Omeprazole
A Possible New Candidate Influencing the Antiplatelet Effect of Clopidogrel*

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Clopidogrel is a prodrug activated in the liver to a metabolite that is a specific and irreversible inhibitor of the platelet P2Y₁₂ receptor. The P2Y₁₂ receptor mediates the amplification of aggregation induced by adenosine diphosphate (ADP) and also other agonists. In addition, P2Y₁₂ inhibition of aggregation induced by adenosine diphosphate also affects coagulation and inflammation (1). These mechanisms serve as the rationale for P2Y₁₂ blockade in high-risk cardiovascular disease. Indeed, following significant clinical benefits reported in major clinical trials, clopidogrel, along with aspirin therapy, is now widely used around the world to prevent thrombotic events in patients with acute coronary syndromes and after coronary artery stenting (2).

In 2003, we first reported (3) evidence of a nonuniform antiplatelet effect of clopidogrel therapy in patients undergoing coronary stenting by serially measuring ADP-induced platelet aggregation and expression of activation-dependent receptors. Platelet inhibition and after-treatment reactivity were normally distributed. Of great potential concern was suggested that clopidogrel nonuniformly inhibited its target and that in some patients the lack of inhibition was profound (3). Other investigators confirmed these results (2). These data served as the rationale for the development of new P2Y₁₂ receptor blockers with superior pharmacodynamic profiles (2).

The mechanisms responsible for clopidogrel response variability and resistance are incompletely defined. Several lines of evidence indicated that clopidogrel nonresponsiveness is a pharmacokinetic problem associated with insufficient active metabolite generation that is influenced by limitations in intestinal absorption, as well as functional and genetic variability in the hepatic cytochrome (CYP) P450 isoenzymes (4–7).

Only 15% of the absorbed clopidogrel dose is converted to an active thiol metabolite (R-130964), mainly by the hepatic CYP isoenzymes (6). Studies by our group (8–10) demonstrated the inverse relation between after-clopidogrel platelet reactivity and CYP3A4 metabolic activity. Stimulation of CYP3A4 activity by rifampin or St. John’s wort enhanced platelet inhibition by clopidogrel, whereas agents that competed with clopidogrel for CYP3A4 (e.g., erythromycin or troleandomycin) attenuated platelet inhibition. Importantly, an interaction with the lipophilic statin atorvastatin that competes for CYP 3A4 has also been demonstrated (8–10). The clinical significance of the lipophilic statin–clopidogrel interaction has not been definitively demonstrated and remains controversial (11). In a recent study, co-administration of ketoconazole (a CYP3A4 inhibitor) did not affect prasugrel (a third-generation thienopyridine) active metabolite generation or prasugrel-induced platelet inhibition. Prasugrel is metabolized by other cytochromes in addition to CYP3A4. However, clopidogrel co-administered with ketoconazole was associated with less platelet inhibition and less active metabolite generation, suggesting that CYP3A4 is a major contributor of clopidogrel active metabolite generation (7). Moreover, the demonstration of a similar half-maximal inhibitory constant for the active metabolites of prasugrel and clopidogrel is strong evidence that suboptimal inhibition of platelet aggregation associated with clopidogrel treatment is due to insufficient active metabolite generation (12). A polymorphism of the CYP3A5 gene affected clopidogrel responsiveness in healthy volunteers and worse outcomes were observed in clopidogrel-treated patients undergoing stenting with the CYP3A5 nonexpressor genotype (13). In addition to CYP3A isoenzymes, involvement of CYP2C9, CYP2C19, and CYP1A2 in clopidogrel active metabolite conversion has been demonstrated (7). The influence of the CYP2C19 genotype on clopidogrel responsiveness in healthy volunteers has also been demonstrated (14). In this issue of the Journal, in a prospective, randomized, double-blind, placebo-controlled study, Gilard et al. (15) further support a potential drug–drug interaction at the CYP2C19 level. In their study of patients undergoing elective coronary stenting, co-administration of the proton pump inhibitor omeprazole with clopidogrel was associated with significantly higher platelet P2Y₁₂ reactivity as mea-

