Pharmacology and therapeutic uses of antiplatelet drugs

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Antiplatelet agents prevent clot formation and growth through prevention of platelet aggregation. Antiplatelet agents are essential for the prophylaxis and pharmacological management of arterial thrombosis. Appropriate use of these agents requires knowledge of their pharmacology and therapeutic uses with appropriate assessment of risks and benefits.

Keywords: antiplatelet, thromboembolism, aspirin, clopidogrel, dipyridamole, ticagrelor, abciximab

Introduction

Platelets are responsible for the initiation of haemostatic mechanisms that repair injury to the vascular endothelium. Injury to the endothelium leads to activation of platelets and pro-coagulant factors. The main physiological platelet stimuli include adenosine diphosphate (ADP), thrombin and collagen.¹ Endothelial injury impairs the production of nitric oxide and prostacyclin and exposes collagen that results in platelet adherence, platelet activation, and secretion of platelet granules. Following activation, platelets undergo significant conformational changes via the GPIIb/IIIa receptor on the platelet surface that make the platelets extremely adhesive and leads to binding of both von Willebrand factor (VWF) and fibrinogen. Secretion of platelet granules like ADP, serotonin, and thromboxane A₂ (TXA₂) stimulate and recruit additional platelets, induce vasoconstriction and have potent mitogenic effects on smooth muscle cells.² The interactions between activated platelets and the clotting cascade, exposure of tissue factor and its interaction with factor VIIa generates activated factor X which converts prothrombin to thrombin. Thrombin converts fibrinogen from a soluble plasma protein into an insoluble fibrin clot.³ Antiplatelet drugs are classified according to their site of action that inhibit platelet adhesion, activation, aggregation by suppressing the TXA₂ pathway, ADP pathway, thrombin and phosphodiesterase (PDE).⁴

Thromboxane A₂ (TXA₂) pathway inhibitors – Aspirin

Aspirin is a non-selective, irreversible cyclooxygenase-1 (COX-1) blocker (only weakly inhibits COX-2). It acetylates a serine residue on the COX-1, inhibiting the production of prostaglandins and TXA₂, a powerful platelet aggregation factor.⁵ The inhibiting effect lasts throughout the lifespan of the platelet (7–10 days).⁶ Low dose aspirin (75–100 mg orally daily) is well established for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD), acute coronary syndromes, myocardial infarction, stable or unstable angina, arterial revascularisation, stroke, transient ischaemic attack, and peripheral arterial disease.⁷ Patients with unstable angina on aspirin treatment have a 50%

risk reduction in the incidence of fatal and non-fatal myocardial infarction.⁸

Its use in primary prevention is still controversial and expected benefits should outweigh its potential risks. It should be avoided in patients with increased risk of bleeding including a history of gastrointestinal (GI) bleeding or peptic ulcer disease, bleeding from other sites, age > 70 years, thrombocytopenia, coagulopathy, chronic kidney disease, and concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and anticoagulants.⁹ The ACC/AHA 2019 guidelines on the primary prevention of cardiovascular disease recommends low-dose aspirin for adults aged between 40 to 70 years who are at higher ASCVD risk and low risk of bleeding. Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk and on a routine basis for primary prevention of ASCVD among adults > 70 years.¹⁰ The United States Preventive Services Task Force (USPSTF) endorses aspirin for primary CVD prevention in adults with a 10-year risk of heart attack or stroke exceeding 10% in individuals who are not at increased risk of bleeding.¹¹ It is also indicated in patients with increased risk factors such as diabetes mellitus, obesity, dyslipidaemia, hypertension, inactive lifestyle, smoking and family history of ASCVD.¹²

Aspirin use has also been shown to be effective in the prevention of colorectal cancer and colorectal adenomas. However, these potential benefits of long-term therapy must be weighed against the potential adverse effects.^{13,14} Higher doses of aspirin also inhibit COX-2, which blocks prostaglandin production leading to anti-inflammatory, analgesic and antipyretic effect therefore used in the treatment of ankylosing spondylitis, fever, pain, osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus amongst others.¹⁵

Gastrointestinal tract irritation, bleeding, hypersensitivity reactions such as bronchospasm, rhinitis, urticaria, angioedema, and drug interactions are the major side-effects associated with aspirin use. Tinnitus, impaired renal function and hepatotoxicity are more likely to be experienced in higher dosages. Elderly patients are more prone to these side-effects even in lower

dosages. It is contraindicated in patients with peptic ulceration, haemophilia, thrombocytopenia and other bleeding tendencies, including severe renal and hepatic insufficiency. Aspirin use should be avoided in children and adolescents due to the possibility of life threatening Reye's syndrome.⁴ It is a highly plasma-protein bound agent, and therefore has the potential to displace other drugs (i.e. antidiabetic agents, methotrexate, warfarin) from their binding sites and thus increase the risk of toxicity. Concomitant use of other thrombolytic agents increases the risk of haemorrhage and gastrointestinal bleeding, and should generally be avoided.¹⁶

