Platelet Glycoprotein IIb/IIIa Receptor Antagonists
Current Concepts and Future Directions

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Abstract

Platelets play a key role in the development of thrombosis. Glycoprotein (GP) IIb/IIIa antagonists are a new class of potent drugs that profoundly inhibit platelet function by blocking the key receptor involved in platelet aggregation.

Several antiplatelet agents with varying characteristics have emerged in the past few years and have been evaluated in a variety of potential clinical settings. Clinical trials have established the effectiveness of these drugs in conditions where thrombosis plays a major contributing role such as unstable angina pectoris, myocardial infarction, and high-risk coronary intervention. Despite their po-
tent antiplatelet effects, GP IIb/IIIa antagonists appear to be remarkably well tolerated, provided that the concomitant use of other anticoagulants such as heparin is managed carefully. Ongoing and future studies will further refine the role of GP IIb/IIIa antagonists, explore new applications, and further test their safety and cost effectiveness in the short and long term.

Platelets play an integral role in the cascade of thrombus formation that follows vascular injury. However, the pathological activation of thrombotic mechanisms can result in ischaemic vascular injury[1-3] (fig. 1). Endothelial damage and overt plaque rupture can result in the exposure of substances that promote platelet adhesion, activation, aggregation, and subsequent thrombus formation. If a thrombus completely occludes a coronary vessel, an acute myocardial infarction (MI) can develop. A nonobstructive thrombus can result in symptoms of unstable angina pectoris or a non-Q wave MI.

Recently, a new group of potent antiplatelet agents have been developed which inhibit platelet aggregation and subsequent thrombus formation by blocking glycoprotein (GP) IIb/IIIa receptors on the surface of platelets (fig. 2). This article briefly reviews key aspects of platelet physiology in relation to GP IIb/IIIa and describes the major compounds currently available, as well as recent relevant clinical trials. It also discusses potential complications related to the use of these drugs, and highlights areas of controversy and potential future directions for their use.

1. Platelets and GP IIb/IIIa Receptors

Platelets are small discoid non-nucleated fragments that circulate in the blood. Because of higher shear forces, they tend to be positioned close to the blood vessel wall interface. When circulating platelets encounter a damaged vessel they adhere to the exposed adhesive glycoproteins, such as GP Ib and Ia/IIa[4] (fig. 3).

Following adhesion, various agonists, including thrombin, collagen, thromboxane A2, serotonin, adrenaline (epinephrine) and adenosine diphosphate (ADP) combine with specific receptors on the platelet’s surface to induce platelet activation.[5] These agonist-receptor interactions are coupled through G proteins to generate secondary messengers which, in turn, induce structural and morphological changes in the platelets and result in the release of platelet granules.[6,7]

During platelet activation, a key receptor on the surface of the platelet, the GP IIb/IIIa receptor, also becomes activated. Although many agonists have the potential to activate platelets, the final common pathway of platelet aggregation proceeds via GP IIb/IIIa[8] (fig. 3).

The GP IIb/IIIa receptor is a member of a family of adhesive receptors (integrins) composed of α and β transmembrane proteins[9] (fig. 4). GP IIb/IIIa itself is composed of αIIb and β3 units and is specific for platelets. There are an estimated 50 000 to 80 000 GP IIb/IIIa receptors on the surface of each platelet.[10] Platelet activation results in a change in the shape of the receptor, which greatly increases its normal low affinity for its natural ligands, specifically, fibrinogen and von Willebrand

Fig. 1. The progression from stable atherosclerotic disease to acute coronary syndromes. Thrombus forms at the site of plaque rupture; it can be occlusive (acute myocardial infarction), subtotal occlusive (unstable angina pectoris), or noncritically occlusive (plaque growth).