Cangrelor A New Drug in A New Era

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Introduction
Platelets play an important role in multiple physiological systems of the body. Some of them are beneficial like making the initial plug of hemostasis in vascular injury and others are harmful like taking part in the pathophysiological thrombosis which precipitate myocardial infarction (MI), stroke, and peripheral vascular occlusions (1). Platelet inhibition is the golden step in pharmacological treatment in percutaneous coronary interventions (PCI). There are many oral anti-platelet drugs like Thienopyridines and ticagrelor (1). Cangrelor is a recent antiplatelet drug which is intravenous, rapid onset and offset, potent and reversible. It is mainly developed to solve the problems of oral anti-platelets including delayed and prolonged anti-platelet activity with inability to reverse the effect when needed. This makes Cangrelor a promising drug in periprocedural treatment in the setting of PCI.

Pharmacokinetics
Cangrelor is intravenous, direct acting drug. It acts on the P2Y12 ADP receptors on the platelet surface. It changes the conformation of the receptor leading to reversible inhibition of the receptor itself (2). Being an active drug, it doesn’t need to be activated by liver. A 30-µg/kg bolus of cangrelor followed by intravenous infusion of 4 µg/kg/min leads to platelet inhibition within minutes of administration. It has rapid onset of action with steady state at 30 minutes in absence of loading dose. Peak plasma concentration is reached within 2 minutes of bolus administration with maximum platelet inhibition within 15 minutes. It has a volume of distribution of 3.9L and is 97-98% plasma protein bound (3). Metabolism is by sequential dephosphorylation by nucleosidases in plasma. This leads to primary metabolite (AR-C69712XX) with negligible antiplatelet effects (4). All other metabolites are inactive. Nearly 93% of metabolites are cleared from plasma in a biphasic manner. Approximately, 50% of the drug and metabolites is excreted within first 24 hours and increase to 75% in next 72 hours (5). 58% of the dose is excreted by kidney and 35% through fecal excretion. Cangrelor has a clearance rate of 50 L/h. Dose adjustment is not needed in renal or hepatic patients. Other variables like age or sex don’t affect its elimination. Only body weight has an important effect on pharmacokinetics of cangrelor which explains its weight-based infusion regimen.

Pharmacodynamics
Cangrelor is a potent, direct, and reversible inhibitor of the P2Y12 receptor and is the first such drug to be administered intravenously. The compound is an adenosine triphosphate analogue with an immediate onset of action after the administration of a bolus dose. The platelet response approaches baseline within 60 minutes after discontinuation of the drug infusion. In a study of patients with acute coronary syndromes, cangrelor produced profound and stable platelet inhibition (>95%) and was well tolerated during a prolonged infusion of up to 72 hours. With these characteristics, cangrelor might be ideally suited to the treatment of patients with acute coronary syndromes. I
Cangrelor in PCI

Cangrelor may be useful in patients undergoing PCI and as a bridge for patients who need to suspend treatment with thienopyridines or ticagrelor to undergo surgery (6). Cangrelor is currently approved by drug regulating authorities for patients undergoing percutaneous coronary intervention (PCI) without prior treatment with a P2Y12 receptor antagonist and not receiving a glycoprotein IIb/IIIa inhibitor, while its use is endorsed with a class IIb recommendation by the European Society of Cardiology guidelines. Several sub-analyses of CHAMPION PHOENIX trial have tried to elucidate the role of cangrelor in PCI, including its usefulness during a 2-hour landmark analysis, impact on intraprocedural stent thrombosis, and reduction in myocardial infarction (MI) rate. In patients with ST elevation MI and in clinical scenarios of disturbed absorption of oral antiplatelet agents or in need of an intravenous agent, cangrelor may surpass oral agents' drawbacks. Transitioning to an agent is mandatory following cangrelor infusion discontinuation, although ticagrelor may be administered earlier without any pharmacodynamic interaction. Nevertheless, the clinical role of cangrelor in conjunction with administration of prasugrel or ticagrelor remains unclear. Accruing real-life experience is expected to improve our understanding of cangrelor's role in everyday clinical practice.

Champion trials

Cangrelor is a new, intravenous, direct, potent, and reversible P2Y12 inhibitor with immediate (within 2 min) onset and rapid offset (half-life of 3 to 6 min and return of platelet function to baseline within 1 h). The CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention) trial demonstrated a significant reduction of periprocedural ischemic events without a significant increase in GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) severe bleeding or in transfusions. These results have been further supported by a patient-level meta-analysis of all phase III trials of cangrelor in the setting of PCI. Because the periprocedural risk of PCI differs widely according to the indication (i.e., ACS or SA) the benefits and risks of cangrelor may vary accordingly. The investigators performed a patient level meta-analysis, aggregating results from 3 large-scale contemporary trials (CHAMPION PCI [A Clinical Trial to Demonstrate the Efficacy of Cangrelor (PCI)], PLATFORM [Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (Platform)], and PHOENIX [A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (PCI) (CHAMPION PHOENIX)]), yielding a pooled cohort of 25,384 patients. The aggregation of patient-level data often yields the highest quality meta-analysis by allowing for analyses of time to event data based on allocated treatment using standardized outcomes. This approach also increases statistical power and is perhaps the only situation where it is reasonable to evaluate whether there are differences between treatments (with some caution) in clinically relevant or common patient subgroups. A point of concern is that glycoprotein IIb/IIIa inhibitors (GPI) use in a clinical trial, as in clinical practice, can be driven by various factors, which can confound the results. The negative effects of confounding by indication, for GPI use in this case, can be lessened through stratification; that is, by separately analyzing the efficacy and safety of cangrelor versus
clopidogrel for upfront and bailout GPI use. Stratified analyses are likely to be more informative and better align with established clinical practice patterns than those in which all GPI users, irrespective of indication, are grouped together. Appropriately, the investigators provide these analyses in their report and supplement. Also, among the trials in the pooled analysis, only the CHAMPION PCI trial allowed for upfront GPI use; thus, the pooled analysis provides little added insight into upfront GPI use with cangrelor. In contrast, approximately 88% of the pooled cohort was GPI-naive and eligible for bailout GPI use; thus, it is this group that most benefits from pooling of the trials.