ADP receptor antagonists

ADP receptor antagonists irreversibly inhibit ADP (P_2Y_1 and P_2Y_{12}) receptors on platelets. Antiplatelet drugs blocking P_2Y_{12} form a cornerstone of therapy for patients at high risk of major atherosclerotic cardiovascular events, particularly those with acute coronary syndrome and those receiving percutaneous coronary intervention.¹⁷ These agents are approved for secondary prevention of events in patients with recent myocardial infarction with or without ST segment elevation myocardial infarct (STEMI), stroke and for secondary prevention of thromboembolic diseases, stroke and transient ischaemic attack, or in patients with aspirin intolerance.¹⁸ Contraindications include active bleeding, intracranial haemorrhage, and severe liver impairment. Drug interactions with aspirin, heparin, warfarin and NSAIDs increase the risk of gastrointestinal bleeding in particular. Common adverse effects include bleeding, gastrointestinal side-effects (bleeding, dyspepsia, abdominal pain and diarrhoea), and CNS effects with dizziness, paraesthesia and headache.¹⁹

P_2Y_{12} irreversible inhibitors – Clopidogrel, Prasugrel, Ticlopidine (not available in SA)

Clopidogrel is activated in the liver and is six times more effective than aspirin in preventing platelet aggregation. It has superior tolerability and fewer incidences of bleeding compared to aspirin and ticlopidine.⁴ Due to competitive CYP2C19 inhibition by omeprazole and esomeprazole, pantoprazole should be used instead in patients requiring a proton pump inhibitor (PPI). Alternatively, another acid-lowering drug should be considered.²⁰ In patients who cannot use warfarin in atrial fibrillation the addition of clopidogrel to aspirin has proven beneficial.¹⁸

Prasugrel, a third generation thienopyridine, irreversibly and competitively blocks the P_2Y_{12} receptor by forming disulphide bridges between cysteine residues, which results in a fast, powerful and sustained inhibition of platelet aggregation compared to clopidogrel.²¹ Prasugrel is more potent than clopidogrel in clinical settings. Prasugrel is rapidly absorbed after oral administration with 80% bioavailability. The maximum antiplatelet effect is experienced two days post initiation of therapy and platelet function is restored within two days of drug discontinuation.²² It can be co-administered with CYP3A4 inhibitors/inducers, statins and PPIs. Prasugrel is contraindicated in patients with a history of stroke or TIA and must be used with caution in patients over the age of 70 years.²³

P_2Y_{12} reversible inhibitors – Ticagrelor, Cangrelor (not available in SA)

Ticagrelor is a reversible P_2Y_{12} receptor blocker. Unlike other thienopyridines, ticagrelor does not inhibit binding of ADP but prevents ADP-induced signalling. This enables ticagrelor to attain near maximum inhibition (~80 %) within one-hour post administration.²⁴ It can be used in combination with aspirin or clopidogrel to prevent thromboembolic events in patients with acute coronary syndrome. Contraindications for ticagrelor use include hypersensitivity, active bleeding, inherited bleeding disorders, intracranial haemorrhage, severe liver impairment, and the concomitant use of CYP3A4 inhibitors/inducers with a black boxed warning regarding bleeding risk with concomitant use of other antithrombotic drugs. It increases plasma levels of statins and digoxin.²⁵ Ticagrelor is also associated with dyspnoea (14.2%), elevated serum creatinine and elevated uric acid.²⁶

Phosphodiesterase inhibitors – Dipyridamole

Dipyridamole blocks the platelet aggregation response by inhibiting phosphodiesterase activity, which is responsible for breaking down cAMP. In addition, the ability of platelets to re-uptake adenosine is impaired, thereby resulting in increased plasma concentrations of adenosine. Dipyridamole is used in combination with other antiplatelet drugs for reducing thromboembolic complications associated with prosthetic heart valves, and is used as add-on therapy to warfarin in the secondary prevention of ischaemic stroke and TIA.²⁷ It is ineffective when used alone.

Glycoprotein IIb/IIIa inhibitors – Abciximab, Eptifibatide, Tirofiban

Glycoprotein IIb/IIIa platelet receptor antagonists block the final pathway in platelet aggregation and clot formation. These drugs are expensive and reserved for high-risk patients undergoing percutaneous coronary interventions, as an adjunct to heparin and aspirin for the prevention of ischaemic complications, short-term myocardial infarction risk reduction in patients with unstable angina, and non-STEMI not responding to conventional therapy.²⁸ Dose reduction in renal impairment is necessary, and major side-effects include bleeding and thrombocytopenia. Although eptifibatide and tirofiban have longer half-lives than abciximab, the effects last shorter due to rapid clearance. Overdose is managed by treatment discontinuation, administering platelets and recombinant factor VIIa.²⁹

Conclusion

General practitioners have an important role to play in the prevention, treatment and risk reduction of thrombosis. In addition to pharmacological management, healthy lifestyle should always be promoted and risk factors such as smoking, obesity, familial hypercholesterolaemia, hypertension, diabetes, family history of premature ASCVD with dyslipidaemia should be assessed and treated accordingly. The decision regarding aspirin for primary prevention must involve a discussion between patients and their clinicians.

