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EDITORIAL COMMENT

Searching for the Ceiling

New Reflections on the Disposition and Metabolism of Clopidogrel*

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Antiplatelet therapy with the thienopyridine clopidogrel has enjoyed unprecedented success over the last decade. Therapy with clopidogrel now forms an integral part of nearly all intracoronary stenting procedures, and long-term clopidogrel is generally recommended for patients who have had drug-eluting stents placed. The background of clopidogrel is rather unusual. The "early" work on stent placement was performed with a combination of aspirin and the thienopyridine ticlopidine (1,2). However, it soon became apparent that, whereas ticlopidine was not well tolerated, clopidogrel was much less noxious and seemed to be similarly effective (3). Paradoxically, this development occurred in the absence of randomized trials comparing its efficacy with that of ticlopidine. More recent developments surrounding clopidogrel have centered on the appropriate dosing of the drug

See pages 612 and 620

and the identification of patients with suboptimal biologic responses (4-6). In fact, if one looks at the earliest dosing studies that were used to support clopidogrel's regulatory approval, it is remarkable to note that doses as low as 25 to 50 mg were initially explored (7). Currently, we know that administration of a 75-mg dose of clopidogrel causes steady state inhibition of the platelet aggregation response to adenosine diphosphate at 24 h, that the response after 300 mg seems to plateau at 6 h, and that the response to 600 mg nears its maximal value at 2 h. Two subsequent studies have indicated that the response in patients undergoing percutaneous coronary intervention (PCI) does not occur more quickly or become more intense when the dose is raised from 600 to 900 mg (8,9).

Although these principles seem simple enough, recent studies indicate the situation is much more complex. Clopidogrel is a pro-drug that is converted in the liver by members of the cytochrome P450 (CYP) 3A, 1A, 2B, and 2C subfamilies. The metabolism of the drug involves a series of intermediate metabolites ultimately yielding the active thiol metabolite, which binds to the platelet purinergic receptor known as P2Y12. Common teaching recently has been that the metabolism of clopidogrel is "bottlenecked" in the liver; the findings of the ISAR (Intracoronary Stenting and Antithrombotic Regimen) trial group seem to confirm this belief. After increasing the loading dose of clopidogrel from 600 mg to 900 mg, von Beckerath et al. (8) reported that levels of the active metabolite were no different between the 2 groups. Recently, Bonello et al. (10) demonstrated that measurements of vasodilator stimulated phosphoprotein (VASP) could be used to titrate the loading dose when sequential doses of 600 mg separated by approximately 24 h were given to patients who had a suboptimal response as determined with the VASP or platelet reactivity index (PRI).

In the current issue of *JACC: Cardiovascular Interventions*, these fundamental beliefs are revisited and expanded (11,12). The PRINC (Plavix Response in Coronary Intervention) trial investigators tested a novel dosing scheme for clopidogrel. In this study, 60 patients undergoing PCI received a 600-mg loading dose of clopidogrel and were then randomized to receive, 2 h later, either a second 600-mg dose or a placebo (there was also a randomization to intracoronary verapamil that had little effect on any measurable platelet parameter.) Patients were rerandomized the next day to receive a daily dose of either 75 mg or 150 mg for 7 days. The principal finding was that, 2 h after the second dose of clopidogrel or placebo was given, platelet aggregation measured with the VerifyNow agglutination assay was more inhibited among patients treated with 2 loading doses of clopidogrel than a single loading dose (42% vs. 24%, $p = 0.01$). The log-transformed rate of increase in platelet inhibition was also 3-fold greater during the 2 h after the second dose was given. At 7 days, aggregation was also more inhibited among patients treated with 150 mg daily compared with 75 mg daily (50% vs. 29%, $p = 0.01$). If confirmed, these findings will add another dimension to our understanding of clopidogrel dosing, because they suggest that timing of the loading dose might be as important as the total quantity given. In other words, while increasing a single loading dose of clopidogrel beyond 600 mg does not increase activity of the drug, it now seems that staggering the increase does exactly this. In fact, closer inspection of the findings of von Beckerath et al. (8) indicates that neither levels of the active metabolite nor levels of the parent compound increase when a single loading dose exceeds 600 mg. Whereas attention largely had focused on the CYP family of enzymes and metabolic activation of clopidogrel, these findings should also impress

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on us the importance of absorption and transport of the drug from the intestinal lumen.

