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Pharmacodynamic Effects During the Transition Between Cangrelor and Ticagrelor

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Objectives This study sought to determine pharmacodynamic effects during transition from intravenous cangrelor to oral ticagrelor and from oral ticagrelor to intravenous cangrelor.

Background Cangrelor is an intravenous antagonist of $P2Y_{12}$ and its use will require transition to and from oral agents.

Methods Patients (n = 12) with stable coronary artery disease who were taking aspirin 81 mg daily were recruited. On study day 1, they received a bolus plus 2-h infusion of cangrelor plus a 180-mg dose of ticagrelor at either 0.5 h (n = 6) or 1.25 h (n = 6). Pharmacodynamic effects (light transmission platelet aggregation in response to 20 and 5 μmol/l adenosine diphosphate, VerifyNow, $P2Y_{12}$ assay (Accumetrics, San Diego, California), vasodilator-stimulated phosphoprotein index, and flow cytometry) were assessed during and after the cangrelor infusion. Patients took 90 mg of ticagrelor twice daily for either 6 (n = 6) or 7 (n = 6) doses. On study day 5, pharmacodynamic effects were assessed before and during a bolus plus 2-h infusion of cangrelor.

Results During cangrelor infusion, extensive inhibition of platelet function reflected by limited residual platelet reactivity was apparent. After cangrelor was stopped, the antiplatelet effects of ticagrelor were preserved despite a modest increase in platelet reactivity.

Conclusions Ticagrelor given before or during infusion of cangrelor did not attenuate the pharmacodynamic effects of cangrelor. The pharmacodynamic effects of ticagrelor were preserved when ticagrelor was given during infusion of cangrelor. Consistent with the reversible binding of ticagrelor, this oral $P2Y_{12}$ antagonist can be administered before, during, or after treatment with cangrelor. (J Am Coll Cardiol Intv 2014;7:435–42) © 2014 by the American College of Cardiology Foundation

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In patients with myocardial infarction, increased platelet reactivity has been associated with a greater burden of thrombus (1). Persistently, high platelet reactivity has been associated with a greater risk of early and later cardiovascular events (2). Consistent with these observations, antiplatelet therapy reduces the risk of subsequent cardiovascular events. The bioavailability of orally administered antiplatelet agents may be delayed in patients with sympathetic activation or ST-segment elevation myocardial infarction (3,4). Accordingly, treatment with cangrelor, a parenteral $P2Y_{12}$ antagonist, is likely to be advantageous during selected intervals in which a rapid onset and offset of effect and consistent suppression of platelet reactivity is desired. The CHAMPION PHOENIX (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trial (5) demonstrated that cangrelor reduced the incidence of ischemic events during percutaneous coronary intervention, without increasing the incidence of severe bleeding. The BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery) study (6) demonstrated that cangrelor can be used to maintain antiplatelet effects in patients scheduled for surgery.

Abbreviations and Acronyms

ADP = adenosine diphosphate

CAD = coronary artery disease

CI = confidence interval

LTA = light transmission aggregometry

MFI = mean fluorescence intensity

PGE1 = prostaglandin E1

VASP = vasodilator-stimulated phosphoprotein

The objective of the present study was to determine pharmacodynamic effects during the transition from intravenous cangrelor to oral ticagrelor and from oral ticagrelor to intravenous cangrelor. Previous studies have demonstrated that cangrelor blocks access to the $P2Y_{12}$ receptor of the metabolites of thienopyridines (7,8). Administration of clopidogrel immediately after discontinuation of cangrelor was not associated with an increased incidence of early thrombotic complications among patients treated in the CHAMPION studies (5,9–11). By contrast, ticagrelor does not require metabolism to become active, and it binds reversibly to the $P2Y_{12}$ receptor (12). Accordingly, the characteristics of ticagrelor suggest that it can be given before, during, and after an infusion of cangrelor without altering pharmacodynamic effects. We recruited 12 patients with stable coronary artery disease (CAD) to determine whether pharmacodynamic effects would be maintained if ticagrelor was given during infusion of cangrelor and whether previous treatment with ticagrelor altered the pharmacodynamic effects of cangrelor.

Methods

Patients. Patients were enrolled in a protocol approved by the University of Vermont/Fletcher Allen institutional review board, and provided written informed consent. Eligible patients were 18 to 75 years of age, had CAD documented by a previous myocardial infarction or coronary revascularization, and were taking 81 mg of aspirin daily. Exclusion criteria included the following: an acute coronary syndrome within the past 12 months; treatment with an anticoagulant or antiplatelet agent other than aspirin; a history of a bleeding diathesis; anemia (hematocrit <35%); severe renal insufficiency (creatinine clearance <30 ml/min); and moderate or severe hepatic insufficiency. Prohibited concomitant medications included strong and potent CYP3A inhibitors, simvastatin and lovastatin at doses more than 40 mg/day, omeprazole or esomeprazole, and digoxin. Use of nonsteroidal anti-inflammatory agents was discouraged during study participation but was not prohibited.

Study design. The study, which is outlined in Figure 1, was designed to determine whether cangrelor and ticagrelor each alter the antiplatelet effects of the other agent. On study day 1, initial treatment was with cangrelor. We determined whether addition of ticagrelor alters antiplatelet effects of cangrelor and whether previous treatment with cangrelor alters antiplatelet effects of ticagrelor. On study day 5, patients have been treated previously with ticagrelor. By stopping therapy 12 or 24 h before day 5, we determined whether previous treatment with ticagrelor alters the antiplatelet effects of cangrelor.

On study day 1, an intravenous catheter was placed in each arm. One arm was used for cangrelor infusion and the contralateral arm for blood sampling (this catheter was kept patent by infusion of normal saline at 50 ml/h). Baseline pharmacodynamic assessment was performed. A 30 μg/kg bolus of cangrelor was administered followed immediately by a 2-h infusion at a rate of 4.0 μg/kg/min. A loading dose of ticagrelor (180 mg) was given after 0.5 or 1.25 h ($n = 6$ for each). Blood for pharmacodynamic platelet function studies was taken after 0.5 or 1.25 h (corresponding to the time of ticagrelor load, $n = 6$ for each), and then at 1.75, 2, 2.25, 2.5, 2.75, 3, 4, and 5.25 h. Pharmacodynamic assessment included light transmission aggregometry (LTA), VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, California), vasodilator-stimulated phosphoprotein (VASP) index, and platelet activation measured with the use of flow cytometry. Patients were assigned randomly to receive either 6 ($n = 6$) or 7 ($n = 6$) doses of ticagrelor to be taken every 12 h. On study day 5, as performed on day 1, intravenous catheters were inserted into each arm and blood was taken for baseline pharmacodynamic assessment. A 30-μg/kg bolus of cangrelor was administered followed immediately by a 2-h infusion at a rate of 4.0 μg/kg/min. Blood for pharmacodynamic assessment was taken after 1 and 2 h. Adverse events were queried throughout study participation that ended with a telephone interview performed on study days 10 to 12.