Table 1: Summary of available antiplatelet drugs

Antiplatelet agents	Indication	Contraindication	Side-effects	Drug interaction	Dose
Thromboxane A2 pathway inhibitors					
ADP receptor antagonists	Secondary prevention of ischaemic heart diseases, ischaemic stroke and TIA. Primary prevention in high ASCVD risk patients only. Should be avoided in patients with increased risk of bleeding including a history of GI bleeding or peptic ulcer disease, bleeding from other sites, age > 70 years, thrombocytopenia, coagulopathy, chronic kidney disease, and concurrent use of NSAIDs, steroids, and anticoagulants.	Dyspepsia and peptic ulceration, haemophilia, thrombocytopenia or other bleeding tendencies, severe renal or hepatic function insufficiency. Should be avoided in children and adolescents due to the possibility of life threatening Reye's syndrome.	Gastric irritation causing abdominal pain, nausea, vomiting and occult or overt mucosal bleeding, chronic administration of high doses may cause gastric erosion and acute haemorrhage, pseudo-allergic reactions such as bronchospasm, rhinitis, urticaria, angio-oedema and anaphylaxis-like shock, tinnitus and decreased hearing, impaired prothrombin time and hepatotoxicity. Patients who are hypersensitive to other NSAIDs are likely to develop similar reaction.	Antidiabetic agents, including insulin: hypoglycaemic effects may be enhanced. Agents inhibiting platelet aggregation, thrombolytic agents and heparin: increased risk of haemorrhage. Agents causing gastric irritation e.g. alcohol, other NSAIDs, corticosteroids: increased risk of gastrointestinal side-effects, including ulceration and blood loss. Methotrexate: plasma concentration of methotrexate may be increased. Warfarin: increased risk of bleeding. Monitor INR more frequently. Zidovudine: the hepatic clearance of zidovudine may be decreased.	75–150 mg daily ACS: 150–300 mg
ADP receptor antagonists	Secondary prevention of thromboembolism stroke, TIA. Therapy to reduce the risk of death in ACS, in aspirin intolerance. Reduction of thrombosis after coronary artery stenting.	Active bleeding e.g. peptic ulcer, intracranial haemorrhage, severe liver impairment.	Bleeding, epistaxis abdominal pain, dyspepsia, diarrhoea, nausea, CNS effects (headaches, dizziness, vertigo, paraesthesia) skin rashes. Rare: neutropenia, bronchospasm, angio-oedema, anaphylaxis, thrombotic thrombocytopenic purpura, intracranial bleeding, haemoptysis, hyperuricemia. Monitoring of full blood count, liver function test and clotting time is recommended.	Aspirin, heparin, warfarin and other thrombolytic: increased risk of bleeding. NSAIDs: increased risk of occult gastrointestinal bleeding. PPIs: competitive CYP2C19 inhibition by omeprazole and esomeprazole. Avoid with clopidogrel.	Clopidogrel: 75 mg daily ACS or stent: 300 mg loading dose Prasugrel: 60 mg loading dose then 10 mg daily
P2Y12 receptor antagonists reversible	Added to aspirin, heparin and other conventional therapy to reduce the risk of death, MI and stroke in patients with ACS.			CYP3A4 inhibitors , e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, atazanavir: increased risk of bleeding. Avoid with ticagrelor. CYP3A4 inducers , e.g. rifampicin, phenytoin, carbamazepine, phenobarbital-reduced efficacy of ticagrelor. Simvastatin: AUC and C_{max} of simvastatin are increased. Avoid doses > 40 mg. Digoxin: increased plasma concentration.	Ticagrelor: 180 mg initially, then 90 mg bd
Phosphodiesterase inhibitors	Secondary prevention of ischaemic stroke and TIA (in combination with aspirin). Reduction of thromboembolism complications of prosthetic heart valves when added to warfarin.				100 mg 4 times daily before meals Low doses: 25–75 mg tds Sustained release: 200 mg bd
Glycoprotein IIb/IIIa inhibitors	Adjunct therapy to heparin and aspirin for the prevention of ischaemic cardiac complications in patients undergoing PCL. Short-term MI risk reduction in patients with unstable angina or non-STEMI not responding to conventional therapy.			Abciximab: 250 mcg/kg over 1 min initial loading dose, followed with 0.125 mcg/kg/min continuous infusion Eptifibatide: 180 mcg/kg initial IV infusion, 2 mcg/kg/min continuous infusion Tirofiban: 0.4 mcg/kg/min for 30 min initial IV infusion, 0.1 mcg/kg/min continuous infusion	

TIA – transient ischaemic attacks, ASCVD – atherosclerotic cardiovascular disease, NSAIDs – nonsteroidal anti-inflammatory drugs, ACS – acute coronary syndrome, PPIs – proton pump inhibitors, MI – myocardial infarction, PCI – percutaneous coronary intervention

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