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Antiplatelet agents

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Introduction

Platelets play an important role in haemostasis after tissue injury. However, due to their inherent function, platelets are also involved in atherosclerotic thrombo-occlusive diseases of the cardiovascular and cerebrovascular systems.[1,2] The formation of a thrombus is currently best explained by a cell-based model, comprising three processes of coagulation-initiation, amplification, and propagation.[3]

By studying platelets' mechanisms of adhesion, activation, and amplification, the ability to develop treatment, management, and prevention of acute coronary syndromes, stent thrombosis, and stroke in individuals at risk, improves.[4] Knowledge of antiplatelet drugs has substantial value in the perioperative setting.[5]

Platelet physiology

The physiology and function of platelets extend beyond coagulation and the scope of this article. To understand the mechanism of platelet inhibition by antiplatelet medication, the basic physiology of platelet activation is pertinent to grasp (Figure 1).[4]

Platelets circulate in blood in a resting state and do not interact with the vessel wall.[4,6,7] Vascular injury or atherosclerotic plaque rupture exposes the vascular subendothelium to circulating platelets.[1,4,6] The glycoprotein (GP) Ib/IX/V receptor complex on platelets binds to exposed von Willebrand factor, initiating platelet adhesion.[1,6] Subsequently, the thrombogenic collagen present in the subendothelial matrix is bound by platelet GP VI and integrin $\alpha 2\beta 1$ receptors.[1,6]

