Clopidogrel and Calcium-Channel Antagonists

Another Drug–Drug Interaction for the Ever-Wary Clinician?*

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The medical management of patients with coronary artery disease is currently dominated by strategies to alter lipid levels and to inhibit platelet aggregation and activation. In fact, one can make a very strong argument that coronary artery stenting would never have achieved its current level of popularity and success had it not been for the pioneering work done by Colombo et al. (1) using the thienopyridine ticlopidine. Ticlopidine has been almost universally replaced by clopidogrel, a second-generation thienopyridine that is considerably better tolerated. Despite clopidogrel’s success for patients receiving intracoronary stents and for patients with acute coronary syndromes, its use is hampered by the consistent finding that as many as 1 of 4 patients receiving clopidogrel have little evidence of antplatelet response to the drug (2–4). The phenotype of clopidogrel “resistance” has been associated with an increased risk of cardiovascular events (3,5) and of stent thrombosis; several prospective investigations are being performed to verify these findings.

Clopidogrel is a pro-drug and is converted in the liver by the members of the cytochrome P450 (CYP) family (predominantly the 3A and 2C groups) to a series of metabolites, the last of which, the thiol metabolite, is an antagonist of the platelet purinergic receptor known as P2Y12 (6). As reviewed elsewhere, ligation of P2Y12 by the active metabolite of clopidogrel prevents adenosine diphosphate (ADP) from activating the receptor and prevents a chain of events that would otherwise lead to platelet shape change, secretion, and aggregation. Among the many tests that have been proposed to assess clopidogrel’s biologic activity, a recent addition has been the development of assays for vasodilator stimulated phosphoprotein (VASP). The VASP assay developed by Schwarz et al. (7) appears to capture most of the activity of P2Y12 and has the advantage that, unlike functional assays such as platelet aggregation, it is pathway-specific for P2Y12 activation. When ADP ligates P2Y12, G protein signaling pathways reduce intracellular levels of cyclic adenosine monophosphate (cAMP), which in turn leads to decreased phosphorylation of VASP. Because phosphorylation inactivates VASP, high levels of dephosphorylated VASP reflect high levels of P2Y12 occupancy by ADP whereas high levels of phosphorylated VASP reflect blockade of P2Y12. The relationship is generally regarded as being linear. For clinical purposes, levels of VASP phosphorylation are indexed for maximal VASP phosphorylation (stimulated by prostaglandin E1) and are reported as the platelet reactivity index (PRI), or VASP phosphorylation index.

In this issue of the Journal, Siller-Matula et al. (8) assessed whether calcium-channel antagonists, specifically verapamil and a number of dihydropyridines, altered the effect of clopidogrel on platelets in patients undergoing coronary arterial stenting. The interaction between calcium-channel antagonists and the metabolism of other drugs is well documented. Diltiazem and verapamil are classified as “moderate” CYP3A inhibitors, and evidence points to the dihydropyridines as inhibitors of CYP3A as well (9). In fact, diltiazem is occasionally used with transplant patients to allow the use of smaller (i.e., less expensive) doses of cyclosporine (7,10). Siller-Matula et al. (8) measured VASP levels in 200 consecutive patients undergoing stent implantation and found that the PRI was significantly higher (implying less clopidogrel effect on platelets) among patients who were receiving calcium-channel antagonists compared with patients who were not. In parallel, electrical impedance measurements of platelet aggregation showed less inhibition in patients who were treated with calcium-channel antagonists. Incubation with calcium-channel blockers of blood samples from patients treated with clopidogrel had no effect on platelet activity (thus excluding a direct effect of the drugs), and multivariable analyses suggested that use of calcium-channel antagonists was an independent predictor of diminished clopidogrel activity. The composite rate of clinical events over 6 months was also higher among patients treated with calcium-channel antagonists.

