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Scientific Update™

Cardiac Surgical Management of Patients on Antiplatelet Agents

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A Review of a Presentation at the 16th World Congress of the World Society of Cardio-Thoracic Surgery (WSCTS)

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Patients with cardiovascular disease are frequently prescribed antiplatelet medications due to an accelerated risk of thrombosis that has been linked with platelet hyperactivity. The clinician must attempt to balance the benefits and risks associated with antiplatelet agents when considering the mode of coronary revascularization therapy. Patients undergoing coronary intervention, who present for urgent cardiac surgery, are almost universally on a regimen of antiplatelet agents that renders them susceptible to excessive bleeding during, and after, the surgery. This issue of *Cardiology Scientific Update* reviews the pharmacologic and strategic management of these patients, the action of antiplatelet agents, as well as the current therapeutic guidelines.

There are 2 categories of antiplatelet agents (APAs): oral agents and intravenous drugs.

Oral agents

Aspirin

Aspirin is still the most commonly used APA. Aspirin is a non-specific inhibitor of cyclo-oxygenase that occurs in the body. In the platelets, aspirin irreversibly acetylates serine-529 of cyclo-oxygenase-1 (COX-1), inhibiting the production of various prostaglandins and thromboxane from arachidonic acid. Aggregation is prevented by limiting calcium entry. However, platelets can still respond to exogenous thromboxane analogs or an aggregatory stimulus that utilizes other pathways. These other pathways are illustrated in Figure 1. It is the inhibition of thromboxane A2 synthesis that mildly reduces platelet activation for 7-10 days, which is approximately the lifespan of a platelet. The effective half-life of orally-ingested aspirin is only around 15 minutes.[1,2]

Aspirin induces potent and irreversible inhibition of platelet cyclo-oxygenase. Despite this, aspirin exerts only a mild antiplatelet effect due to the multiplicity of alternative pathways of platelet activation *in vivo*. With exposure to aspirin, there is minimal prolongation of bleeding time, modest inhibition of in vitro aggregation, and only a slight decline in normal hemostatic function at the clinical level. Sensitivity to aspirin therapy is not consistent across the population and there are subsets of patients whose genetic make-up renders them insensitive to the anti-thrombotic effects of aspirin. This is thought to occur in 5%-10% of the population.[3] When using point of care assay to measure aspirin sensitivity, Chen and colleagues studied a cohort of coronary intervention patients who were appropriately pretreated with clopidogrel. The authors found aspirin resistance to be a risk factor for myonecrosis after coronary intervention with an odds ratio of 2.9 (95% confidence interval [CI], 1.2 – 6.9).[4]

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs irreversibly affect platelet function via the COX pathway. Generally, the half-lives of these agents are shorter

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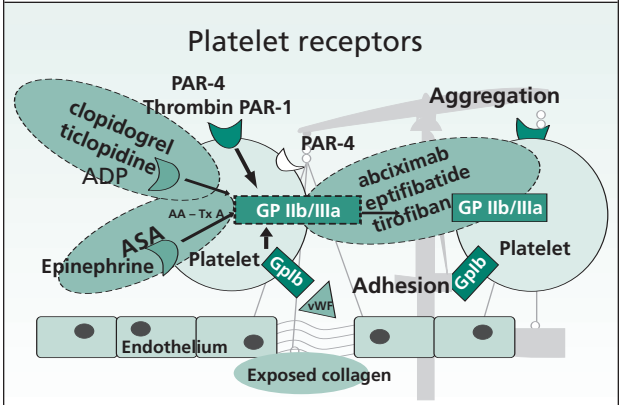
Figure 1: The mechanism of action of antiplatelet agents



GpIb = Von Willebrand receptor; ADP = adenosine diphosphate;
PAR-1 = protease-activated receptor 1
PAR-4 = protease-activated receptor 4

and the antiplatelet effect weaker than with other antiplatelet agents. These drugs are currently being investigated as an alternative or adjunctive to aspirin or thienopyridine therapy in patients with acute coronary syndromes undergoing percutaneous coronary intervention.