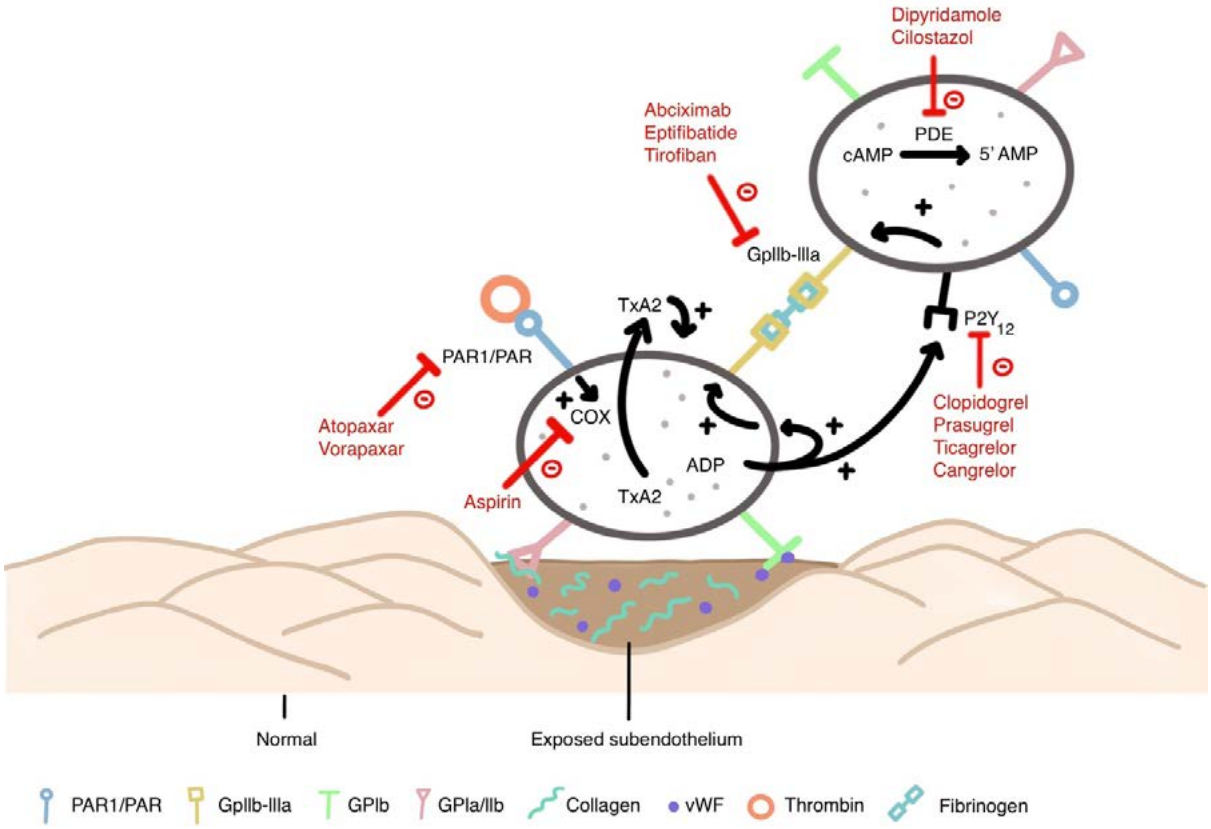

Figure 1: An overview of platelet response to vessel damage and antiplatelet receptor binding sites[1,6,8]

During activation, changes to platelet morphology and mobilisation of intracellular calcium result in the release of adenosine diphosphate (ADP) and thromboxane A2 (TxA2), which maintain platelet activation as well as promote activation of the final common pathway for platelet aggregation via the GP IIb/IIIa receptors.[1,6,7] The P2Y12 receptor on platelets is a critical binding site for ADP to maintain GP IIb/IIIa receptor activation.[1,6]

Stable thrombus formation occurs due to the binding of platelets to each other via activated GP IIb/IIIa receptors to fibrinogen.[1,6,7] Thrombin, P-selectin, and CD40L are agonists in platelet activation that facilitate thrombus formation and adhesion.[1,6] Protease-activated receptors (PARs) undergo proteolytic cleavage by serine protease thrombin, one of the most potent drivers of platelet activation and aggregation.[6] Furthermore, thrombin converts fibrinogen to fibrin, which creates a fibrin and platelet matrix resulting in a stable thrombus.[6]

Drug classes (Table I)

Table I: Antiplatelet drugs classified according to class[8]

Class	Drugs
Cyclooxygenase inhibitors	Aspirin
ADP receptor inhibitors	Clopidogrel, prasugrel, ticlopidine, ticagrelor, cangrelor
Phosphodiesterase inhibitors	Cilostazol
GP IIb/IIIa receptor antagonists	Abciximab, tirofiban, eptifibatide
Adenosine reuptake inhibitors	Dipyridamole
Protease-activated receptor (PAR-1) antagonist	Vorapaxar

Cyclooxygenase inhibitors

Aspirin

Aspirin irreversibly acetylates cyclooxygenase-1 (COX-1) at low doses.[8,9] Inhibition of COX-1 within platelets prevents the synthesis of TxA2.[5] In addition to COX-1, COX-2 is also inhibited by aspirin at higher doses and is responsible for the anti-inflammatory effects.[9,10] Aspirin is rapidly absorbed by the upper gastrointestinal tract, reaches peak plasma concentration in 20–40 minutes, is mostly metabolised by the liver, and has a half-life of 15–30 minutes.[9,10]

The effect of aspirin lasts for the life of the platelets (7–10 days); however, platelet function recovers by 10% per day due to the production of new platelets.[10] Adverse effects commonly include dyspepsia, gastritis, peptic ulcers, and more rarely anaphylaxis.[4,10]

ADP receptor inhibitors

Clopidogrel

Clopidogrel is a prodrug that is metabolised in the liver and is considered a thienopyridine.[3,6,9] Approximately 15% of clopidogrel is metabolised by cytochrome P450 (CYP450) isoenzymes via a two-step process to its active form.[6,9] The remainder of the absorbed drug is converted by hepatic carboxylesterase 1 to an inactive molecule.[6,9] The active metabolite selectively binds the G-coupled P2Y12 receptor irreversibly on platelets preventing the binding of ADP on the receptor.[4,6] The reliance on CYP450 for metabolism predisposes clopidogrel to drug-drug interactions.[6,9] Genetic polymorphisms and drugs that inhibit CYP2C19, such as proton-pump inhibitors, are implicated in the variable response of clopidogrel.[3,6]

