EDITORIAL COMMENT

Reversal of Antithrombotic Therapy

Is it Necessary and Sufficient?*

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The management of patients with thrombotic conditions often includes 1 or more antithrombotic agents to reduce the likelihood of recurring events. Although antithrombotic drugs, when administered at approved doses in thoughtfully selected patients, are both effective and safe, complications do occur, and there are clinical settings where bleeding is anticipated.

Accordingly, a robust dialogue among clinicians and patients has centered on drug antidotes and reversal agents. The U.S. Food and Drug Administration has exercised expedited review programs, including breakthrough designation and accelerated approval tracks, targeting the development of reversal agents for direct oral anticoagulants (1).

In this issue of *JACC: Basic to Translational Science*, Angheloiu et al. (2) report a series of in vitro and ex vivo flow studies employing bovine serum albumin-sorbents-hydroxyl groups linked to nitrogen in central hydrophobic structures (benzenes) in solution with ticagrelor, a platelet $P2Y_{12}$ receptor antagonist, and human blood mixed with ticagrelor. There was successful removal of ticagrelor, with peak removal of 99% and 94% from whole blood and 99.9% and 90% from plasma during 10 h and 3 to 4 h of recirculating, respectively.

TICAGRELOR

Ticagrelor is a cyclopentyl-triazolo-pyrimidine antagonist of the platelet $P2Y_{12}$ receptor (3). Binding studies demonstrate that it exhibits potent, rapid, and reversible binding. The rapid on/off receptor kinetics and dynamic state of equilibrium suggest that: 1) the inhibitory effect should closely mirror the level of drug exposure; and 2) the drug should be accessible to an antidote. Ticagrelor has 1 active metabolite: AR - C124910XX. The pharmacokinetics of ticagrelor and its metabolite are predictable, with plasma concentrations being dose-proportional after initial dosing and stable at steady-state. Absorption is rapid, with CMax being achieved at 2 to 3 h after oral administration and a t1/2 of 7.1 to 12 h (for both ticagrelor and its active metabolite).

BLEEDING RISK

In the PLATO (PLATelet inhibition and Outcomes) trial (4), 18,624 patients with acute coronary syndrome (ACS) were randomized to either ticagrelor or clopidogrel. Patients treated with ticagrelor and those receiving clopidogrel experienced similar rates of PLATO major bleeding (11.6% and 11.2%, respectively; p = 0.43) (5). Noncoronary artery bypass grafting-related major bleeding occurred with greater frequency in ticagrelor-treated patients (p = 0.03) as did nonprocedure-related major bleeding (p = 0.01). Fatal bleeding was infrequent and occurred in 20 and 23 patients receiving ticagrelor and clopidogrel, respectively. There were 11 intracranial hemorrhagic events among patients randomized to ticagrelor, and 2 such events with clopidogrel. Major bleeding in either treatment group was associated with higher short-term mortality but not with long-term mortality (6). Spontaneous bleeding was associated with both short- and long-term mortality.

REVERSING TICAGRELOR: WHEN AND HOW?

The decision to reverse the pharmacodynamic effects of a platelet antagonist must be based on sound clinical judgment and a clear understanding of the potential risk and benefits, including acute thrombotic events, among patients predisposed because of an underlying condition. There are 3 clinical scenarios where reversal may be indicated:

- Active bleeding, particularly severe or life-threatening.
- Unscheduled, urgent, or emergent procedures that carry a high bleeding risk.
- Major trauma with anticipated bleeding.

After the decision to reverse has been made, the question then becomes: how will reversal be achieved? There are currently no evidence-based options for ticagrelor reversal, underscoring the potential importance of a strategy proposed by Angheloiu et al. (2).

