

Newer Antiplatelet and Antithrombotic Drugs on the Horizon

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ABSTRACT

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Aspirin is a highly successful antiplatelet drug & still retains its status as the 'front-line' antiplatelet drug; however, increased understanding of platelet biology has led to the development of new antiplatelet drugs that are potentially more effective. Now, more researches in platelet biology has led to this fact that there are more than 90 other metabolic pathways leading to platelet aggregation that are independent of arachidonic acid and therefore not inhibited by aspirin, hence, several more drugs are being developed, aimed at controlling different phases of platelet function such as platelet aggregation & adhesion. The newer drugs now offer potentially greater and more specific control over platelet function. Definitely, these drugs are going to be significantly more expensive than aspirin, and their eventual role in the clinical arena will ultimately depend on both their efficacy and their cost-effectiveness. As we approach the next millennium, it is envisaged that our increased understanding of platelet function, coupled with advances in technology and drug manufacture, will result in even greater improvements in the therapeutic control of platelet thrombus.

KEY WORDS: Prasugrel; Ticagrelor; Antiplatelet Drug Therapy; Pathophysiology of Platelet Aggregation

INTRODUCTION

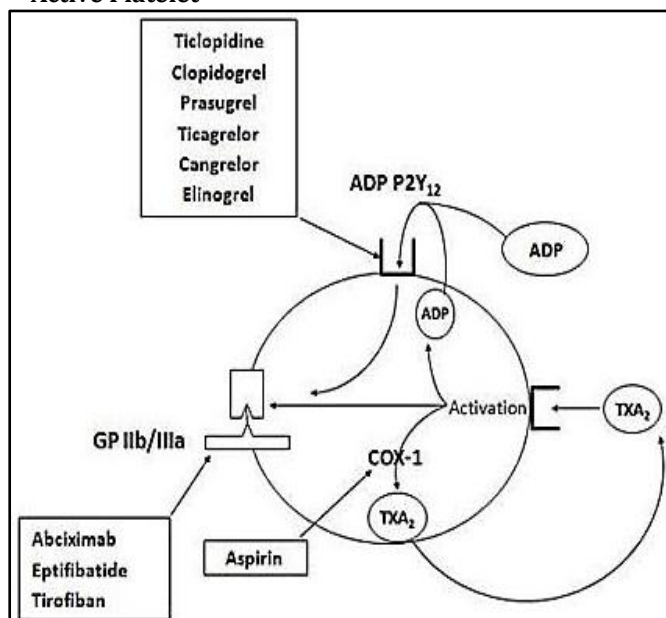
Platelets have been implicated in the formation of rapidly progressing atherosclerotic lesions, and play a key role in acute arterial thrombosis. For many years, aspirin has been shown to reduce the risk of serious ischemic events in several cardiovascular disease states including stroke, myocardial infarction, unstable angina and following coronary artery bypass surgery. Although aspirin has been the mainstay of antiplatelet therapy for several decades, it is acknowledged as a relatively weak inhibitor of platelet activity. Aspirin inhibits cyclo-oxygenase,

irreversibly blocking the conversion of arachidonic acid to thromboxane A₂ (TXA₂) - a potent stimulus of platelet aggregation. However, there are more than 90 other metabolic pathways leading to platelet aggregation that are independent of arachidonic acid and therefore not inhibited by aspirin, hence, therefore the need for inhibition of other platelet activation pathways has led to the development of various other antiplatelet drugs. An improved understanding of the underlying mechanisms involved in thrombogenesis has paved the way for further development of newer antiplatelet drug therapies. Various clinical studies have

probed the effectiveness and risk profile of the newer antiplatelet drugs in comparison with currently available drugs. These drugs are more efficacious than aspirin in reducing ischaemic complications following coronary angioplasty. The development of novel therapies against platelet-dependent thrombosis and the concurrent improvement of existing therapeutic strategies thus is a paramount focus of pharmaceutical research. Currently, efficiency, dosing and indications of established antiplatelet substances are being re-evaluated, whilst new, so far unrecognized molecular targets for inhibition of platelet activity come up front.