Although this evidence should be regarded as preliminary (several more direct tests of the hypothesis, such as measurement of serum levels of the active metabolite of clopidogrel and more direct assessment of CYP3A4 activity, were not performed), the findings should impart important lessons. The average age of patients undergoing coronary stenting is in the mid-60s. Patients in this age group often have a variety of diseases and are usually treated with multiple medications. The potential for drug–drug interac-

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tions in this group is astounding. The number of binary combinations present for a particular patient can be calculated as the binomial coefficient of the number of medications the patient taking. For a patient taking $n$ medications, there are $\frac{1}{2} n(n-1)$ potential pairings of drugs. In fact, in 2006 and 2007, in the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry of unselected patients undergoing stent implantation, the median number of medications per patient was 5 (excluding over-the-counter medications and supplements), yielding 10 potential pairings per patient. A recent study (11), involving 1,601 patients over the age of 65 years using a total of 11,180 prescribed drugs, indicated that there were 24 combinations per person. In 46% of patients, 1 or more known drug–drug interactions could be identified (11). In that study, the number of combinations leading to subtherapeutic effects was approximately equal to the number leading to potential adverse drug reactions. The findings of Siller-Matula et al. (8) should, if nothing else, remind us that patients undergoing coronary artery stenting have multiple drug interactions that can alter the activity of some of the drugs upon whose effects the success of the procedure depends, and that we often take for granted. Some examples include the interaction of aspirin with nonsteroidal anti-inflammatory drugs (12) and with the histamine H2 receptor blocker ranitidine (13), the interaction of clopidogrel with atorvastatin (14), and with the proton–pump inhibitor omeprazole (15), and even the possible interaction of clopidogrel with quantities of caffeine that are found in commercially available coffee (16).

Several caveats nonetheless should be kept in mind when considering whether and to what degree this study should influence clinical practice. First and foremost, the clinical implications of these findings are not clear. Platelets perform multiple functions in the thrombotic process. Although the finding that atorvastatin can interfere with the effect of clopidogrel, probably through competition for CYP3A4 (14), has been replicated in ex vivo studies, other studies dispute the presence of the interaction (17), and clinical observations from several databases have failed to support the hypothesis that rates of myocardial infarction or stent thrombosis are elevated among patients treated with atorvastatin and clopidogrel compared to clopidogrel alone (18–20). It is theoretically possible that the databases reflect a balance between the effects of atorvastatin in preventing myocardial infarction, on the one hand, and its diminishing the in vivo effect of clopidogrel, on the other. However, it is also possible that the degree to which the biologic effect of clopidogrel is decreased is not clinically significant and/or that the wrong measure of platelet activity was tested in the ex vivo studies. Another issue that is important in interpreting the findings of the current study is of statistical confounding. It is likely that in the current study, patients with more severe disease (and therefore at high risk) were more likely to receive calcium-channel blockers than patients who did not receive them. Although correction for age, gender, and diabetes mellitus did not appear to diminish the independent predictive ability of calcium-channel blockade, it is possible that unmeasured confounders played an important role here by increasing platelet activation or decreasing clopidogrel metabolism. Finally, it is worth pointing out that, although this study was not designed with adequate power to assess clinical events, those events that occurred more frequently among patients treated with calcium-channel antagonists consisted largely of revascularization, an event whose frequency would not be expected to be influenced by clopidogrel.

Thus, while the findings of Siller-Matula et al. (8) cannot be considered as providing definitive evidence for a clinical interaction between calcium-channel antagonists and clopidogrel, they certainly should give the clinician reason for pause. Patients are frequently treated with multiple medications, many of which are costly, noxious, and occasionally downright hazardous. Calcium-channel antagonists provide a sterling example of this issue. In the 2002 American College of Cardiology/American Heart Association guidelines for the management of patients with stable angina pectoris (21) and the 2007 guidelines for the management of acute coronary syndromes (22), nondihydropyridines have received class I and IIa status, respectively, for the management of symptoms. It is important for clinicians to ask themselves whether the drugs they prescribe are being given to relieve symptoms (for which there is modest evidence), or solely to modify the disease process (for which there is no evidence), and to recognize the potential to exchange unwittingly the disease-modifying properties of some drugs, such as clopidogrel, for ill-defined or absent properties of other drugs.

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