PLATELET TRANSFUSION. One might assume that transfusing platelets would reverse the effect of a platelet antagonist; however, this is not the case for ticagrelor (7). Platelet aggregation was determined employing impedance aggregometry on whole blood and light transmission aggregometry on platelet-rich plasma using adenosine diphosphate (ADP) or arachidonic acid as agonists for ticagrelor and aspirin, respectively. Platelet supplementation was undertaken using washed platelet suspensions to increase the platelet count by ≥60%. Platelet supplementation completely restored arachidonic acid-induced platelet aggregation in aspirin-treated samples, whereas it failed to correct ADP-induced aggregation in ticagrelor-treated samples.

In the APTITUDE-ACS (Antagonize P2Y$_{12}$ Treatment Inhibitors by Transfusion of Platelets in an Urgent or Delayed Timing After Acute Coronary Syndrome or Percutaneous Coronary Intervention Presentation-Acute Coronary Syndrome) study, patients presenting with ACS or for elective percutaneous coronary intervention received loading doses of clopidogrel (600 mg, n = 13; or 900 mg, n = 12), prasugrel 60 mg (n = 10), or ticagrelor 180 mg (n = 10) (8). The potential effect of platelet transfusion on reversal of inhibition was assessed ex vivo by mixing platelet-rich plasma from blood sampled at baseline in increasing proportions with platelet-rich plasma sampled 4 h after the drug loading dose. The restoration of residual platelet aggregation significantly decreased with increasing potency of the P2Y$_{12}$ receptor antagonist drug (83.9 ± 11%, 73 ± 14%,

66.3 ± 15%, and 40.9 ± 19% for clopidogrel 600 mg, clopidogrel 900 mg, prasugrel, and ticagrelor, respectively; p for trend <0.0001). In a recently published study of healthy volunteers, autologous platelet transfusion given 24 or 48 h following a 180-mg loading dose of ticagrelor had minimal effect on platelet aggregation (9). Case reports suggest that even large-volume platelet transfusions, although increasing the circulating platelet count, do not reverse the effects of ticagrelor-mediated inhibition of platelet activation and aggregation (10).

MONOCLONAL ANTIBODY. Buchanan et al. (11) developed an antigen-binding fragment (Fab) to ticagrelor and its major active metabolite (TAM). The Fab had a 20 pmol/l affinity for ticagrelor—100× stronger than ticagrelor's affinity for the platelet P2Y$_{12}$ receptor. The antidote neutralized the free fraction of ticagrelor and also reversed its antiplatelet activity both in vitro, employing human platelet-rich plasma, and in vivo in mice. The antidote normalized ticagrelor-dependent bleeding in a mouse model of acute surgery. Last, the antidote had a circulating half-life of approximately 12 h—similar to ticagrelor (9.8 h) and TAM (12.4 h). The ticagrelor-specific neutralizing Fab, MEDI2452, binds unbound ticagrelor and TAM in a 1:1 ratio (12) and restores ADP-induced platelet aggregation.

HEMADSORPTION. The hemadsorption technique described by Angheloiu et al. (2) was highly effective in removing ticagrelor, but it did so slowly. Thus, in its current form, the technique would offer less of an option for emergent indications, but could instead be used when slow removal was clinically acceptable—perhaps to facilitate a needed surgical procedure that would otherwise be delayed. There are, however, remaining issues that the investigators must address if the technology undergoes further development. These include: removal of TAM, the cause(s) of thrombocytopenia, the need for albumin infusions, and the effect of hemadsorption on unintended removal of other drugs.

THE FUTURE OF ANTITHROMBOTIC DRUG REVERSAL

The concomitant development of antithrombotic drugs and reversal agents, with clear guidance for their use, should proceed expeditiously. A regulatory pathway of development that promotes innovation and rewards forethought of safety platforms, coupled with carefully constructed clinical trials and registries that capture the benefits (and potential risks) of reversal in common practice scenarios,

is needed to determine whether drug-specific (precision) reversal is both necessary and sufficient, particularly with life-threatening events such as intracranial hemorrhage, to affect outcomes among patients with and those at risk for serious bleeding.

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