The onset of action occurs in a dose-dependent fashion, a loading dose of 300 mg is required to achieve a therapeutic effect in 6–8 hours.[4,10] The effect lasts for the life of the platelets and the offset of action is 5–7 days.[9] Bleeding is a common side effect presenting as epistaxis or gastrointestinal bleeding, as well as dermatological manifestations such as skin rashes and pruritis.[4,10] A rare life-threatening complication is neutropaenia, which occurs more frequently with ticlopidine.[10]

Prasugrel

Prasugrel is a third-generation thienopyridine similar to clopidogrel as a prodrug and its metabolite irreversibly inactivates the P2Y12 receptor.[3,4,9] In contrast to clopidogrel, the active thiolactone metabolite of prasugrel provides a rapid onset of action, more reliable bioavailability, and less drug-drug interactions with CYP450.[6,9] Due to its potent antiplatelet effects, prasugrel is more effective than clopidogrel at preventing thrombosis; however, at an increased risk of serious and fatal bleeding.[10] Prasugrel should be stopped 7–10 days before surgery.[9]

Ticagrelor

Ticagrelor is classified as a cyclopentyltriazolopyrimidine.[6] It is a non-competitive allosteric antagonist with reversible binding for the P2Y12 receptor.[10] As a result of its reversible binding to the ADP receptor, it has a bioavailability of 36% and variable efficacy depending on plasma concentration.[9] Ticagrelor is not a prodrug and does not need to be metabolised to have an effect; however, its metabolite is equally effective at inhibiting the P2Y12 receptor.[4,6] It is metabolised in the liver by CYP450 isoenzymes CYP3A4 and CYP3A5.[3,6,9] Drugs that are metabolised by or inhibit CYP3A4 and CYP3A5 can potentially delay the metabolism of ticagrelor.[4,9] The metabolism of digoxin is affected when administered concurrently with ticagrelor and careful monitoring of digoxin levels should be instituted.[6,9,10]

Ticagrelor reaches maximum plasma concentration within 1.5 hours of administration and has a plasma half-life of seven hours.[9] Offset of action is five days and it should be withheld for seven days before surgery.[9] The side effect profile of ticagrelor is similar to thienopyridines, but there are additional respiratory and adverse cardiac effects of ticagrelor-dyspnoea and bradycardia.[4,6,10]

Cangrelor

Cangrelor, a reversibly binding inhibitor of the P2Y12 receptor, is an adenosine triphosphate analogue that acts directly on the receptor.[6] It is one of the newer antiplatelet drugs administered

by intravenous infusion, has an immediate onset of action, and a plasma half-life of 3–5 minutes.[6,9] The metabolism of cangrelor occurs rapidly in the plasma by plasmatic ectonucleotidases to an inactivated metabolite.[6]

The unique properties of cangrelor make it ideal for procedural therapy as platelet function returns to normal after one hour of stopping the infusion.[6,9] Caution should be taken when administering cangrelor with thienopyridine drugs as their active metabolites are unable to effectively bind the P2Y12 receptor at the same time.[6]

Phosphodiesterase inhibitors

Cilostazol

As a phosphodiesterase-3 inhibitor, cilostazol is primarily a vasodilator indicated for the treatment of claudication.[4,11] It prevents platelet aggregation and encourages vasodilation by preventing the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) within platelets and vascular smooth muscle cells.[4,11] Elevated cAMP levels also decrease protein kinase A activity and reduce the release of P-selectin.[11] Cilostazol reaches peak plasma concentration in three hours with an elimination half-life of 11–13 hours.[4,10]

Cilostazol's effect on platelet aggregation is reversible.[11] The side effect profile of cilostazol includes anaemia, thrombocytopenia, and agranulocytosis.[4,10] Cilostazol is contraindicated in congestive heart failure.[10]

