GENETICS IN YOUR PRACTICE

Will Plavix Be the Pharmacogenetic Exemplar?

BY MICHAEL F. MURRAY, M.D.

Pharmacogenetics is the use of a patient's genetic information to inform the selection or dosing of medications. In general, pharmacogenetics involves "gene-drug" pairs, where DNA sequence variants of the gene are linked either to variation in the drug's metabolism or to alterations in the drug's target. Pharmacogenetics are predicted to assume center stage as genomic medicine begins to drive many of the innovations in clinical care in the 21st century. The problem with this prediction has been that until now there has not been a defining example of how this will be applied broadly in clinical practice.

So, what will bring a breakthrough application in pharmacogenetics? I believe that a true breakthrough into the mainstream will occur when the gene-drug pair has many or all of these characteristics:

► **A widely used drug.** There are currently some excellent examples of gene-drug pairs as models for the clinical application of pharmacogenetics; however, they happen to be with drugs used by only a small number of subspecialists. A true breakthrough application will need to be a widely used medication.

► **An "essential" drug.** Although we may eventually get to pharmacogenetics testing for almost all medications, a true breakthrough application will not be for a drug for which the application is usually elective (e.g., onychomycosis therapy) or for a drug that has equivalent substitutes inside or outside of the class (e.g., a diuretic for hypertension).

► **Potentially severe consequences from use of the drug without pharmacogenetics guidance.** The motivation for using a pharmacogenetics approach is mainly safety or efficacy. The breakthrough application will need to help the prescriber avoid morbidity or mortality associated with side effects or ineffective treatment.

► **A narrow therapeutic window.** Aminoglycoside antibiotics are classic examples of drugs with a narrow therapeutic window, where underdosing can lead to disease progression and overdosing can cause adverse effects.

► **Pharmacoeconomic advantage.** The application of new technology to guide gene-drug decision making will be more attractive for clinical uptake in instances where it offers cost savings.

► **Straightforward genetic interpretation.** Much of current genetic testing deals with complex interpretations of sequence data where variants unique to the individual patient have to be judged as causative, noncausative, or of unknown significance. In 2009 the most straightforward diagnostic genetic testing is based on screening for common variants that confer increased relative risk.

► **Validated significance of gene-drug pair.** There will always be varied levels of confidence in any data set; however, replication of significant correlation in more than one large, well-designed study will be the most likely to be associated with rapid clinical uptake.

A subset of patients placed on the antiplatelet agent clopidogrel (Plavix) experiences clinical failures such a stent thrombosis; this has been dubbed "clopidogrel resistance." Better targeting of clopidogrel therapy to sensitive patients and away from resistant patients via genetic testing may become a routine application in pharmacogenetics. Such an application has the potential to bring with it some or all of the characteristics discussed above.

Earlier this year, three major research studies (two published in the New England Journal of Medicine and one published in Lancet) demonstrated a significant association between common variants of the cytochrome p450 2C19 (CYP2C19) gene, the use of clopidogrel, and outcomes in the treatment of cardiovascular diseases. The biological explanation for this association is that this cytochrome p450 gene plays an essential role in the metabolic transformation of clopidogrel from prodrug to active compound.

These observations are being further studied and confirmed, but there is a suggestion from the current data that a single common variant of CYP2C19 may explain a large part of "clopidogrel resistance."

Unless further research shows evidence to the contrary, it appears likely that clinical application of CYP2C19 testing to guide clopidogrel use will provide a defining example of the gene-drug pair.

This application will also have a significant pharmacoeconomic impact if it can be employed as a one-time test in an individual patient to determine clopidogrel sensitivity and thereby allow the effective use of a generic form of clopidogrel (the drug's patent expires in 2011) as an alternative to newer drugs in this class. ■

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Registry Fails to Find Adverse PPI-Clopidogrel Interaction

BY MITCHEL L. ZOLER

ORLANDO — Patients with coronary disease who combine clopidogrel with a proton-pump inhibitor risk clinical consequences that remain unclear but are of concern, several reports indicate.