MECHANISM OF ACTION

Figure-1: Site of Action of Different Drugs on an Active Platelet



WHY DO WE NEED NEWER ANTIPLATELET AGENTS?

Existing anti-platelet therapy is highly effective in preventing atherothrombotic complications but due to some reasons, significant number of patients continues to experience recurrent complications despite being properly treated. This has led to big research efforts in fields of pharmacokinetics, interactions of current antiplatelet drugs & their genetic background to provide new antiplatelet drugs with better preventive properties but without increased bleeding risk.

Issues with Aspirin (Aspirin Resistance)

While aspirin still retains its status as the 'front-line' antiplatelet drug, aspirin resistance identified in 1978, initially in patients undergoing cardiac catheterization and later in stroke patients. Though no formal definition of aspirin resistance exists, it may involve clinical failure of therapeutic dose of aspirin (75-150 mg for at least 5 days) to protect individuals from arterial thrombotic events or laboratory methods indicating the failure of aspirin to inhibit platelet activity.^[1] Previous studies have estimated that 8-45% of the population is aspirin resistant.^[2]

Various mechanisms for this resistance are as follows:

- i. Reduced accessibility of aspirin to receptor site due to concomitant intake of other NSAIDs^[3]
- ii. Genetic polymorphism of enzymes like COX-1, COX-2 or thromboxane A2 synthase,
- iii. Increased reactivity of platelets towards other aggregating factors^[4]
- iv. Alternate pathways of thromboxane synthesis, poor patient compliance^[5]

Bleeding time, flow cytometry, light transmittance aggregometry are some of the measures to assess aspirin resistance, Light transmittance aggregometry being the most useful method.

Clopidogrel Resistance

There is a wide variation in individual responsiveness to clopidogrel. There are non-responders and semi-responders. Variation in response may be due to variety of reasons like, decreased sensitivity of some patients to the clopidogrel effects. Situational factors, such as increased platelet activity in smokers, diabetics or hypercholesterolemia patients aggravate the situation.^[6]

NEWER ANTIPLATELET AGENTS

Prasugrel: Prasugrel (CS-747, LY640315) is a novel member of the thienopyridine class of oral

antiplatelet agents. Like other thienopyridines, prasugrel is a prodrug that is inactive *in vitro*. Prasugrel's distinct chemical structure permits efficient conversion to its active metabolite with a less rigorous dependence on specific cytochrome P-450 enzymes. Preclinical studies indicated that prasugrel is approximately 10- and 100-fold more potent at inhibiting *ex vivo* platelet aggregation and *in vivo* thrombus formation than clopidogrel and ticlopidine, respectively. While the active metabolites of prasugrel and clopidogrel resulted in similar levels of platelet inhibition *in vitro*, the amount of each active metabolite generated *in vivo* was quite different—prasugrel (60 mg) resulting in an approximately 12-fold greater exposure to its active metabolite compared with clopidogrel (300 mg). This observation provides a mechanistic basis for the faster, greater, and more consistent inhibition of platelet aggregation observed with prasugrel.^[7] Dose of prasugrel is single 60 mg oral loading dose and then continue at 10 mg orally once daily.^[8]

Prasugrel is a P2Y₁₂ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

The adverse effects in decreasing order of prevalence being as follows:

| | |
|--------------|------|
| Hypertension | 7.5% |
| Headache | 5.5% |
| Dyspnea | 4.9% |
| Nausea | 4.6% |
| Hypotension | 3.9% |
| Bradycardia | 2.9% |
| Rash | 2.8% |
| Pyrexia | 2.7% |

Other important adverse events reported included severe thrombocytopenia, abnormal hepatic function, allergic reactions, and angioedema, all of which occurred rarely in <0.5% of prasugrel treated patients. Anaemia occurred in 2.5% of prasugrel treated patients.^[9]

FDA has also issued a warning which will be on the drug labeling as follows, "a boxed warning alerting physicians that the drug can cause significant, sometimes fatal, bleeding. The drug should not be used in patients with active pathological bleeding, a history of mini strokes (transient ischemic attacks) or stroke, or urgent need for surgery, including coronary artery bypass graft surgery."

