Dual antiplatelet therapy in acute coronary syndrome

Health & Medicine, Disease

Platelets are small cell fragments, produced by megakaryocytes in the bone marrow and lungs, which circulate in the blood and play a crucial role in haemostasis. They exist in the body for an average of 8-12 days before being destroyed by phagocytosis in the spleen. During their lifespan, platelets sense endothelial damage through receptors on the platelet surface and first become activated at these sites of vessel injury by the interaction with von Willebrand factor (vWF) and collagen exposed beneath the damaged endothelial lining. This triggers several positive feedback loops that amplify the activating signal, consisting of the release of contents stored in granules. Contents include adenosine diphosphate (ADP), serotonin, platelet-activating factor and thromboxane A_2, which in turn activate additional platelets. Adhesion of platelets to the vessel wall leads to aggregation, forming a platelet plug.

This is an essential process to reduce the risk of death following trauma or childbirth but poses the risk of unwanted platelet activation at sites of atherosclerotic disease in the coronary circulation. In some cases, plaques become unstable and fracture, triggering platelet activation and the formation of an occlusive thrombus at that site. This starves the myocardium of oxygen and nutrients, resulting in acute coronary syndrome (including myocardial infarction and unstable angina) or ischemic stroke. Dual antiplatelet therapy (DAPT) is beneficial in this setting as it targets key pathways of platelet activation by decreasing platelet aggregation and inhibiting thrombus formation. Agonists such as ADP, thromboxane A_2 and thrombin act through G protein-coupled receptors (GPCRs), which have proven to be key targets for platelet-directed therapy. GPCRs form a large

protein family of receptors, detecting ligands outside of the cell, activating signalling pathways and subsequently cellular responses. They consist of a single polypeptide chain, folded into a globular shape and embedded into a cells plasma membrane. Seven hydrophobic transmembrane domains span the entire width of the membrane, consisting of an extracellular N-terminus and an intracellular C-terminus. The extracellular loops form part of the regions at which signalling molecules bind to the GPCR. The intracellular domains interact with heterotrimeric G proteins so that when an agonist binds to the receptor, the GPCR undergoes a conformational change which then triggers the interaction with the G protein. G alpha subunits bind guanosine triphosphate (GTP) when active and guanosine diphosphate (GDP) when inactive. The G protein complex also dissociates into the GTP-bound alpha subunit and a beta-gamma dimer when active. Both stays attached to the plasma membrane but are free to convey messages in the cell by interacting with other membrane proteins and enzymes that produce second messengers. The ability of antiplatelet therapy to reduce mortality and morbidity provides strong evidence that myocardial infarction is a platelet-related disease. However, there is still a considerable number of patients with arterial thrombosis, even though they are on current antiplatelet therapy.

Many current and investigational antiplatelet agents target platelet surface receptors (for example, $P2Y_{12}$ and glycoprotein IIa/IIIa), protease-activated receptor-1 (PAR-1), cyclooxygenase-1 (COX-1) and phosphodiesterases (PDE). DAPT consists of a combination of aspirin and a $P2Y_{12}$ platelet receptor

inhibitor to obtain greater effectiveness than with either agent alone. Aspirin works as an antiplatelet agent by irreversibly blocking the enzyme COX-1 inside platelets, which is needed to produce a platelet activator called thromboxane A_2 from arachidonic acid. Oral aspirin is rapidly absorbed from the stomach and small intestine, reaching peak plasma levels in 30–40 minutes and inhibiting platelet function by 60 minutes. Maximum effect is achieved with a daily dose of 75-100mg. Side effects include bleeding and gastrointestinal toxicity (such as heartburn and indigestion). It selectively targets the COX pathway so platelet activation can occur through other pathways, usually additional agents are required for full antithrombotic function.

A limitation of aspirin is that it is a weak antiplatelet agent. ADP is a platelet agonist, causing platelet shape change, aggregation and thromboxane A_2 generation through effects on P2Y1 and P2Y12 and P2X1 receptors. P2Y12 receptor inhibitors are categorised into prodrugs, an inactive compound which can be metabolised in the body to produce a drug and active antagonists. The thienopyridines, clopidogrel and prasugrel, are prodrugs whereby its active metabolites irreversibly bind to the receptor during the entire life span of the platelets. Ticagrelor and cangrelor are active P2Y12 receptor antagonists that do not necessarily require metabolic conversion and are reversible inhibitors. Clopidogrel is currently the most widely used oral antithrombotic agent. A limitation is that active metabolite generation and the degree to which clopidogrel inhibits platelet function vary between

patients. Available data shows that up to 30% of patients who receive the standard dose of clopidogrel have an inadequate antiplatelet response.