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The optimal antiplatelet treatment in an emergency setting

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ABSTRACT

The P2Y₁₂ receptor is the molecular target for thienopyridines, namely clopidogrel and prasugrel, of which the active metabolites formed in the liver covalently bind to the P2Y₁₂ receptor and also for direct, reversible antagonists such as ticagrelor, cangrelor, and elinogrel. There are several limitations of P2Y₁₂ orally administered inhibitors especially if used in patients with acute coronary syndrome treated with PCI. Cangrelor has the advantage over all orally administered agents of being a very potent, quickly reversible and direct-acting P2Y₁₂ antagonist, reaching consistent optimal platelet inhibition minutes after the start of the infusion. The results of three major currently available clinical trials (CHAMPION PLATFORM, CHAMPION PCI, and CHAMPION PHOENIX) show cangrelor to be relatively safe and more effective than clopidogrel in patients with acute coronary syndromes and undergoing coronary interventions. The BRIDGE study demonstrated the feasibility of the use of cangrelor as a bridging therapy in patients awaiting cardiac surgery who require prolonged platelet P2Y₁₂ inhibition.

Cangrelor is not available yet; however, the pharmacodynamic properties of cangrelor (prompt and potent onset of action and fast offset) make it a desirable drug in an emergency setting, particularly in patients undergoing coronary interventions and in patients awaiting cardiac surgery who require prolonged platelet inhibition.

Key words: antiplatelet treatment, platelet inhibition, emergency

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The initiation of thrombus formation caused by vessel wall injury is mediated by von Willebrand factor bound to subendothelial matrix. The formation of a stable thrombus requires integrin activation, a process in which P2Y₁₂ plays an important role [1]. Downstream signalling events of the P2Y₁₂ receptor are essential for platelet full aggregation and thromboxane generation induced by other agonists [2, 3].

Because of the critical role of P2Y₁₂ in platelet activation, compounds which target this platelet receptor have been developed and widely used in the prevention and treatment of thrombotic events [3–5]. Blockade of the P2Y₁₂ receptor prevents initial activation and amplification of responses to platelet stimuli while leaving the final common pathway of platelet aggregation intact. Moreover, blockade of this receptor inhibits other platelet-derived proaggregatory, procoagulant, and proinflammatory factors that may have an additional impact on the clinical outcome [6]. This receptor is the molecular target for thienopyridines: i.e. clopidogrel and prasugrel, of which the active metabolites formed in the liver covalently bind to the P2Y₁₂ receptor [7, 8], as well

as the molecular target for direct, reversible antagonists such as ticagrelor, cangrelor, and elinogrel [9–11].

There are several limitations of P2Y₁₂ orally administered inhibitors especially if used in patients with acute coronary syndromes (ACS) treated with PCI. Inter-individual variability of the pharmacokinetic and pharmacodynamic response, widely described for clopidogrel, is one of the most important limitations [12–14]. Several studies have demonstrated that a substantial subset of patients treated with dual antiplatelet therapy with aspirin and clopidogrel do not reach adequate levels of platelet inhibition at the time of PCI [15, 16]. Moreover, these patients are at a higher risk for the occurrence of atherothrombotic events [17–21]. The PLATO study and the TRITON study provided evidence that the more potent effect of ticagrelor as well as prasugrel on P2Y₁₂ inhibition results in a significant reduction of athero-thrombotic events compared to clopidogrel in patients with acute coronary syndromes [4, 5]. However, even treatment with oral antiplatelet agents that are more potent than clopidogrel, such as prasugrel and ticagrelor, may not result in maximal platelet

inhibition in high-risk patients undergoing PCI [22, 23]. Oral P2Y₁₂ inhibitors cannot provide reliable inhibition in patients who are unable to swallow or rapidly absorb medication taken orally, such as those who are sedated, intubated, in shock, or with nausea or vomiting. In patients with ST-segment elevation MI (STEMI), nausea has been reported in almost two thirds of all patients and vomiting in nearly one third [24, 25]. These limitations, of particular importance in the acute care setting, prompted the investigation for a novel effective P2Y₁₂ inhibitor [26].

Cangrelor has the advantage over all orally administered agents of being a very potent, quickly reversible and direct-acting P2Y₁₂ antagonist, reaching consistent optimal platelet inhibition minutes after the start of the infusion [14, 27].

Unlike thienopyridines, it does not require hepatic activation. The very rapid onset of action of cangrelor is the result of intravenous administration and small initial volume of distribution restricted to the blood compartment [28]. The drug is rapidly metabolised through dephosphorylation by an endonucleotidase located on the surface of vascular endothelial cells with an elimination half-life of 2.9 to 5.5 minutes. The rapid on-off feature of cangrelor enables temporary suppression of platelet activation on top of oral antiplatelet treatment during PCI [29, 30].

Steinhubl et al. [31] described the interaction between clopidogrel and cangrelor in healthy volunteers. A bolus and infusion of cangrelor provided immediate and almost complete inhibition of platelet aggregation, and activation rapidly reversed upon termination of the infusion. A loading dose of clopidogrel, given alone or started immediately after a cangrelor infusion, led to the anticipated degree of platelet inhibition after about 2 h. However, when both drugs were administered simultaneously, clopidogrel was unable to inhibit platelet aggregation. These observations suggest that cangrelor's high affinity for the P2Y₁₂ receptor prohibits clopidogrel's active metabolite from forming the necessary disulfide bridge with cysteine residues in the extracellular domain of this receptor [7, 31].

Ravnefjord et al. [32] reported a lack of interaction between cangrelor and ticagrelor. The mechanism of action of reversible inhibitors is similar and inhibition of platelet aggregation (IPA) reflects plasma concentrations of these agents. Thus, when a cangrelor infusion is stopped and rapidly cleared from the plasma, ticagrelor binds to the receptors as they become available maintaining P2Y₁₂ antagonism [31].