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sured by a flow cytometry assay employing monoclonal antibodies specific for vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) (15). The results support the researchers’ prior observational study (16). The VASP-P assay exploits coupling of P2Y_{12} to a G-protein that inhibits adenylyl cyclase. Vasodilator-stimulated phosphoprotein phosphorylation is phosphorylated by cyclic adenosine monophosphate (cAMP)-regulated protein kinases. In the assay, platelet VASP is first maximally phosphorylated by prostaglandin E1 stimulation. The assay is then repeated with the addition of ADP; a fall in the level of VASP-P after ADP stimulation serves as a marker of unblocked P2Y_{12} receptors and persistent P2Y_{12} reactivity. The determination of VASP-P has advantages over light-transmittance aggregometry as a measure of clopidogrel responsiveness by being a specific indicator of P2Y_{12} reactivity. Platelet aggregation in response to ADP is mediated by P2Y_{1} and P2Y_{12} and thus does not indicate only P2Y_{12} reactivity. In addition, platelet aggregation must be determined soon after blood drawing, whereas VASP-P is a stable marker lending potential applicability to multicenter investigations. However, it is also known (17) that VASP-P levels in platelets are influenced by nitric oxide, prostaglandins, and epinephrine through effects on cAMP levels. Nevertheless, analysis of VASP-P currently is the most specific P2Y_{12} assay available.

In the current study, using the definition of Barragan et al. (18) for “bad” clopidogrel responders that correlated with an increased risk of stent thrombosis, the authors reported a 4.31 greater chance of being a clopidogrel “bad” responder when patients were treated with omeprazole and clopidogrel as compared to clopidogrel alone. This study gains significant clinical interest because proton pump inhibitors are commonly co-administered with clopidogrel in the hope of attenuating gastrointestinal bleeding. However, there are no data to support prophylactic proton pump inhibitor administration with clopidogrel in reducing gastrointestinal bleeding in asymptomatic elective stent patients. Moreover, there are no guideline recommendations for this therapy.

Although the current investigation is a prospective, randomized trial, this study is limited by the fact that the incidence of clopidogrel nonresponsive patients in each group is not known and, as such, the investigation lends itself to selection bias. Ideally, this study should have recruited only known clopidogrel-responsive patients. Similarly, because the primary premise of this study is that the omeprazole–clopidogrel drug–drug interaction is via a CYP2C19 competitive or noncompetitive inhibitory mechanism, all known patients with CYP2C19 polymorphism should be excluded. Because heterozygous CYP2C19*2/*1 genetic polymorphism leads to substantial decrease in the phenotypic expression of CYP2C19 as compared to the wild-type CYP2C19 (*1/*1) with the incidence of CYP2C19*2 polymorphism ~29% (19), excluding all patients with CYP2C19 polymorphism would ensure that the difference observed in platelet reactivity between the 2 groups is not due to more patients with the CYP2C19 polymorphism in the omeprazole + clopidogrel group. This study also assumed that omeprazole inhibited the metabolic activation of clopidogrel at the level of hepatic CYP2C19. However, intestinal CYP3A4 and CYP2C19 are also important oxidative enzymes in drug metabolism (19,20). Whether the variability in expression of the intestinal efflux P-glycoprotein transport system mediated by multidrug resistance gene-1 genetic variability may play a role in the omeprazole–clopidogrel interaction is not addressed in this study (5).

CYP2C19 does not appear to be a major hepatic pathway for clopidogrel metabolism, and its influence on clopidogrel-induced platelet inhibition may be limited (7). The influence of omeprazole may be more important in patients who also receive high-dose lipophilic statins that may potentiate significant drug–drug interactions with clopidogrel. Moreover, the authors did not conduct any mechanistic investigations and, therefore, other pathways may be responsible for their observed effects. Thus, the present study is a hypothesis-generating study. An improved patient selection scheme and pharmokinetic/pharmacodynamic investigations as previously conducted with ketoconazole are required before any clinical significance can be attributed to this reported drug–drug interaction or any suggestions are made that cardiologists should delete omeprazole therapy when clinically indicated in patients treated with dual antiplatelet therapy (7).

Finally, there are emerging data from overall small studies (21) demonstrating heightened thrombotic risk in patients with high platelet reactivity to ADP following coronary stenting. The unresolved issue that remains is whether superior inhibition of platelet aggregation by P2Y_{12} inhibitors will lead to overall net clinical benefits. At this time, there is a need for a definitive large-scale trial to determine whether high platelet reactivity determined by an ex vivo test truly identifies the patient at risk for thrombotic events. If the relationship indeed exists, and if subsequent studies can demonstrate that lower platelet reactivity in the individual patient leads to better outcomes, then the “one size fits all” approach to treatment that we currently employ will vanish. At that time, the observations of Gilard et al. (15) will have increased relevance. We will then live in the era of personalization, where measurements of platelet reactivity in all patients with cardiovascular disease will be routine and treatment will be adjusted accordingly (21). However, a lot of work remains before we are there.

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