The most recent report, on 535 patients from the University of Pittsburgh who received clopidogrel and aspirin following placement of a coronary stent, showed that the combined rate of death, myocardial infarction, or need for revascularization during the year following stenting was about the same regardless of whether patients also took a proton-pump inhibitor (PPI), Dr. Jose P. Ramirez reported at the annual meeting of the American College of Cardiology.

The combined rate of death, MI, or need for revascularization was 23% with a PPI and 24% without a PPI.

DR. RAMIREZ

The finding that coadministration of a PPI in patients with coronary artery disease who also required clopidogrel did not result in a significantly increased rate of adverse coronary events contrasts with findings from several other reports over the past 6 months that found a significant, adverse interaction between the two drugs. Perhaps most notable was a study published in March that reviewed more than 8,000 patients with acute coronary syndrome treated at any of 127 Veterans Affairs hospitals. The analysis found that patients treated with a PPI on top of their clopidogrel had a significant 25% increased risk of death or rehospitalization for acute coronary syndrome during a median follow-up of 17 months (JAMA 2009;301:937-44).

The possible danger from coadministration of a PPI and clopidogrel arises because clopidogrel is a prodrug the liver converts to an active form with a cytochrome P450 enzyme, 2C19. Recent findings show that all PPIs except pantoprazole inhibit 2C19 and thus blunt clopidogrel's antiplatelet efficacy.

"The reason we're seeing studies on either side of the fence is because of confounding and ascertainment bias," said Dr. Elliot M. Antman, director of the cardiac unit at Brigham and Women's Hospital in Boston. "Every one of these studies tried to get at this by triangulating, not in a prospective, randomized study. You don't know if the patients took the [PPI] drug they were prescribed, and there may have been selection biases for patients at increased risk of bleeding" who were prescribed a PPI, he said in an interview. "Given these limitations, it's almost like the flip-flopping on drug-eluting coronary stents, bad versus good."

The new analysis reported by Dr. Ramirez included 535 patients who received a coronary stent at the University of Pittsburgh Medical Center and were entered into the National Heart, Lung, and Blood Institute's Dynamic Registry of coronary stent recipients during 2004 and 2006. Among these patients, 138 (26%) also received prescriptions for a PPI. Their average age was 63, and a third were women. About three-quarters underwent an elective stenting procedure, and slightly more than half received a drug-eluting coronary stent.

During the year following stent placement, the combined rate of death, myocardial infarction, or need for coronary revascularization—the primary end point for this analysis—was 23% in the patients prescribed a PPI and 24% in those who did not receive a prescription, a difference that was not statistically significant, reported Dr. Ramirez, a cardiologist at the University of Pittsburgh. The results were similar among the subgroups getting drug-eluting stents and those receiving bare-metal stents. The data available did not include information on what types of PPIs were prescribed.

Given the current uncertainty about the effect of administering a PPI to patients, "I'd go back to the ACC, American Heart Association, American College of Gastroenterology statement from last October," said Dr. Antman, who was a member of the guideline committee (Circulation 2008;118:1894-909). "We said focus use of gastrointestinal-protective medications on patients in whom the risk of gastrointestinal bleeding is high, and not use these medications in a blanket fashion in all patients."

His second, personal suggestion was that when treatment of a patient on clopidogrel with a PPI is necessary, there is "biologic and pharmacologic reason to believe the interaction might be less significant" with pantoprazole, although Dr. Antman cautioned that he "does not want to be seen as advocating one drug over another."

He added that "in theory," the potential interaction with a PPI is less likely to be an issue for prasugrel, a second-generation drug similar to clopidogrel. That's because prasugrel does not require activation by a hepatic enzyme. Analysis of how prasugrel-treated patients were affected by concurrent use of PPIs is now underway in a post hoc analysis of data from the pivotal prasugrel trial, said Dr. Antman, one of the primary researchers involved in assessing the drug. A Food and Drug Administration advisory committee recommended approval of prasugrel last February, but as of mid-May, the agency had not issued its approval decision. ■