Both cangrelor and GPI achieve >90% steady-state inhibition of platelet aggregation, through different mechanisms. Therefore, the rationale for using 2 potent intravenous antiplatelet medications simultaneously, particularly in a planned fashion, is not clear. These data suggest that there does not seem to be any significant advantage to upfront GPI use with cangrelor. There were no significant differences in the primary efficacy or safety endpoints between cangrelor and clopidogrel, although there were few patients with upfront GPI use. Unlike with upfront GPI use, there was a significant reduction in the primary efficacy outcome with cangrelor in the GPI-naive group. The absolute risk difference for the primary efficacy endpoint was 0.8% in favor of cangrelor (4.0% vs. 4.8%; odds ratio: 0.82; 95% confidence interval: 0.72 to 0.93). It is reassuring that the event rates were numerically lower for all 4 of the components comprising the composite endpoint, and statistically significant for myocardial infarction (MI) and stent thrombosis. The absolute reduction in Q-wave MI, although statistically significant, was only 0.1%, suggesting that much of the benefit may have been caused by a reduction in post-procedural MI, characterized more so by biomarker elevation. Also, the stent thrombosis definition was protocol-specific; the number of Academic Research Consortium definite stent thrombosis events is not clearly reported. In aggregate, these data suggest cangrelor is most beneficial for reducing ischemic events in GPI-naive patients.

This report also highlights the critical importance of the bleeding definition used in evaluating drug safety. Using the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) bleeding definition, the absolute increase in major bleeds with cangrelor was 1.6%, corresponding to a 71% increase in the odds compared with clopidogrel (odds ratio: 1.71; 95% confidence interval: 1.46 to 1.99; p = 0.003) in GPI-naive patients. Using this definition, the bleeding rate exceeds the 0.8% absolute reduction in ischemic events with cangrelor. In addition, cangrelor was also associated with significant increases in GUSTO (Global Use of Strategies to Open Occluded Arteries) severe or moderate bleeding, TIMI (Thrombolysis in Myocardial Infarction) major or minor bleeding, and ACUITY major or minor bleeding. Blood transfusions were also greater with cangrelor in GPI-naive subjects. These observations are consistent with the more potent antiplatelet effect of cangrelor compared with clopidogrel. Thus, although cangrelor did not increase the rate of GUSTO severe or life-threatening bleeding, the primary safety endpoint, the totality of these data suggests there is some increase in bleeding in GPI-naive patients, who represent most of the patients in this analysis and are the patients most likely to be treated with cangrelor. It should be noted that these trials excluded patients at heightened risk for bleeding.
The pooled analysis also shows that GPIs significantly increase bleeding with both cangrelor and clopidogrel. The bleeding rates across multiple definitions and the need for blood transfusion were significantly greater with upfront GPI use compared with bailout use. This may be explained, in part, by the prolonged infusion period with GPI. The low rates of GPI use during PCI in these studies are consistent with a more general global trend. Factors that may be driving this include a greater appreciation for the significance of bleeding, combined with the advent of newer, more potent antiplatelet medications, and uncertainty regarding the prognostic significance of periprocedural MI. The present report shows significant regional variations in practice patterns, with about two-thirds of GPI use in the pooled cohort occurring in the United States—a disparity that may be caused, in part, by tepid recommendations for upfront GPI use in international guidelines.

**Conclusion**

Overall, cangrelor is a potent, short-acting P2Y 12 ADP receptor antagonist that may be useful when surgical coronary revascularization procedures are needed. During a pharmacodynamic comparison, cangrelor demonstrated superior platelet inhibition to clopidogrel even when an effective loading dose of clopidogrel was used. However, when both drugs were administered simultaneously, clopidogrel was unable to mitigate platelet aggregation and activation. Thus, defining the potential pharmacologic interaction between clopidogrel and cangrelor is paramount for optimizing antiplatelet function when transitioning from acute to chronic settings. The results of several studies suggest that the high affinity of cangrelor for the P2Y 12 receptor prohibits the active metabolite of clopidogrel from forming the necessary bond with its cognate receptor during the 2-hour cangrelor infusion used in this study. In addition, it should be noted that the active metabolite of cangrelor is unstable; hence, it might not be expected to be available for binding to the P2Y 12 receptor >2 hours after the administration of a 600-mg loading dose. These findings may have important clinical implications as cangrelor advances into phase III testing. Parenterally administered cangrelor seems to be most useful in the acute setting.

**References**

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