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GP IIb/IIIa Inhibitor in Myocardial Infarction

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Summary

Glicoprotein IIb/IIIa inhibitors are powerful platelet anti-aggregatory agents which have showed its great utility in the pharmacological management of patients undergoing acute coronary syndrome. Among the many related drugs currently used, a monoclonal antibody (abciximab), two non-peptidic GP IIa/IIIb receptor antagonists (Tirofiban and Lamifiban), and a peptidic antagonist (epitifibatide) all show, between them, important pharmacokinetics differences. Thus risk/benefit derived from its used should be considered based on each patient clinical profile.

Resumen

INHIBIDOR DE LAS GLICOPROTEÍNAS IIB/IIIA EN EL INFARTO AL MIOCARDIO

Los inhibidores de la glicoproteína IIb/IIIa son poderosos agentes antiagregantes plaquetarios y han demostrado gran utilidad en el manejo farmacológico de pacientes con síndrome coronario agudo. Existen varios compuestos de este grupo, en uso actualmente: un anticuerpo monoclonal (abciximab), dos antagonistas no peptídicos del receptor GP IIa/IIIb (tirofiban y lamifiban) y un antagonista peptídico (epitifibatide). Estos compuestos presentan entre sí importantes diferencias farmacocinéticas. Por lo tanto los riesgos y beneficios de su uso deben considerarse en función del perfil clínico de cada paciente.

Palabras clave: Antiagregantes plaquetarios. Antagonistas de receptores GP IIb/IIIa. Síndromes coronarios agudos.
Key words: Platelet anti-aggregatory. GP IIb/IIIa receptors antagonists. Acute coronary syndromes.

Introduction

Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors are potent platelet anti-aggregatory agents and the use of these agents has emerged as an essential pharmaco-therapeutic intervention in the management of high risk patients with acute coronary syndromes. The final common pathway for platelet aggregation is the binding of fibrinogen to the GP IIb/IIIa receptors on the surface of the platelets. Binding of fibrinogen and platelet-surface GP IIb/IIIa receptors are associated with cross-linking and formation of platelet thrombus. There are between 50,000 – 80,000 GP IIb/IIIa receptors on the surface of each platelet. The receptors become receptible to bind fibrinogen after being activated by the conformational changes associated with endothelial damage. The GP IIb/IIIa inhibitors prevent platelet aggregation by blocking the common pathway for binding fibrinogen to GP IIb/IIIa receptors.[1] The GP IIb/IIIa inhibitors prevent platelet aggregation and decrease the size of the platelet thrombi at the site of erosion, fissuring or rupture of the vulnerable, unstable atherothrombotic plaque. It is now well established that the disruption of the vulnerable plaque, i.e. erosion or rupture associated with the endothelial damage, initiates platelet aggregation and formation of platelet thrombi.

The platelet-aggregation is also stimulated by thrombin, adenosine diphosphate (ADP), catecholamines, collagen, thromboxane A_2 and shear stress. However, platelet aggregation by these mechanisms is also prevented by the GP IIb/IIIa inhibitors.

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The mechanism of action of GP IIb/IIIa inhibitors is different from those of other anti-platelet agents such as aspirin and clopidogrel. Aspirin inhibits cyclooxygenase (prostaglandin synthetase), which prevents formation of thromboxane A_2 from arachidonic acid. Arachidonic acid is formed from a platelet diglyceride by a diglyceride lipase.[2] Platelets contain a membrane phospholipase C which when activated hydrolyzes endogenous phosphatidylinositol to form the diglyceride. The inhibition of thromboxane A_2 – dependent platelet aggregation by aspirin is irreversible.

Clopidogrel and ticlopidine, both prodrugs, are thienopyridine derivatives and block platelet surface ADP receptors and inhibit ADP-induced platelet aggregation.[1] These agents also reduce responses to other agonists that require ADP. It should be appreciated that the platelet aggregatory stimuli such as ADP, epinephrine, collagen and thrombin not only stimulate synthesis of arachidonic acid but also directly activates GP IIb/IIIa receptors. The GP IIb/IIIa inhibitors prevent platelet aggregation irrespective of the mechanisms of activation of the GP IIb/IIIa receptors.[1]

Inhibition of platelet aggregation also facilitates prevention of platelet adhesion. Vascular endothelial injury exposes extracellular matrix. Von Willebrand factor (vwf) binds to the platelet receptor glycoprotein Ib. The platelet-vwf complex then binds to subendothelium (platelet adhesion).[2]

Glycoprotein Iib/IIIa Inhibitors – Classification (Table 1)[3]

Three GP IIb/IIIa inhibitors, Abciximab, Tirofiban, and Eptifibatide are in present use in the management of the subsets of acute coronary syndrome. Abciximab is a monoclonal antibody to the GP IIb/IIIa receptor. It does not possess specificity for GP IIb/IIIa receptor and its binding to the receptor is not rapidly reversible. Its use is also associated with antigenecity.