GP IIb/IIIa receptor antagonists

Abciximab

Abciximab is the earliest of the GP IIb/IIIa receptor antagonists.[7,10] It is a recombinant monoclonal antibody that binds reversibly on platelets' GP IIb/IIIa receptor.[6,7] Abciximab has the highest affinity for the GP IIb/IIIa receptor amongst the antiplatelet drugs.[9] Platelet binding occurs rapidly after administration, and despite its short plasma half-life of 10–30 minutes, it has a much longer biological effect.[6,9] Platelet function is adequate 48 hours after cessation of intravenous infusion; however, due to its high affinity for the receptor, residual activity of abciximab may be found in the circulation after 15 days.[3,9] The most common side effect of GP IIb/IIIa inhibitors is bleeding.[4,10] Other side effects of abciximab are thrombocytopenia, nausea, and chest pain.[4,10]

Tirofiban

Tirofiban is a synthetic nonpeptide small molecule.[7,10] It is a peptidomimetic analogue of tyrosine and mimics the sequencing arginine-glycine-aspartate (RGD) that reversibly inhibits the GP IIb/IIIa receptor.[6,7,10] The onset of action and efficacy is dose-dependent and platelet inhibition occurs at five minutes, the plasma half-life is two hours, and the return to normal platelet function takes 4–8 hours.[6,9] The metabolism and clearance of tirofiban are affected by renal dysfunction as 65% of the drug is excreted by the kidneys.[3,6] Tirofiban has a faster onset of action relative to abciximab, but less affinity for the GP IIb/IIIa receptor results in a shorter duration of action.[6] Of note, tirofiban is associated with coronary artery dissection.[4]

Eptifibatide

Eptifibatide, like tirofiban, is a reversible synthetic GP IIb/IIIa antagonist. But eptifibatide is a cyclic heptapeptide that is sequenced lysine-glycine-aspartate (KGD), like the integrin antagonist barbourin found in snake venom.[6,7] Eptifibatide has a rapid onset of action and its receptor occupancy and level of platelet inhibition are dose-dependent.[9] It has predominant renal excretion and a plasma half-life of two hours with an offset of action of four hours.[3,6,9]

Adenosine reuptake inhibitors

Dipyridamole

Dipyridamole is both an adenosine reuptake inhibitor as well as a phosphodiesterase-5 inhibitor.[3,4] It prevents the cellular uptake of adenosine, thereby decreasing the platelets' ability to adhere to the vessel wall and it inhibits phosphodiesterase, which in turn leads to increased intracellular cAMP, decreased intracellular calcium, and enhanced effectiveness of prostacyclin.[3,4] Dipyridamole can be administered both orally and intravenously.[4] It is less effective at preventing platelet aggregation than it is at preventing platelet adhesion.[3] It is a potent coronary artery vasodilator but a comparatively weak antiplatelet agent and is often prescribed in combination with aspirin for the prevention of cerebrovascular accidents.[3,4]

PAR-1 antagonist

Vorapaxar

Vorapaxar falls into a relatively new class of antiplatelet drugs that bind to and inhibit the PAR-1 and thrombin receptor activating peptide (TRAP) on platelets.[4,5,10] The PAR-1 is responsible for platelet activation when bound to thrombin.[1] Vorapaxar is a fast-acting, reversible, dose-dependent peptide inhibitor of PAR-1.[6,10] A dose of 5–40 mg of vorapaxar may result in more than 90% reduction of platelet aggregation due to the inhibition of TRAP.[6] Vorapaxar does not affect the coagulation properties of thrombin or interfere with the conversion of fibrinogen to fibrin.[6,10] It has an extended half-life of eight days and is metabolised by CYP3A4 in the liver.[10] Contraindications to vorapaxar include a history of stroke and transient ischaemic attack as administration carries an increased risk of intracranial haemorrhage.[10] Although rare, other side effects associated with vorapaxar are anaemia, skin rashes, and headaches.[4,10]

Conclusion

Antiplatelet agents are useful in the prevention and management of thrombo-occlusive vascular diseases.[8] The ideal antiplatelet agent still does not exist; however, as the understanding of signalling pathways and receptors improves, so does the ability

to create better drugs.[6] Antiplatelet agents under development, such as picotamide, terutroban, and PZ-128 may provide a better alternative to agents currently available.[6]

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