Analyzing Genetic Variables and Self-Medication

BY RANDOLPH FILLMORE

"Hispanic ethnicity has emerged as an important risk factor for impaired glucose tolerance or latent type 2 diabetes and kidney disease," says **Thomas Dowling, PharmD, PhD, FCP**, associate professor and vice chair for research and scholarship in the Department of Pharmacy Practice and Science (PPS). "Hispanics/Latinos with diabetes are 4.5 to 6.6 times more likely to suffer from severe kidney failure with an accompanying trend in the prevalence of Hispanic people receiving hemodialysis."

These realities make it imperative to gain a better understanding of ethnic variability in drug response, explains Dowling, noting especially that as many of the drugs prescribed for these conditions are metabolized in the liver by specific enzymes, not enough is known about ethnicity, genetic variability, and drug response.

Dowling has designed a study with his colleagues, Magaly Rodriguez de Bittner, PharmD '83, BCPS, CDE, professor and PPS chair, and Ligia Peralta, MD, an associate professor of pediatrics at the University of Maryland School of Medicine. They are using genotype analysis to evaluate biochemical markers and serum markers, and measuring urine protein excretion and Glomerular Filtration Rate (GFR) to investigate drug metabolic activity in Hispanic-Americans with diabetes.

According to Dowling, two important drug-metabolizing enzymes that are subject to variability based on genetic factors are enzymes CYP3A and CYP2C9. Tests with Hispanic volunteers will reveal variations in genes that regulate CYP3A and CYP2C9 activity. Also, diabetes knowledge and awareness of diabetic complications among study participants will be evaluated using a new health status survey tool designed by Toni Biskup, MD, an internal medicine/pediatric resident at the University of Maryland Medical Center.

"We expect that our study will provide important new information regarding the prevalence of diabetic control, nephropathy, and metabolic capacity in Hispanic-Americans with diabetes," explains Dowling. "This information should also provide a better understanding of the association between patient-related factors such as renal function, liver function, genetic variability, and drug response."

The Hispanic/Latino population is the fastest growing minority in the nation, notes Dowling. This group, almost 13 percent of the U.S. population, is nearly twice as likely to die from diabetes than other groups and has higher rates of hypertension and obesity when compared with non-Hispanic whites.

"We need a much better understanding of glycemic control and drug therapy outcomes in Hispanic-Americans," concludes Dowling. "We have assembled a multidisciplinary research team with experience in the pharmaceutical care of Hispanic-Americans with type 2 diabetes and the capacity to carry out clinical research in the campus' National Institutes of Health-funded General Clinical Research Center and the Genomics Core Facility."

Queries about genetic variables that might influence response to drug therapy are among the many questions prompted by the unraveling of the human genome almost a decade ago. The subsequent quest to develop 'personalized medicine' takes into account individual genetic variables to understand why some medications are less effective or more likely to cause harm in specific patient populations.

Stuart T. Haines, PharmD, FCCP, FASHP, a professor and pharmacotherapy specialist in PPS, is examining the genetic variables of the PPAR gamma gene and response to certain antidiabetic medications. In the project's early years, genetic links to various diseases were investigated. More recently, questions of pharmacogenetics are being posed and,

Stuart Haines, Thomas Dowling, and Kristin Watson

researchers hope, answered.

One study looks closely at the PPAR genes.

"The PPAR genes are responsible for regulating glucose and lipid transportation in various tissues in the body," explains Haines. "The antidiabetic drugs, called glitazones, are PPAR-agonists and accelerate glucose transport by making the cells more sensitive to the effects of insulin."

According to Haines, some people have robust responses to the drug while others have weaker responses. If people with variants of this gene respond differently to these drugs, genetic variance may explain the variability in response.

Questions about the effect of genetic variables and response are also being examined for two widely used antiplatelet agents—aspirin and clopidogrel (Plavix). This study is being carried out with participants from the Amish community through the Amish Research Clinic in Lancaster, Pa., and is part of the ongoing work of Alan Shuldiner, MD, of the University of Maryland School of Medicine, who established the clinic and the study in the mid-1990s.

"We know these medications are not 100 percent effective and patients taking them continue to have cardiovascular events," explains Haines. "We also know that some patients respond to platelet inhibition more than others. Genetic variation may explain this, but we don't know which genetic variables might explain it."

Differences in drug metabolism, absorption, binding at the site of action, and even variations in the platelets themselves may play a role, speculates Haines.

Charmaine Rochester, PharmD, BCPS, CDM, CDE, an associate professor in PPS, has recently assumed responsibility for the day-to-day oversight of all medication-related issues in the aspirin-clopidogrel research program.

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Photograph by Robert Burke

> *"'Self-administration of medication,' or SAM programs conducted in hospitals, have been shown to improve patient self-preparation prior to discharge, improve patient medication knowledge, and improve medication adherence after discharge."*
>
> —KRISTIN WATSON

after discharge," explains **Kristin Watson, PharmD, BCPS**, an assistant professor in PPS. "However, clinical outcomes associated with SAM programs are not clear."

According to Watson, up to 40 percent of patients discharged after hospitalization for heart failure either die or are rehospitalized within three months. In an effort to document whether SAM programs can improve on these outcomes, she joined colleagues Kelly Summers, PharmD, BCPS, an assistant professor in PPS; and Patricia Uber, PharmD, an assistant professor of medicine at the University of Maryland School of Medicine, in evaluating the effects of a SAM program for heart failure patients.

Their study compares outcomes for patients in an inpatient, structured education SAM program to a control group without the SAM program. Caretakers responsible for giving medications once the patient is home are included in the program. Prior to discharge, caretakers and patients in the SAM group work with their nurse at all medication dosing times to determine their ability to self-administer medications. The patients in the SAM group will receive medication counseling from their pharmacist(s) and nurses.

"Our objective is to compare rates of hospitalization, emergency department visits, worsening quality of life or death between the SAM group and the group that did not have the SAM intervention," Watson explains. "We will also evaluate the association between scores on a disease state test and improvements in the primary endpoint."

They expect that their results will lead to similar evaluations of the effectiveness of SAM programs for other chronic disease states, such as diabetes and asthma.

"The Joint Commission's 2009 Patient Safety Goals encourage getting patients involved with their care," concludes Watson. "We expect that the results of this study will show that when patients become involved proactively in their care while still in the hospital, their outcomes after discharge will improve."

Watson also sees an expanded role for the inpatient pharmacist through SAM programs. Direct patient care is at the forefront of the changing role of the pharmacist, and strengthening self-administration of medication is another step in that important direction.