Tirofiban is a small nonpeptide antagonist of the GP IIb/IIIa receptor. It does not exert immunogenic antigenicity. It does possess a high degree of selectivity for the GP IIb/IIIa receptor; and its effects are rapidly reversible within four to six hours. It is rapidly acting and its platelet antiaggregatory effect is observed within five minutes of administration.

Eptifibatide is a cyclic peptide inhibitor of the GP IIb/IIIa receptor and produces rapid inhibition of platelet aggregation. It possesses high specificity for the GP IIb/IIIa receptor and its effects are rapidly reversible, within two to four hours after discontinuation of its administration. It also does not exert any antigenicity.

Lamifiban, is a synthetic nonpeptide with a very selective GP IIb/IIIa receptor antagonist. It has a relatively short half-life, approximately four hours. Several clinical trials are now being performed to evaluate its efficacy. Its pharmacodynamic effects are rapidly reversible. The pharmacodynamic properties of the GP IIb/IIIa inhibitors in current clinical use are summarized in Table I.[1]

Glycoprotein IIb/IIIa inhibitors – Clinical Use *(Table II)*

The GP IIb/IIIa inhibitors have been demonstrated to decrease the risks of adverse cardiac events including the risks of mortality in all the clinical subsets of acute coronary syndrome.[1,4-6] Their use has the potential to decrease the extent of myocardial damage. The beneficial effects of the GP IIb/IIIa inhibitors are particularly evident in the high risk patients.

The GP IIb/IIIa inhibitors are being increasingly used in patients with St-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). The use of GP IIb/IIIa inhibitors has been shown to decrease the risk of the no-reflow phenomenon and the extent of myocardial damage. In patients undergoing angioplasty or stenting, the use of GP IIb/IIIa inhibitors is associated with reduced risks of restenosis.

Table I. The Pharmacodynamic properties of the glycoprotein IIb/IIIa inhibitors in clinical use in the management of acute coronary syndrome.

Property	Abciximab	Tirofiban	Eptifibatide
Molecular	Monoclonal Antibody	Small Nonpeptide	Cyclic peptide Inhibitor
Specificity for GP IIb/IIIa	NO	YES	YES
Rapid Reversibility	NO	YES	YES
Evidence for Antigenicity	YES	NO	NO

Table II. Potential indications for intravenous glycoprotein IIb/IIIa inhibitors.

Patients Undergoing PCI
High Risk Patients
Elevated biomarkers
Age > 65 yrs
≥ 0.5 mm ST depression
Ejection fraction < 50%
Hemodynamic instability
Diabetes
Patient already receiving aspirin
Previous myocardial infarction
Previous CABG
Recurrent myocardial ischemia
Inpatients awaiting CABG

Adapted from:
White HD, Non-ST-Elevation Acute Coronary Syndromes: Unstable Angina and Non-ST Elevation Myocardial Infarction. In Textbook of Cardiovascular Medicine. Ed. Eric J. Topol 2nd Edition, Lippincott, Williams & Wilkins, Philadelphia, Chap. 17, pp 351-384, 2002.

In large-scale clinical trials, the efficacy of a GP IIb/IIIa inhibitor, abciximab and a lower dose of a fibrinolytic agent (t-PA or TNK-*t*-PA) were tested. A reduction in the risks of in-hospital reinfarction and refractory ischemia was observed with the combination therapy, however there was no significant difference in the risks of mortality. An excess of bleeding complications are expected with combination therapy although an increased incidence of fatal intracerebral hemorrhage was not observed in these clinical studies. The GP IIb/IIIa inhibitors are also used in combination with aspirin and clopidogrel in patients undergoing angioplasty and/or stenting for STEMI.