In a second report from this study, the PRINC investigators tie these findings to genotypic variation in the pharmacodynamics of clopidogrel. With a candidate gene approach, they identified carriers within the study of a number of common alleles known to be associated with loss or gain of CYP function or intestinal absorption. The size of their study precluded analyses of some rarer polymorphisms. Among patients with the wild-type 2C19 allele (2C19*1*1), platelet aggregation responses to the 600-mg single dose and the 1,200-mg staggered dose were similar, as were responses to the 75- and 150-mg maintenance doses. In contrast, carriers of the loss of function alleles, 2C19*2 and 2C19*4, had lower aggregation responses than 2C19*1*1 subjects. Unlike the 2C19*1*1 subjects, they also had a greater response to the staggered loading dose than to the single 600-mg dose and also had more inhibition of aggregation after 7 days of a 150-mg versus 75-mg maintenance dose. Carriers of the 2C9*2 and -*3 alleles also had less response than subjects with 2C9*1*1 genotypes. In other words, increasing the loading dose in a staggered fashion had its greatest impact in patients who carried alleles associated with diminished CYP 2C9 or 2C19 function. The study also yielded 2 surprising findings: first, carriers of CYP 2C19*17, an allele associated with marked gain of enzyme function, did not have a heighted response to clopidogrel; second, a well-characterized mutation of the P-glycoprotein (P-gp) efflux transport protein (which shares considerable substrate specificity with CYP 3A4) was associated with only a minimal trend toward increased response to clopidogrel. The P-gp is believed to play an important role in the reverse transport of absorbed clopidogrel (as well as other drugs) from the intestinal wall back into the intestinal lumen. This finding is in contrast to the report by Taubert et al. (13), which showed a 2.5-fold decrease in the Cmax of clopidogrel and 2-fold decrease in its active metabolite among individuals with the MDR1 3435 T/T genotype, which is a loss of function mutation of P-gp. Although the 2 former unexpected findings might simply be the result of a small sample size, they are particularly surprising in a study that seems to highlight the importance of absorption kinetics.

Interventionalists who fear that their lives are becoming increasingly complex should be aware of one simple fact—it is. Now, in addition to whether a 300- or 600-mg loading dose of clopidogrel is indicated, the clinician must also be aware of multiple drugs that interact with clopidogrel, such as atorvastatin (14), omeprazole (15), calcium channel antagonists, and even coffee (16) and cigarette smoke (17); the importance of staggering a clopidogrel loading dose; and genetic variants of the enzymes that regulate metabolism and possibly absorption of clopidogrel, not to mention the complexity of deciding whether to measure platelet response to clopidogrel. Even the current reports from the PRINC investigation leave several important questions unanswered. For example, is the correct number of loading doses 2, or would 3 or 4 staggered doses lead to even higher levels of platelet inhibition? Should 150 mg be given as a single daily maintenance dose or, given the approximate 1- to 2-h half-life of the active metabolite (18), would split (twice daily) dosing be more effective, because platelets freshly released from the bone marrow might then be exposed to a second dose later in the day? Is 150 mg daily given as a single dose for 7 days long enough to produce a meaningful clinical result, or might not a longer course of 150 mg be more effective? Finally, there are 2 overwhelmingly important questions that these studies do not even address. Is there a bona fide clinical indication for measuring platelet aggregation or agglutination in patients receiving clopidogrel (or even genotyping them for known CYP alleles)? How would platelet inhibition with this strategy stack up against more potent antagonists of P2Y12 that have less variable effects, such as prasugrel or AZD6140?

All semblance of sanity should not be abandoned, however. All of the observations described in the preceding paragraph must be regarded as exploratory. Although much attention has been paid to observations that myocardial infarction and stent thrombosis are more common in patients characterized as clopidogrel non-responders, it is important not to lose sight of fundamental clinical principles. Several findings from clinical databases suggest that not all interventions that alter the platelet response to clopidogrel have much clear clinical relevance. For example, the in vitro interaction between clopidogrel and atorvastatin has not been shown to influence the risk of ischemic events in several large clinical databases (19,20). Similarly, although the investigators of the ISAR reloading study reported that in patients maintained on maintenance clopidogrel reloading with a 600-mg dose led to further inhibition of platelet aggregation (21), the ARMYDA (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty) trial investigators performed a randomized clinical trial in which this strategy had no effect on outcomes (22). Preliminary clinical studies of the effect of CYP genotype have also been disappointing. Trenk et al. (23) reported that CYP 2C19*2 carriers were more likely to have increased platelet reactivity while on clopidogrel, and that increased platelet reactivity was associated with a higher event rate 1 year after coronary stenting. However, the most important link, a clinical association between CYP 2C19 genotype and clinical events (death and myocardial infarction), was not detected, possibly as a consequence of the infrequency of events.

Thus there is good reason for equipoise among interventionalists who need to know more about clopidogrel dosing. The GRAVITAS (Gauging Responsiveness with A Verify Now Assay–Impact on Thrombosis and Safety) study will

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 6, 2008
DECEMBER 2008:628–30

examine, in 6,600 patients undergoing PCI, the clinical importance of a poor platelet aggregation response to clopidogrel and will test whether increasing the maintenance dose of clopidogrel to 150 mg daily will be of clinical benefit (24). The OASIS 7 (Organization for the Assessment of Strategies for Ischemic Syndromes) study will compare a 300-mg loading dose of clopidogrel with a 600-mg loading dose, and will compare a 75-mg maintenance dose for 7 days with a 150-mg dose (25). Therefore it seems that some clarity will come to this issue, albeit slowly.

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