A NOVEL UPDATE ON ANTI-PLATELET AGENTS

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ABSTRACT

Anti-platelet drugs play a serious role in the therapy of patients having thrombotic events. These drugs are the linchpin in the therapy of cardiovascular disease. They remain active in preventing aberrant platelet activation in patho-physiological conditions like myocardial infarction, ischemia and stroke. At present, there are different agents that are approved and available for medical use and mentioned as per guidelines for the treatment and prevention of ischemic actions in the setting of acute coronary syndrome and percutaneous coronary intervention: (1) cycloxygenase-1 inhibitor: aspirin. (2) Adenosine diphosphate or P2Y12 receptor antagonists: clopidogrel, ticlopidine, prasugrel, and ticagrelor and (3) glycoprotein IIb/IIIa inhibitors: abciximab, eptifibatide and tirofiban. GPIs at present are available only in parenteral dosage form and therefore their usage only for the acute phase treatment of ACS patients. Those were being used as clinically distinct protective effects. So these were decrease the possibility of ischemic incidents without drastically increasing the rate of bleeding. Clinical trials are undergo other new anti-platelet agents also been introduced. Without doubt, the new anti-platelet agents are rising in number. Consequently, the effects of those anti-platelet agents in actual patients assure study. Expectantly, new selective anti-platelets with high anti thrombotic efficacy and low bleeding side effects are able to determine.

KEYWORDS: anti-platelet agent, antagonist, thrombotic disease, new therapy.

INTRODUCTION

Platelets were essential for repair the endothelium and mainly haemostasis. But they also have a role in the development of thrombus and acute coronary syndromes. ACS refers to a
range of acute myocardial ischemic states which include unstable angina, (NSTEMI) and (STEMI).[1] It remains a important global problem with very high mortality and morbidity. The majority of the drugs were invented for intense on targeting either surface receptor of enzymes in the platelet for protecting the unwanted clot formation.[2] Generally used anti-platelets namely aspirin, clopidogrel, and ticlopidine are effective drugs to prevent thrombotic diseases. Unfortunately many of the current antiplatelet agents face limitations in their utility due to the difference of genetic in the ability to metabolize pro-drugs, such as the case with clopidogrel, acquired allergic responses such as is seen with heparin and aspirin, and resistance as has been reported with aspirin. Currently accepted antiplatelet drugs consist of a narrow therapeutic window and limited efficacy. Additional limitations founded in the application with the developments medical field, the anti-platelet agents were increasing day by day.[3]

**Thromboxane A2 pathway or Cox1 inhibitors**

Aspirin act irreversibly inactivated cyclo-oxygenase activity and it reduce the conversion of arachidonic acid to prostaglandin H2 (PG H2) and synthesis of Thromboxane A2, which is a potent induces of platelet aggregation and vasoconstriction.[4,5] Aspirin has been demonstrated as very effective across the entire range of ACS. A meta-analysis observed in group of patients having NSTEMI in ACS the antithrombotic trialists collaboration, nearly 46% reduction in vascular incidents were observed with aspirin.[6] The different studies were observed an association between aspirin poor responsiveness and a higher risk of recurrent ischemic incidents.[7]

**ADP/P2Y₁₂ receptor inhibitor**

Adding to ticlopidine and clopidogrel, P2Y₁₂ receptor antagonists now include two approved oral agents, prasugrel and ticagrelor.[7] The P2Y₁₂ receptors are G protein couple (GPCR) purinergic receptors belonging to the P2 family.[8] Adenosine diphosphate exerts its effects on platelets via the P2Y₁ and P2Y₁₂ receptors. Although both the receptors are required for aggregation, activation of the P2Y₁₂ pathway plays the principal role, leading to sustained platelet aggregation and stabilization of the platelet aggregate. 17 P2Y₁₂ receptor antagonists are prescribed for prevention of ischemic incidents in both the acute and long-term phases of treatment.[9]
**Clopidogrel**

It’s a generation of thienopyridines, a family of nondirect, orally administered form of thienopyridines in three generations are available and it includes clopidogrel, prasugrel and ticlopidine. It inhibits the ADP receptor on platelet cell membranes. It is a pro-drug, which requires CYP2C19 enzyme for its activation. The drug particularly and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is very important in the activation of platelets and at last cross-linking by the protein fibrin. Platelet reduction can be established in approximately two hours after a loading dose of oral clopidogrel, but the onset of action is slow. These anti-platelet agents that permanently block the platelet ADP P2Y12 receptor, are approved currently for clinical use. After approval of clopidogrel in 1997, it replaced by ticlopidine because its more favorable safety profile.\(^{[10]}\) It’s an oral prodrug requiring metabolism by the hepatic cytochrome P450 enzyme system to generate active metabolite. The usage of clopidogrel in addition to aspirin (dual antiplatelet therapy) became standard form of therapy in managing NSTE in ACS and STEMI. Specifically there undergoing PCI.\(^{[11]}\)

A combination of antiplatelet therapy with aspirin and clopidogrel is recommended as per the guidelines for patients with ACS, including those with unstable angina (UA) or non-ST elevation acute coronary syndromes (NSTEMI), ST-elevation myocardial infarction (STEMI), and for patients undergoing.\(^{[12-14]}\) However, DAPT with aspirin and clopidogrel should not be recommended for first prevention.