Thienopyridine anti-thrombotic agents

There are 3 adenosine diphosphate (ADP) receptors on the platelet surface.[5,6] Normal activation of one of the ADP receptors is critical for platelet activation through inhibition of adenylyate cyclase. In conjunction with other secondary measures generated from the activation of the other surface receptors, the subsequent reduction in cyclic adenosine monophosphate (AMP) in the platelet decreases platelet activation and allows expression of the glycoprotein (GP) IIb/IIIa receptor, which mediates platelet aggregation. The thienopyridines – ticlopidine and clopidogrel – partially block this process and, thus, platelet activation and aggregation. They irreversibly antagonize the Gi protein-linked ADP receptor and the lifespan of the effective platelet.

Despite the apparent efficacy of ticlopidine, it is rarely used due to undesirable side-effects (eg, aplastic anemia, neutropenia, and thrombocytopenia purpura). Its efficacy has been compared to equipotent doses of the newer thienopyridine derivative, clopidogrel. Ticlopidine was shown to be inferior to clopidogrel in terms of its antiplatelet effect and protection from adverse myocardial outcomes.[7]

Clopidogrel bisulfate (Plavix™) is a thienopyridine prodrug that is metabolized by the cytochrome P-450 system to an activated compound that irreversibly binds the Gi-linked ADP receptor on the platelet's surface, partially blocking the activation by ADP. Clopidogrel has largely replaced ticlopidine in clinical practice due to a much lower incidence of adverse hematological side-effects (mentioned above). However, there is raised awareness that the incidence of side-effects with clopidogrel is probably higher than previously recognized.

The effective half-life of the active metabolite is short and daily dosing is required to maintain the overall antiplatelet effect.[8] While it is believed that the antiplatelet activity of clopidogrel lasts approximately 7 days, as with aspirin, a transfusion of fresh platelets can effectively reverse clopidogrel action, although circulating platelets, already bound to clopidogrel, remain inhibited. Like aspirin, clopidogrel is believed to affect forming platelets for the megakaryocyte. It has not yet been demonstrated how long this effect may be clinically relevant following the cessation of clopidogrel therapy.

Intravenous drugs

Glycoprotein IIb/IIIa receptor inhibitors

The GP IIb/IIIa receptor on the platelet surface is the base for the fibrin crosslinking responsible for platelet aggregation. Unlike the thienopyridines that decrease effective aggregation by 40%-50%, GP IIb/IIIa inhibitors directly block the fibrinogen receptor, preventing aggregation altogether. Currently available GP IIb/IIIa inhibitors include abciximab (Reopro™), eptifibatide (Integrilin™), and tirofiban (Aggrastat™).

Abciximab

Abciximab is a human-murine chimeric monoclonal antibody fragment that binds to the nonspecific GP IIb/IIIa receptor, preventing platelet aggregation. The effective half-life is approximately 12 hours, with approximately 50% inhibition of platelet function remaining 24 hours after stopping the infusion. Once the infusion is stopped, the anticoagulant effects of abciximab can be reversed by transfusion with fresh platelets.

Eptifibatide and tirofiban

Eptifibatide is a cyclic heptapeptide based on the KGD amino acid sequence that selectively binds the GP IIb/IIIa receptor. The effective half-life is approximately 2 hours, with platelet function returning to >50% of normal within 4 hours after discontinuation. Despite its short half-life, the effects of eptifibatide are not reversible by the transfusion of fresh platelets. Eptifibatide clearance is dependent on renal elimination.

Tirofiban is a non-peptide tyrosine derivative that binds selectively to the GP IIb/IIIa receptor. Like eptifibatide, its effective half-life is short at only 2 hours, and platelet function returns to >50% of normal within 4 hours. These 2 agents are not reversible with the transfusion of platelets.[9] Clearance depends upon both renal and biliary elimination.

However, their short half-life allows an earlier operation if necessary.

The differential ability of platelet transfusion to reverse the effects of these agents stems from the stoichiometric ratios of the drug:receptor *in vivo*. With abciximab, the ratio of the drug receptors is nearly 1:1 because unbound drug is degraded by plasma protease. Since < 4% of the administered dose remains unbound after 2 hours, the overall effect of this long-acting and "irreversible agent" can be reversed once the infusion is discontinued. In contrast, the short-acting alternative agents, eptifibitide and tirofiban, continually bind and dissociate from the GP IIb/IIIa receptor and the free drug receptor ratio is > 1:1. For this reason, transfusion platelets are antagonized by these agents for a few hours following discontinuation of the infusion. Fortunately, the short half-life of these 2 agents, makes emergency platelet transfusions rare and generally unnecessary in real-life situations. One can simply allow these agents to wear off.

