



Pharmacogenetics: What PAs need to understand and why

The field of pharmacogenetics changes on what seems to be a daily basis. The constant coming forward of groundbreaking information underscores the need for practicing PAs to have a fundamental understanding of basic pharmacogenetic concepts. These concepts are not entirely new; the idea of a pharmacogenetic influence was first explained in the 1950s. However, with the advent of newer drugs, as well as a better understanding of existing drugs, pharmacogenetics takes on greater importance as clinicians realize the impact it can have on patient care.

Cytochrome P-450 system We must start at the beginning. A large part of our current understanding of pharmacogenetics is centered on the cytochrome P-450 (CYP450) system, the major drug-metabolizing system of the body. Genes responsible for encoding CYP enzymes are identified by the letters “CYP,” as are the enzymes themselves. CYPs are the major enzymes involved in drug metabolism and bioactivation. They account for approximately 75% of total drug metabolism and are responsible for most of the pharmacogenetic issues we see.

Although the CYP enzymes number more than 50, from a clinical perspective, we care primarily about a handful of them. Together CYP2C9, CYP2C19, CYP2A6, and CYP2D6 metabolize a good number of frequently used drugs. Overactivity (seen in extensive metabolizers and resulting in subtherapeutic effectiveness) or underactivity (seen in poor metabolizers and resulting in toxicity) of these enzymes encompass some

of our pharmacologic dilemmas. A few of the drugs metabolized by the CYP450 system are listed in Table 1.

Transport proteins Other genetic influences exist. Drug-transport proteins, such as P-glycoprotein, may also affect drug response. P-glycoprotein is one of the most recognized drug-transport proteins to exhibit genetic polymorphism. In addition to acting as an efflux pump to get toxic substances out of cells, P-glycoprotein has a role in the distribution of chemotherapeutic agents, digoxin, cyclosporine, and protease inhibitors. P-glycoprotein can also affect drug absorption via its presence in the GI tract, hepatocytes, kidney, and blood-brain barrier. For instance, cellular overexpression of P-glycoprotein causes decreased absorption and increased efflux of certain therapeutic agents out of cells, which may result in treatment failure resulting from reduced activity of the drug. More important, underexpression may cause significant toxicity at normal doses; for example, overwhelming toxicity that occurs with use of a chemotherapeutic agent may be

due to a lack (or variant form) of some enzyme responsible for metabolism of that particular agent. This can be seen in the metabolism of 6-mercaptopurine, in which a lack of thiopurine methyltransferase may result in toxicity requiring significant dose reductions.

Adverse impact PAs must understand the principles of pharmacogenetics because of the possible adverse impact genes can have on patients’ response to medication. When a drug “fails” or causes significant toxicity, most unresponsive patients (as well as the clinicians treating them) assume that the drug, acting as an isolated entity, is responsible. In reality, this response may be due to a patient-specific pharmacogenetic issue rather than to the drug.

The problems with impaired metabolism are not limited to niche-area drugs, such as chemotherapy agents; we are seeing the results of impaired medication metabolism in the primary care arena as well. Ethnicity has been shown to have a significant influence on how certain medications are metabolized. Certain ethnic groups have

TABLE 1. Some drugs affected by genetic variations in the CYP enzyme group and the possible manifestations

Drug	Pharmacogenetic variation	Manifested reaction
Codeine	Defective <i>CYP2D6</i> gene, so conversion to morphine cannot take place	Decreased analgesia
Diazepam	Prolonged sedative effects in poor metabolizers	Increased sedation
Glipizide	Prolonged hypoglycemic effects in poor metabolizers	Hypoglycemia
Nortriptyline	Inadequate response in ultrarapid metabolizers	Poor control of depression
Phenytoin	Defective <i>CYP2C9</i> gene, resulting in overdosage	Ataxia, confusion
Warfarin	Defective <i>CYP2C9</i> gene, resulting in decreased clearance	Bleeding

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already been identified as having polymorphisms that impact their ability to metabolize certain drugs, as is seen with rosuvastatin in the treatment of Asian Americans. Data have shown that this ethnic group may accumulate the drug and therefore be at greater risk for myopathies and rhabdomyolysis. To reflect this change, FDA-approved labeling recommends that Asian Americans begin with a 5-mg dose of rosuvastatin rather than the starting dose of 10 to 20 mg typically used for other populations.

Other commonly used drugs have also been implicated. In 2007, the FDA approved changes in labeling for warfarin because of pharmacogenetic concerns. This change elucidates the need to consider that certain genetic differences may cause patients to respond differently to dosing of warfarin; patients with variations in two specific genetic sites may need lower warfarin doses than patients without these genetic variations. *CYP2C9* is responsible for the metabolism of warfarin. Another gene, known as the vitamin K epoxide reductase gene (*VKORC1*), helps regulate warfarin's role in anticoagulation by assisting in the activation of vitamin K. Since vitamin K is a direct antidote to the effects of warfarin, that particular gene must work correctly, as the fragile balance between bleeding and coagulation can be affected.

Take-home lessons What does this mean for clinicians? Several tenets apply: First, awareness of these pharmacogenetic influences can serve as an ally in your treatment of patients, especially with such commonly prescribed drugs as rosuvastatin and warfarin. Second, DNA testing can be done if you suspect a pharmacogenetic-based problem. Such testing is especially useful for a patient who will require a drug for a significant period of time and for whom no alternative exists. The DNA test determines the patient's genotype, or genetic constitution, which in turn is used to help predict the phenotype (the observed biologic effect in the patient). One criticism is that knowledge of the

genotype does not necessarily translate to the phenotype. Moreover, while DNA testing may be useful for some patients, others will have genotypes that are rare or have not yet been discovered, so testing cannot yet be applied universally. Prices for testing vary, so check with the laboratory service your practice or institution uses. While high-tech testing may seem like a good idea, limited applicability, cost, insurance coverage, and privacy concerns may hamper this modality's use. No current recommendations advocate testing in all patients receiving potentially problematic drugs; in fact, a recent statement by the Centers for Medicare and Medicaid Services (CMS) verified that genetic tests to help guide warfarin dosing would not be cost-effective for Medicaid recipients; in the view of CMS, more information is needed to confirm the utility of testing.

Pharmacogenetics is not going away. Rather than applying a "one-size-fits-all" approach to prescribing, you should avail yourself of the current information and keep it in your prescribing toolbox. You never know when you may have to use these principles to safely guide your patient's drug therapy. **JAAPA**

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DRUGS MENTIONED

Codeine
Cyclosporine (Neoral, Sandimmune, Gengraf, generics)
Diazepam (Diazepam Intensol, Valium, generics)
Digoxin
Glipizide (Glucotrol, generics)
6-Mercaptopurine (Purinethol, generics)
Nortriptyline (Aventyl, Pamelor, generics)
Phenytoin (Dilantin, Phenytek, generics)
Rosuvastatin (Crestor)
Warfarin (Coumadin, Jantoven, generics)

SUGGESTED READINGS

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- Ray T. CMS rejects Medicare payment for genetic-based warfarin dosing. May 5, 2009. GenomeWeb Daily News Web site. <http://www.genomeweb.com/node/916187?emc=el&m=380314&l=&v=09c60dac80>. Accessed June 11, 2009.

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