These findings have potentially important clinical implications, because patients treated with cangrelor, in particular those undergoing a PCI, would be expected to continue long-term oral platelet P2Y₁₂ inhibition [33, 34]. Initiation of oral therapy with a thienopyridine before

termination of a cangrelor infusion may result in an important gap in platelet inhibition. This might be particularly critical following stent placement. Thus, to achieve sustained platelet inhibition in patients treated with cangrelor, the administration of irreversible, oral P2Y₁₂ antagonists should be started after the cangrelor infusion has been terminated [31, 35–37]. On the other hand, lack of interaction between cangrelor and ticagrelor may suggest choosing the latter for maintenance treatment if cangrelor was used in the acute setting. This however should be clinically tested.

The results of three major clinical trials regarding the use of cangrelor in patients with acute coronary syndromes and undergoing coronary interventions are currently available: CHAMPION PLATFORM [38], CHAMPION PCI [39], and CHAMPION PHOENIX [40].

Both the CHAMPION PLATFORM [38] and CHAMPION PCI [39] trials were prematurely stopped, following a decision by the interim analysis review committee that the studies would not show the persuasive clinical efficacy of cangrelor. Despite favourable pharmacodynamic properties, cangrelor was not superior to clopidogrel in reducing the incidence of ischaemic events in either of these CHAMPION trials [38, 39].

Taken together, both CHAMPION trials may provide an insight into the optimal timing of periprocedural antiplatelet blockade with clopidogrel [38, 39, 41]. The examination of secondary composite endpoints suggests a more robust effect in the CHAMPION PLATFORM trial (600 mg of clopidogrel at the end of the procedure) than in the CHAMPION PCI trial (600 mg of clopidogrel at the beginning of the procedure), though this is only a speculative observation.

As both CHAMPION studies used similar inclusion/exclusion criteria, and death, myocardial infarction, or ischaemia-driven revascularisation (including stent thrombosis) at 48 hours were their primary endpoints, the studies were pooled [41]. A total of 13,049 patients were included. No effect of cangrelor with regard to the primary endpoint was revealed with the original MI definition. However, after application of the new universal definition of MI, a significant reduction of the primary endpoint with cangrelor compared to a 600-mg loading dose of clopidogrel was observed (3.1% cangrelor vs 3.8% clopidogrel; OR 0.82 [95% CI 0.68–0.99], $P = 0.037$). Regarding safety measures, there was an increase in clinically significant bleedings using the ACUIITY scale with cangrelor, mainly because of the increased occurrence of groin haematomas [38, 39, 41].

The knowledge gained in CHAMPION PLATFORM [38] and in CHAMPION PCI [39] resulted in new questions to be answered, leading to the CHAMPION PHOENIX trial [40]. In this, a total of 10,942 patients requiring PCI for stable angina or acute coronary

syndrome were enrolled and received an infusion of cangrelor or placebo. Patients treated with cangrelor obtained a loading dose of clopidogrel at the end of infusion, while patients receiving placebo obtained a loading dose of clopidogrel at the time of the PCI procedure. Treatment during the procedure was followed by a standard maintenance dose of an oral P2Y₁₂ inhibitor and aspirin. The rate of the primary composite efficacy endpoint of death from any cause, myocardial infarction (according to the universal definition of MI), ischaemia-driven revascularisation, or stent thrombosis at 48 hours, was significantly lower in the cangrelor group than in the clopidogrel group. The observed reduction of ischaemic event odds of 22% in patients treated with cangrelor was not accompanied by a significant increase in severe bleeding or in the need for transfusions compared to patients on clopidogrel [40].

Cangrelor has been shown to be relatively safe and more effective than clopidogrel in patients treated with PCI for stable coronary artery disease and acute coronary syndromes.

Currently available oral P2Y₁₂ inhibitors may increase the risk for bleeding in patients requiring urgent surgical revascularisation. On the other hand, cessation of the antiplatelet therapy for nearly a week before surgery, necessary in patients on oral P2Y₁₂ inhibitors, carries a greater risk of serious ischaemic events [4, 5, 29, 42].

The BRIDGE study demonstrated the feasibility of the use of cangrelor for bridging therapy in patients waiting for cardiac surgery who require prolonged platelet P2Y₁₂ inhibition [43]. Another approach proposed for a bridging strategy with the use of small molecule glycoprotein IIb/IIIa inhibitors, in particular tirofiban and eptifibatide, presents some of the advantages of cangrelor including the rapid onset of action as well as consistent and strong platelet inhibition. However, tirofiban and eptifibatide have a slower offset of action, requiring 4–6 hours to return to baseline platelet function, while only one hour is required in patients treated with cangrelor. Moreover, both these Gp IIb/IIIa inhibitors used at doses recommended for ACS treatment are associated with increased bleeding risk [43, 44].

Extracorporeal circulation and hypothermia are routinely used in an emergency setting. Both these procedures cause platelet activation and dysfunction, possibly followed by bleeding and thromboembolic complications [45]. Despite the promising results of initial research, knowledge regarding the efficacy of cangrelor in these specific subsets of patients is limited [46]. However, due to very potent platelet inhibition, this agent may be very useful in clinical situations leading to an increase in platelet reactivity.

Conclusion

Cangrelor is not available yet in routine clinical practice, however the pharmacodynamic properties of cangrelor (prompt and potent onset of action and fast offset) make it a desirable drug in an emergency setting, particularly in patients undergoing coronary interventions and in patients awaiting cardiac surgery who require prolonged platelet inhibition.

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