Ticagrelor (AZD 6140): New non-thienopyridinic antiplatelet drug with some pharmacokinetic advantages over prasugrel and clopidogrel (mainly because is not a pro-drug and does not need hepatic transformation into an active metabolite and its reversible platelet inhibition). Like the thienopyridines prasugrel, clopidogrel and ticlopidine, ticagrelor blocks ADP receptors of subtype P2Y₁₂. In contrast to the other antiplatelet drugs, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the blockage is reversible. The main clinical trial with this drug has been the PLATO study, in which 18,624 patients with NSTEMI (moderate-to-high-risk) or STEMI undergoing PCI were randomized to receive clopidogrel (300 mg loading dose then 75 mg maintenance) or ticagrelor (180 mg loading dose then 90 mg twice daily maintenance). The primary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. After 12 months, patients receiving ticagrelor had a 16% reduction of the primary endpoint, with no increased risk of major bleeding. Nevertheless, some concerns have been raised related to other side effects due to adenosine receptor blocking effects (RESPOND study) almost 15% of patients referred had dyspnoea or bradyarrhythmias compared with 8% with prasugrel.^[10]

Ticagrelor is an investigational drug that is currently under review by the FDA and was recently (December 2010) approved for use in Europe. In July 2010, the FDA Cardiovascular and Renal Drugs Advisory Committee voted 7 to 1 in favor of approving ticagrelor for the treatment of ACS, but in December 2010, the FDA did not approve ticagrelor for use in the US and appears to be delaying a final approval decision pending further analyses of PLATO study data. Although no specific reasons have been made publicly available by the FDA explaining the delay in deciding whether or not to approve ticagrelor in the US, it is widely speculated that one reason for this delay is the unexplained lack of efficacy of ticagrelor in the US population of the PLATO trial, as previously. Some speculate that the FDA might require a US-based trial in a US population that is sufficiently powered to determine if there truly is a geographic difference in response to the drug.^[11]

Cangrelor (AR-C69931MX): Cangrelor is an intravenous, direct-acting and reversible P2Y₁₂ receptor antagonist. Cangrelor has a rapid onset and offset of action and achieves significantly greater degrees of platelet inhibition compared with clopidogrel. Cangrelor has been studied as an intravenous infusion in doses of 2 or 4 µg/kg/min. It inhibits platelet aggregation with rapid onset and offset and does not require metabolism for therapeutic activity. Published Phase II trials have demonstrated safety and inhibition of platelet aggregation. Cangrelor is a promising investigational medication for inhibition of platelet aggregation in acute arterial coronary events. Phase II trials have shown safety and a greater inhibition of platelet aggregation over clopidogrel. Phase III trials will provide more definitive information on clinical efficacy and safety. Until then, the role of cangrelor is uncertain.^[12]

Vorapaxor (SCH 530348): It causes inhibition of thrombin receptor-activating, peptide-induced platelet aggregation. It is given orally in OD doses. Maximum effect occurs as early as 1 hour. In the phase II TRA-PCI trial, 1,031 patients undergoing

PCI were given Oral loading doses of SCH 530348 (10, 20, or 40 mg) VS placebo. No increase in TIMI major and minor bleeding when SCH 530348 was added to standard dual antiplatelet therapy. Non-statistically significant 46% reduction in cardiovascular events at the highest SCH530348 dose tested compared with standard antiplatelet therapy. Vorapaxar is currently being evaluated in two large-scale multinational phase III trials (TRA*CER and TRA 2°P-TIMI 50) for the treatment and prevention of cardiac events in almost 30 000 patients with acute coronary syndromes and those with prior myocardial infarction or stroke, as well as patients with acute coronary syndrome and those with peripheral arterial disease.^[13]