Guidelines for patients taking antiplatelet medications who require surgery

Aspirin is the most commonly prescribed antiplatelet medication. The majority of patients should continue aspirin up until the time of their surgery since the threat of thrombosis is greater than that of bleeding.[10] Although a plethora of evidence suggests that bleeding is increased with aspirin, it is not enough to require increased transfusions and re-explorations.[11] However, there are exceptions, such as the hyper-responders and the 10% of patients who are aspirin-resistant. Both of these groups may be difficult to identify. However, when they are identified, aspirin should be stopped in high-responders for 2-3 days prior to surgery and the dose should be increased to ≥ 650 mg a day in patients who are aspirin-resistant.

Clopidogrel causes more bleeding than aspirin.[12] Evidence strongly suggests that clopidogrel should be stopped at least 5 days before an operation, particularly if the patient has received a loading dose of 300 mg.[13] If there is a compelling reason to proceed with the operation, aprotinin has been demonstrated to limit bleeding.[14-16] These platelet ADP receptor blockers are becoming more common and may become the standard of care in the therapeutic armamentarium.

GP IIb/IIIa inhibitors (ie, abciximab, eptifibatide, and tirofiban) should be stopped between 4 and 24 hours before surgical procedures (Table 1). If this is not possible, the operation should be performed with regular heparin dosing and with platelets ready immediately after procedures.

Antifibrinolytics may be helpful in patients taking combinations of these medications.[17] For example, patients on aspirin and clopidogrel may benefit from the use of antifibrinolytics. However, some studies suggest that there is an increased incidence of serious complications in some patients, presumably secondary to treatment with aprotinin.[18-20] Antifibrinolytics continue to be used, although there is a large body of evidence suggesting the contrary. In addition, these patients tend to be the sickest, requiring the most immediate operations. Limiting bleeding eliminates one of the factors for these patients who are at high risk for a bad outcome.

Table 1: Basic strategies for management of patients with elective or emergency cardiac surgery

Drug	Risk of bleeding	Elective surgery	Emergent surgery
Aspirin	Low	Continue until surgery platelets if bleeding excessive	Platelets if bleeding excessive
Clopidogrel	High	Stop at least 5 days prior to surgery	Platelets anti-fibrinolytics (aprotinin)
NSAIDs	Low	Stop 3 days prior to surgery	Platelet transfusion as necessary
Abciximab	High	Stop infusion between 12 and 24 hours	Stop transfusion reversible with platelets
Eptifibatide	High	Stop infusion – 6 hours	Cannot be reversed with platelets
Tirofiban	High	Stop infusion – 6 hours	Aprotinin

A study conducted at St. Michael's Hospital revealed that the collective economic cost for patients who return to the hospital because of bleeding is approximately $4700 (CDN). In addition, there is an increase in adverse events, including ventilation requirements, atrial fibrillation, and infection. Therefore, it is incumbent upon the cardiovascular practitioner to attempt to limit these bleeding episodes. One of the most important strategies is to adhere to guidelines that have been developed for the various antiplatelet regimes.

The American College of Cardiology/American Heart Association (ACC/AHA) 2004 Guidelines for coronary bypass surgery states that, "Several studies have demonstrated a greater risk for post-operative hemorrhaging in patients treated with low-molecular heparin, abxicimab, and clopidogrel." It is important, therefore, to understand the pharmacokinetics of these agents to reduce the risk. For instance, no increase in bleeding was observed when clopidogrel was withheld for 5 days before an operation. However, in some instances, the need for surgery supersedes this risk.

The Society of Thoracic Surgeons Practice Guidelines Series, for aspirin and other APAs (eg, NSAIDs, ADP receptor blockers, and GP IIb/IIIa receptor inhibitors) during the coronary revascularization executive summary 2005, states:

"For urgent/emergent cases, the small risk of bleeding is outweighed by the benefits of aspirin." This led to a Class 2a recommendation to continue aspirin until the time of coronary artery bypass graft (CABG) surgery in urgent/emergent patients, Level A + B evidence. Because of the risk of excessive post-operative bleeding, ADP receptor blockers should be stopped 5-7 days before CABG. This is also a Class I recommendation Level B evidence of the ACC/AHA."

