The Pharmacodynamics of Switching Between P2Y12 Receptor Antagonists*

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The P2Y12 receptor antagonists are key components of the medical and invasive management of coronary artery disease. These agents reduce recurrent cardiovascular events in the setting of acute coronary syndrome (ACS), decrease the incidence of thrombotic events after percutaneous coronary intervention (PCI), and prevent recurrent events in patients with histories of remote myocardial infarction or stenting. However, the P2Y12 antagonists are not interchangeable; they differ in pharmacology and the patient populations in which their safety and efficacy have been demonstrated. The superiority of ticagrelor and prasugrel over clopidogrel was demonstrated in clinical trials with median treatment durations of approximately 1 year, with ischemic benefit observed both early and late after randomization, arguing against changing agents over the course of therapy. However, in actual clinical practice, switching may be required before the completion of the appropriate treatment duration for various reasons, such as intolerance or insurance coverage. Switching to a new agent may be problematic, particularly in the early phase of therapy after ACS and/or PCI, because insufficient platelet inhibition during the transition period could increase the risk for cardiovascular events. The safety and clinical efficacy of changing P2Y12 antagonists have not been evaluated in adequately powered, prospective studies outside of the PLATO (Platelet Inhibition and Patient Outcomes) trial, in which 46% of patients were exposed to clopidogrel prior to randomization. Yet despite this paucity of data, there is an unmet need for a simple framework to inform clinicians how to appropriately transition between P2Y12 antagonists. For example, are there any drug-drug interactions? Is a loading dose (LD) always needed? Pharmacodynamic (PD) studies act as useful surrogates to answer these questions, short of large, clinical trials that are unlikely to ever be performed. Such a “how-to-switch” guide for clinicians is essentially complete with the addition of the prasugrel-to-ticagrelor transition study presented by Angiolillo et al. (1) in this issue of JACC: Cardiovascular Interventions.

The effect on platelet inhibition when switching between P2Y12 antagonists depends on the mechanisms of action and pharmacologic characteristics of the different agents. There are currently 3 classes of P2Y12 antagonists available: the thienopyridines, clopidogrel and prasugrel; the nucleotide mimetic, cangrelor; and the cyclopentyltriazolopyrimidine ticagrelor. The thienopyridines require biotransformation into a highly labile active metabolite with a short half-life that exerts its antiplatelet effect by irreversibly blocking the P2Y12 receptor’s adenosine diphosphate (ADP)-binding site. The body converts prasugrel into active metabolite more efficiently than clopidogrel, resulting in more rapid and intensive inhibition after a prasugrel LD as well as at steady state during maintenance dosing. The residual antiplatelet effects of clopidogrel and prasugrel persist for as long as 7 and 9 days, respectively (2). The findings of PD studies are consistent with these characteristics: switching a patient directly from a clopidogrel maintenance dose (MD) to a prasugrel MD results in a slow increase in inhibition over several days, whereas a switch using a prasugrel LD followed...
by an MD results in a rapid increase in inhibition within hours and then achievement of a new steady state of more intensive inhibition (3). Conversely, transitioning directly from a prasugrel to a clopidogrel MD results in a decrease in platelet inhibition over several days and achievement of a new, lower steady-state level of inhibition (4). Switching from prasugrel to clopidogrel using an LD would likely provide a more consistent and reliable transition given that a clopidogrel MD alone may require as long as 1 week to reach steady state.

Cangrelor is an intravenous, nucleotide-mimetic, directly acting P2Y<sub>12</sub> receptor antagonist indicated as an adjunct to PCI in patients who have not been treated with P2Y<sub>12</sub> inhibitors; therefore, all patients who receive this drug must be switched to oral agents. A cangrelor bolus followed by infusion provides near complete P2Y<sub>12</sub> receptor occupancy and inhibition of ADP-induced P2Y<sub>12</sub> platelet aggregation within minutes of administration. Once the infusion is discontinued, circulating drug is rapidly metabolized by plasma endonucleotidases, and complete platelet recovery occurs within 1 h. The mechanism of action of cangrelor is not entirely clear, although competitive binding at the ADP-binding site has been proposed (5). This model is generally consistent with PD studies that demonstrate a substantial interaction when a thienopyridine is administered during cangrelor infusion, such that a clopidogrel LD should be administered at the end of the infusion, and a prasugrel LD should be administered at the end of infusion or up to 30 min before it is stopped. Ticagrelor, which appears to bind at a site separate from cangrelor, can be administered at any time during cangrelor administration.