Elinogrel (PRT060128): Elinogrel is a novel, small molecule antiplatelet compound in the P2Y₁₂ADP receptor antagonist class. It inhibits the ADP receptor (P2Y₁₂) on platelets to block platelet aggregation and prevent thrombosis. Both oral and intravenous formulations are under trial. Maximum platelet inhibition occurs at 20 minutes. Offset of action is within 1 day. INNOVATE PCI, a phase II trial study which showed that patients who received either 100 mg or 150 mg of elinogrel had better antithrombotic effect than patients who were treated with clopidogrel. Now under phase 3 trials.^[14]

Picotamide: It is a combined inhibitor of thromboxane A₂ synthase and receptor and, at variance with aspirin, does not interfere with endothelial prostacyclin (PGI₂) production. Randomized placebo controlled trial (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics [DAVID] study), 1209 patients who were 40–75 years of age with type 2 diabetes for ≥5 years and PAD patients were stratified by centre and allocated to twice daily picotamide, 600 mg (n=603), or aspirin, 320 mg in the morning and a placebo tablet in the evening (n=606), showed that mortality was significantly lower amongst patients who received picotamide (3.0%) than in those who received aspirin (5.5%).^[15]

DZ-697B: Inhibits collagen and ristocetin-mediated platelet functions. DZ697b in dose of 360mg significantly improved thrombus size, compared with clopidogrel, in healthy volunteers (-26.4 vs. -18.7; $p < 0.05$). The oral agent DZ-697b shows potent, dose-dependent, antiplatelet properties. Bleeding time prolongations with even the highest tested dose of DZ-697b is significantly shorter than 300mg clopidogrel.^[16]

ATOPAXAR (E 5555): Atopaxar (E5555) is a reversible protease-activated receptor-1 thrombin receptor antagonist that interferes with platelet signaling and inhibits the release or expression of the inflammatory markers that have been linked to a high risk of events in patients with acute coronary syndrome, including the release of sCD40L, interleukin 6 and the expression of P selectin. In patients after ACS, atopaxar significantly reduced early ischemia on Holter monitoring without a significant increase in major or minor bleeding. Larger trials are required to fully establish the efficacy and safety of atopaxar.

TRIPLE ANTIPLATELET THERAPY

Triple antiplatelet therapy based on IV GPIIb/IIIa inhibitors is more effective than aspirin-based dual therapy in reducing vascular events, MI and death in patients with acute coronary syndromes (STEMI and NSTEMI). A significant increase in minor bleeding complications was observed among STEMI and elective PCI patients treated with a GP IIb/IIIa based triple therapy. In patients undergoing elective PCI, triple therapy had no beneficial effect and was associated with an 80% increase in transfusions and an eightfold increase in thrombocytopenia. The balance between benefit and hazard in patients treated for NSTEMI-ACS and STEMI lay in favour of giving three antiplatelet agents (typically aspirin, clopidogrel and an intravenous GPIIb/IIIa receptor antagonist) thereby supporting guidelines promoting this approach. However, there were no or only few data available for the use of triple antiplatelet therapy for preventing recurrence in patients with chronic IHD, acute or chronic stroke or peripheral artery disease.

Further research is now required to assess the role of triple antiplatelet therapy in such patients.^[17,18]

CONCLUSION

New antiplatelet agents can provide better inhibition of platelet aggregation and have been shown to improve cardiovascular outcomes. Nevertheless, patients should be carefully treated considering individual clinical condition and thrombotic risk.

Oral agent prasugrel reduces cardiovascular mortality in patients undergoing ICP after ACS, but increases the bleeding risk moderately. This drug should be considered for patients with previous confirmed stent thrombosis or showing a high degree of platelet reactivity despite receiving the clopidogrel/aspirin combination.

Promising results with ticagrelor, a non-prodrug with reversible blockade of the ADP-P2Y₁₂ receptor opens the possibility for this drug to be used in coronary patients with high thrombotic risk.

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