Conclusion

Antiplatelet medications comprise part of the armamentarium for treating cardiovascular patients. Over the past 10 years, these medications have expanded as newer and more powerful drugs and new strategies have been developed to prevent clotting. Aspirin remains the mainstay of oral medications, however, and most patients should be on aspirin. Those who are aspirin-resistant or hyper-responders should be identified, if possible, and a replacement alternative should be used.

The thienopyridine antithrombotic agents are powerful antiplatelet medications that are being administered as increasing numbers of patients present emergently or urgently requiring surgical intervention. There is overwhelming evidence, however, that these drugs (specifically clopidogrel) cause more bleeding than other oral agents and that they should be stopped for 5 days before any cardiac surgical procedure. If an emergent situation arises, the use of an antifibrinolytic agent is recommended.

Intravenous drugs are used largely in the cardiac cath lab and coronary care units. The advantage of the GP IIb/IIIa receptor inhibitor, abciximab, is that its effects are reversible with transfusion of fresh platelets if urgent surgery is required. However, eptifibatide and tirofiban cannot be reversed with platelets and are dependent on renal clearance. Their half-lives are shorter and the recommended time required for clearance is at least 12 hours. Antifibrinolytics have also been used in this setting to decrease bleeding.

New medications are being tested in ongoing clinical trials that will no doubt provide new strategies for antiplatelet therapy in the future.

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References

1. Mustard JF, Packham MA. Factors influencing platelet function: adhesion, release and aggregation. *Pharmacol Rev* 1970;22:97.
2. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest* 1968;47:2169.
3. Bybee KA, Powell BD, Valeti U, et al. Preoperative Aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005;112(supp I): I-286-292.
4. Chen WH, Lee PY, Ng W, Tse HF, Lau CP: Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 2004;43(6):1122-1126.
5. Bhatt DL, Chew DP, Hirsch AT, et al. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;103:363-68.
6. Daniel JL, Danglemeier C, Jin J, et al. Molecular basis for ADP-induced platelet activation. 1. Evidence for three distinct ADP receptors on human platelets. *J Biol Chem* 1998;273(4):2042-2049.
7. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;102(6):624-629.
8. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost* 2000;84:891-6.
9. Tcheng JE. Clinical challenges of platelet glycoprotein 11b/111a receptor inhibitor therapy: bleeding, reversal, thrombocytopenia and retreatment. *Am Heart J* 2000;139:S38-45.
10. Ferraris VA, Ferraris SP, Royston BD, Despotis G. Guidelines for the use of antiplatelet drugs in cardiac surgery. *Heart Surg Forum Rev* 2006;4(I).
11. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its operative withdrawal versus bleeding risks with its continuation – review and meta-analysis. *J Intern Med* 2002;257:399-414.
12. Mehta RH, Magnus Ohman E, Pollack CV, Peterson ED. Acute clopidogrel use and outcomes in patients with non-ST segment elevation acute coronary syndromes undergoing coronary artery bypass. *J Am Coll Card* 2006;48(2):281-6.
13. Sun JCJ, Crowther MA, Warkentin TE, Lamy A, Teoh KH. Should aspirin be discontinued before coronary artery bypass surgery? *Circulation* 2005;112:e85-e90.
14. Murkin JM, Lux J, Shannon NA, et al. Aprotinin significantly decreases bleeding and transfusion requirements in patients receiving aspirin and undergoing cardiac operations. *J Thorac Cardiovasc Surg* 1994;107:554-61.
15. Lindvall G, Sartipy U, van der Linden J. Aprotinin reduces bleeding and blood product use in patients treated with Clopidogrel before coronary artery bypass grafting. *Ann Thorac Surg* 2005;80:922-7.
16. Herbert JM, Bernat A, Maffrand JP. Aprotinin reduces clopidogrel-induced prolongation of the bleeding time in the rat. *Thrombosis Research* 1993;71:433-441.
17. Lemmer JH. Clinical experience in coronary bypass surgery for abciximab-treated patients. *Ann Thorac Surg* 2000;70:S33-7.
18. Mangano DT, Tudor JC, Dietzel C. The risk associated with Aprotinin in cardiac surgery. *N Engl J Med* 2006;354:353-65.
19. van der Linden J, Lindvall G, Sartipy U, et al. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: a double-blind, placebo-controlled, randomized clinical trial. *Circulation* 2005;112:1276-80.
20. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: A systematic review and meta-analysis of randomized clinical trials. *J Thor Cardiovasc Surg* 2004:128(3):444-448.

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