropriate* therapies, and whether or not a therapeutic agent's typical dosing regimen should be *adjusted*.[3-5] However, patient-to-patient differences in responses to drug therapy that impact these therapeutic objectives are common. Studies indicate that the most frequently used pharmaceuticals are effective in only 25-60% of patients.[6] It should also be noted that patients experience **adverse drug events (ADEs) or reactions (ADRs)** at rates that are alarmingly high. According to the National Action Plan for Adverse Drug Event Prevention,[7] it has been estimated that in the United States, ADEs are responsible for one third of the *total* hospital adverse events,[8] impact approximately 2 million hospital stays annually,[8,9] and extend the length of hospital stays by 1.7 to 4.6 days.[9-11] The same report also notes that ADRs account for over 3.5 million outpatient office visits,[12] as many as 1 million emergency department visits,[13] and approximately 125,000 hospital admissions each year in the United States.[13] In addition to the human costs of ADRs, the economic costs are also significant. National estimates suggest that ADRs to therapeutic agents add as much as $3.5 billion to U.S. healthcare costs each year.[14]

Differences in patient responses to medications, including those differences that lead to potential ADRs, may arise from many sources, including environmental-, genetic-, and disease-based factors. Of the many genetic factors that may influence the way patients respond to therapeutic agents, differences in the enzymes involved in drug metabolism are known to play a major role. Studies have suggested that the majority of ADEs might be preventable with the appropriate use of pharmacogenetic profiling of drug-metabolizing enzymes (DMEs).[15-19] For example, antithrombotic agents are involved in most of the fatal ADRs.[20] Warfarin is one of the most commonly used antithrombotic drugs in the world, but individual patient responses to this agent vary widely. A large part of the interpatient variability in the response to warfarin therapy is believed to be due to pharmacogenetic differences in two key polymorphic enzymes: the CYP450 2C9 (CYP2C9, one of the primary metabolic enzymes responsible for inactivating warfarin) and the vitamin K epoxide reductase complex subunit 1 (VKORC1, the target through which warfarin exerts its therapeutic effects).[21,22] Increasing evidence suggests the use of pharmacogenetic profiling of these two polymorphic enzymes, in combination with other clinical data, results in more appropriate warfarin dosing regimens that may reduce potential ADRs.[23-25]

CLINICAL PEARL

A majority of ADEs or ADRs may be preventable with the appropriate use of pharmacogenetic profiling, for example, by using *CYP2C9* and *VKORC1* genotyping in patients prior to the initiation of warfarin therapy to select optimal dosing regimens.

Several factors complicate our understanding of the impact that pharmacogenetic differences in DMEs play in a patient's responses to pharmaceutical therapy. First, metabolism is only *one* of the many things that occur in vivo on exposure to a therapeutic agent.