Ticagrelor is a reversibly binding, allosteric P2Y<sub>12</sub> receptor antagonist that interacts at a ligand-binding site distinct from that for ADP. It has a rapid onset of action and achieves high levels of platelet inhibition. Unsurprisingly, platelet inhibition falls when switching from ticagrelor to clopidogrel (6). Transitioning to clopidogrel without a LD is probably unwise, given that the bulk of ticagrelor’s effect is gone by approximately 48 to 72 h of discontinuation, and a clopidogrel MD requires approximately 5 to 7 days to reach steady-state inhibition. Conversely, platelet inhibition rapidly increases when moving from clopidogrel to ticagrelor using an LD. The safety and clinical efficacy of this strategy in the setting of ACS was established by the PLATO trial. In the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, which examined the safety and efficacy of ticagrelor in the long-term setting, therapy was initiated with an MD, irrespective of prior P2Y<sub>12</sub> therapy.

Because both prasugrel and ticagrelor are superior to clopidogrel in ACS, it makes clinical sense to substitute one of these agents for the other if a patient must discontinue for a reason other than bleeding and there are no contraindications present. However, there has been a paucity of PD or clinical data to inform the appropriate strategy for switching between these “best-in-class” P2Y<sub>12</sub> antagonists. Angiolillo et al. (1,3,7) have provided critical information to help fill this evidentiary vacuum through a series of studies, including the latest in this issue. In a previous study of more than 100 subjects with stable coronary artery disease, this group demonstrated that switching patients from ticagrelor to a prasugrel MD was associated with an increase in platelet reactivity (i.e., less platelet inhibition), a phenomenon that was partially, but not completely, mitigated by transitioning with a prasugrel LD (7). Prior studies have shown that on average, ticagrelor results in lower levels of platelet reactivity according to ex vivo platelet function tests than prasugrel, and therefore the observed increase in reactivity seen after transitioning to prasugrel is not particularly surprising. However, the investigators could not exclude an interaction between prasugrel and ticagrelor given the observed pattern of changes in platelet reactivity. The presence of a potential interaction between ticagrelor and prasugrel is provocative, as it cannot be explained by our current understanding of their mechanisms of action. Thankfully, the clinical significance of such an interaction, if one exists, may be negligible: none of the subjects switched from ticagrelor to prasugrel reached levels of high on-treatment reactivity associated with increased thrombotic risk (8). In the present study, Angiolillo et al. (1) examined the PD effects of the opposite switch, from prasugrel to ticagrelor. A total of 82 patients who were treated with prasugrel after PCI for ACS were randomly assigned to either continued prasugrel or switching to ticagrelor 90 mg twice daily MD with or without an LD. With either dosing strategy, ticagrelor led to a transient and significant decrease in platelet reactivity within 2 h of administration. At 1 week, when one would anticipate a negligible remaining prasugrel effect, platelet reactivity was numerically lower and noninferior in the patients assigned to ticagrelor compared with prasugrel. Therefore, no interaction was observed. The lack of a PD benefit with an LD strategy for the ticagrelor
transition might be due to substantial P2Y12 receptor occupancy by irreversibly bound prasugrel active metabolite, and therefore the larger ticagrelor dose could provide no incremental platelet inhibition beyond that provided by the lower MD. Importantly, there was no PD downside to transitioning with the ticagrelor LD, as platelet reactivity was broadly similar for the 2 strategies at multiple time points over the first 48 h. The findings of this study are strengthened by the incorporation of several types of platelet function tests, which in this particular case is critical because the VerifyNow P2Y12 test (Accriva Diagnostics, San Diego, California) lacks discrimination at very low levels of platelet reactivity. The clinical applicability of the study is further enhanced by its inclusion of prasugrel-treated patients with ACS, rather than the healthy volunteers or subjects with stable coronary artery disease who are more commonly enrolled in PD assessments.

Synthesizing the PD data for the multitude of possible strategies to transition between oral P2Y12 antagonists can be a daunting task. With the caveat that switching straightaway with an MD may be sufficient in select circumstances, the simplest approach, to start with an LD, will always ensure an optimal PD response. This is particularly important in the acute phase of ACS or in the months following stent implantation, when a short period of incomplete platelet inhibition may increase clinical risk. Although robust safety data for such a simple strategy are lacking, there are no signals of harm from the small studies that have been performed to date. Also, before deciding how to switch agents, ensure that the patient needs to switch, and if so, switch to an agent that will provide the greatest clinical benefit. Given the proven clinical superiority of ticagrelor and prasugrel over clopidogrel, it would appear preferable to maintain patients in the first year post-ACS on 1 of these agents. The studies by Angiolillo et al. (1,3,7) have taught us how to do this right.

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