**Prasugrel**

As compared with clopidogrel, prasugrel has a lot of pharmacological advantages since it could be efficiently converted to the active metabolic form and displays a rapid onset of action. It has greater degree of reduction in platelet aggregation.\(^{[15,16]}\) Comparatively lower doses of prasugrel has higher response in platelet inhibition than higher dose of clopidogrel.\(^{[17]}\)

The TRITON-TIMI 38 Trial to Assess Improvement intherapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction 38 trial evaluated the clinical and efficacy of prasugrel (loading dose 60 mg followed by a maintenance dose 10 mg), compared with standard clopidogrel (loading dose 300 mg followed by daily maintenance dose 75 mg) therapy in patients with moderate to high risk ACS undergoing PCI.\(^{[18]}\) Patients werepre-treated with clopidogrel were not eligible for this study and patients
were randomized only after coronary anatomy was established, with the exception of patients presenting with STEMI in PCI, whom allocation to randomized treatment was allowed before coronary anatomy was known.\[19\] NCE guidelines recommended use of prasugrel (in place of clopidogrel) in patients undergoing PCI for STEMI, as well as NSTE in ACS patients with stent thrombosis during clopidogrel treatment or with diabetes mellitus\[^{20,21}\].

**Ticagrelor**

The PLATO trial compared clopidogrel with ticagrelor, both in combination with aspirin, in ACS patients.\[^{22}\] Ticagrelor drastically reduced the occurrence of the 12-month composite end point (consisting of death from cardiovascular causes, stroke and MI) compared to clopidogrel is highly significant. The dose of aspirin used in the study was 75–100 mg. The overall occurrence of haemorrhage risks for ticagrelor and clopidogrel was similar, as was the rate of serious bleeding (0.3% vs 0.3%, p=0.66). Ticagrelor, however, had a higher propensity to cause intracranial haemorrhage (0.3% vs 0.2%, p=0.06). The rate of bleeding related to urgent coronary artery bypass grafting was 7.4% with ticagrelor and 7.9% with clopidogrel.\[^{23}\] The benefit of ticagrelor appears to be more in patients with lowering body weight and not taking cholesterol lowering drugs.\[^{24,25}\] Overall, ticagrelor has more effect in preventing ischaemic incidents, with same rate of hemorrhagic risk. However, as compared with ticagrelor, clopidogrel is found to be more effective in those patients with:

- Chronic dyspnoea
- Increased risk of intracranial haemorrhage
- Bradycardia or a history of ventricular pauses
- A risk of non-compliance due to the twice-daily dosing requirement of ticagrelor.

**Table no 1 Pharmacological classifications of P2Y\(_{12}\) drugs available**

<table>
<thead>
<tr>
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<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
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</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>CPTP</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral</td>
<td>Oral (bid)</td>
<td></td>
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<tr>
<td><strong>Receptor Blockade</strong></td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Loading dose</strong></td>
<td>300 mg or 600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>2–8 h</td>
<td>30 min–4 h</td>
<td>30 min–2 h</td>
</tr>
<tr>
<td><strong>Offset of action</strong></td>
<td>7–10 days</td>
<td>7–10 days</td>
<td>3–5 days</td>
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**Glycoprotein IIb/IIIa receptor inhibitors**

It’s a most potent inhibitor of platelet activity as they selectively and comprehensively block the receptor necessary for the final common pathway of platelet aggregation. Because GPIIb/IIIa receptor inhibitor does not block TXA2. The production of TXA2 from the
activated platelets, The concomitant use of aspirin may still enhance their anti-thrombotic activity. Three currently available drugs in this class includes: Abciximab, Eptifibatide, and tyrofiban. These are very potent antiplatelet agents and are used intravenously during acute management of high risk patients who are with NSTE in ACS or STEMI planned for an early invasive strategy. ACC/AHA and ESC guidelines, recommends the use of GPIIb/IIIa inhibitors prior to the 1st 25hrs of presentation who have increased troponins, ST segment depression or diabetes mainly as an adjunct to PCI procedures.[26-28]

**Antiplatelet Agents under Clinical Development**

Cangrelor, the parent compound of ticagrelor, is the first reversible, direct-acting, intravenous P2Y12 inhibitor.[26] Cangrelor have a dose adjusted pharmacodynamic effect, with potent inhibition of purinergic-mediated platelet activation, rapid onset and offset of action, shorter half-life of 3–6 min, and started again platelet function within ~30–60 min.[28-30] Such pharmacodynamic features make the use of cangrelor especially interesting in clinical scenarios where acute antiplatelet inhibition is desired and there is no time for pretreatment (i.e. ST-elevation MI, ad hoc PCI), the patient is unable to assume pills (i.e. cardiogenic shock, vomiting, orotracheal intubation), or surgical procedures is demanded while avoiding the harmful effects of with-drawing antiplatelet therapy.[31]

Cangrelor still has a role, due to its pharmacological features, as a bridging strategy in the settings of patients needed surgery but who require treatment with a P2Y12 antagonist to prevent thrombotic risk, such as in ACS patients or those treated with drug-eluting stents.[32,33] The BRIDGE (after discontinued thienopyridines in patients undergoing surgery were maintenance the platelet reduction with cangrelor) trial a prospective, randomized double-blind, placebo controlled, multicenter trial in patients with an ACS or treated with the coronary stent on a thienopyridine pending CABG.[34] To receive either placebo or cangrelor at a dose of (0.75µg/kg/min) known in dose-finding phase of the trial.[35] Therefore, cangrelor may represent a future option for therapy in patients with ACS or treated with coronary stents who require surgery.[36,37]

**CONCLUSION**

Ticagrelor and prasugrel have some advantages than clopidogrel. Platelet inhibition is more rapid with prasugrel, and for both drugs the rates of ischaemic incients and stent thrombosis are statistically lower. However, the risk of haemorrhage is higher than with clopidogrel. Pre-operative management of patients on dual-antiplatelet therapy is a controversial area. The
risks of myocardial ischaemia and haemorrhage need to be balanced with caution for each individual patient

REFERENCES


