Genetic variation associated with poorer response, cardiovascular outcomes with use of clopidogrel

August 25 2009

Patients with a certain genetic variation who received the antiplatelet drug clopidogrel had a decreased platelet response to treatment and among those who had percutaneous coronary intervention (procedures such as balloon angioplasty or stent placement used to open narrowed coronary arteries) had an increased risk of having a cardiovascular event in the following year than patients who did not have this variant, according to a study in the August 26 issue of *JAMA*.

"Dual antiplatelet therapy, including clopidogrel and aspirin, inhibits platelet function, preventing ischemic events and improving outcomes following acute coronary syndromes [such as heart attack or unstable angina] and percutaneous coronary intervention (PCI)," the authors write as background information in the article. Clopidogrel therapy improves outcomes by inhibiting adenosine diphosphate (ADP; a nucleotide)-stimulated platelet activation. However, variability in response to clopidogrel is well established, with nonresponsiveness related to recurrent ischemic events. Some research has suggested that genetic variations may affect clopidogrel response, specifically the gene variant CYP2C19*2.

Alan R. Shuldiner, M.D., of the University of Maryland School of Medicine, Baltimore, and colleagues performed a genome-wide association study of ADP-stimulated platelet aggregation to identify genes associated with variation in clopidogrel response. In the

Pharmacogenomics of Antiplatelet Intervention (PAPI) Study (2006-2008), the researchers administered clopidogrel for 7 days to 429 healthy Amish persons and measured platelet response. The population in this study (Old Order Amish) are a relatively homogeneous group in which confounding variables (factors that can influence outcomes), including medication usage and lifestyle, are minimized. A genome-wide association study was performed followed by genotyping the loss-of-function cytochrome P450 (CYP) 2C19*2 variant. Findings in the PAPI Study were extended by examining the relation of CYP2C19*2 genotype to platelet function and cardiovascular outcomes in an independent sample of 227 patients undergoing percutaneous coronary intervention.

The researchers found that platelet response to clopidogrel was highly heritable. "Indeed, follow-up genotyping indicated that the loss-of-function CYP2C19*2 variant was associated with clopidogrel response and could account for most of the association signal detected in the initial genome-wide association study. The CYP2C19*2 genotype accounts for approximately 12 percent of the variation in clopidogrel response. With age and sex, approximately 22 percent of the variation in clopidogrel response can be explained. Although substantial and highly significant, the majority of the variation in platelet response to clopidogrel remains unexplained," the authors write.

In the sample of clopidogrel-treated patients undergoing PCI, after 1 year of follow-up, carriers of the CYP2C19*2 genotype were more likely (20.9 percent vs. 10.0 percent) to have a cardiovascular ischemic event or death compared with noncarriers.

"CYP2C19 genotype may prove useful in helping clinicians choose the most effective antiplatelet therapy and dose for a given individual. Those with the CYP2C19*2 genotype may benefit more from an antiplatelet regimen that does not include clopidogrel, such as the third-generation thienopyridine prasugrel, or ticagrelor and cangrelor. Like clopidogrel,

these agents inhibit ADP-stimulated platelet aggregation but are not as dependent on CYP2C19 for activation. Genotype-directed decisions regarding which antiplatelet agent to use in a specific patient may also have an important economic impact if costs of equally efficacious medications differ greatly. Whether CYP2C19*2 carriers may benefit from increased dosing of clopidogrel is not yet known," the authors write.

"Prospective randomized clinical trials will be necessary to determine the efficacy of CYP2C19 genotype-directed therapy in evidence-based clinical decision making."

More information: *JAMA*. 2009;302[8]:849-858

Source: JAMA and Archives Journals (news : web)