In patients with non St-elevation MI or unstable angina, the use of GP IIb/IIIa inhibitors is associated with decreased risk of adverse cardiovascular events including mortality and morbidity.[4-6] The GP IIb/IIIa inhibitors can be used during PCI, before PCI ("upstream" treatment) and in patients treated with medical therapy alone. The "upstream" treatment has been tested in a number of clinical trials. The results of these studies suggest that a substantial reduction in the risk of death and myocardial infarction occur in the period before PCI.[5] It should be realized however that the benefits occur primarily in the reduction of the risk of myocardial infarction than of death. In the high risk patients such as with evidence for myocardial ischemia or necrosis, the absolute and relative benefits are substantially greater. The benefits of the use of GP IIb/IIIa inhibitors are also greater in those patients who undergo PCI. In patients requiring coronary artery bypass surgery, the prior use of GP IIb/IIIa inhibitors does not increase morbidity and may also decrease the risks of mortality and/or myocardial infarction.

In the Gusto IV trial,[7] the patients with NSTEMI/UA were randomized to receive either abciximab or placebo in addition to contemporary medical treatments. In the treatment group with abciximab, the mortality and morbidity was higher. In

Table III. Critical evaluation for GP IIb-IIIa therapy.

General contraindications	Eptifibatide	Tirofiban HCl	Abciximab
• Known hypersensitivity to any component of the products • Caution when administering GP IIb-IIIa inhibitors in the presence of other drugs that affect hemostasis • Active internal bleeding or a history of recent bleeding diathesis • History or stroke within 30 days or any history of hemorrhagic stroke • Major surgical procedure or trauma (within 4-6 weeks) • Severe uncontrolled hypertension (systolic > 180 mm Hg or diastolic > 110 mm Hg) • Concomitant use of another parenteral GP IIb-IIIa inhibitor	• Dependency on renal dialysis • Platelet count < 100,000 mm^3 • Serum creatinine ≥ 4.0 mg/dL	• History of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation or aneurysm • History of thrombocytopenia following prior exposure to tirofiban HCl • Severe physical trauma within the previous month • History, symptoms, or findings suggestive of aortic dissection • Acute pericarditis • Thrombocytopenia (platelet count < 100,000 mm^3) • Use with caution in patients with severe renal insufficiency (CrCl < 30 mL/min)	• Recent GI or genitourinary bleeding (within 6 weeks) • Administration of abciximab may result in human anti-chimeric antibody (HACA) formation that could potentially cause allergic or hypersensitivity reactions • History of cerebrovascular accident within 2 years or CVA with a significant residual neurological deficit • Administration of oral anticoagulants (unless PT < 1.2 times control) • Thrombocytopenia (platelet count < 100,000 mm^3) • Intracranial hemorrhage, neoplasm, arteriovenous malformation or aneurysm

Table IV. Indications for GP IIb-IIIa Inhibitors.

Indication	Eptifibatide	Abciximab	Tirofiban
UA/NQMI with PCI	X	Refractory UA	X
UA/NQMI medically managed	X		X
Elective PCI	X	X	
Urgent/emergency PCI	X	X	

other trials with the use of tirofiban or eptifibatide, there was a beneficial effect in the high risk patients with NSTEMI/UA. Thus the use of these GP IIb/IIIa inhibitors are indicated in the management of the high risk patients with NSTEMI/UA along with conventional medical therapy.

The relative advantages and disadvantages of the currently used GP IIb/IIIa inhibitors are summarized in *Table III*. The general contraindications for the use of these agents are history of hypersensitivity to any component of these products with concomitant use of other drugs that can affect homeostasis, and presence of active bleeding or a history of recent bleeding. The use of the GP IIb/IIIa inhibitors is also contraindicated in patients with history of stroke within thirty days or with history of hemorrhagic stroke. These agents should not be used in patients with major surgical procedure or trauma within four to six weeks. The GP IIb/IIIa inhibitors should be used with caution in patients with uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).

It is apparent that there are differences between the presently available GP IIb/IIIa inhibitors in their efficacy in the clinical subsets of the acute coronary syndrome. Some agents are effective in patients undergoing PCI and others also in patients having medical therapy *(Table IV)*.

In conclusion, the GP IIb/IIIa inhibitors are potent antagonists of platelet aggregation, and their beneficial effects have been demonstrated in the management of high risk patients with acute coronary syndrome.[8-10] However, the risks and benefits for the use of the GP IIb/IIIa inhibitors in general and of a specific agent in particular, should be assessed in individual patients considering the clinical profile of the patient and the analysis of all the results of the clinical trials.

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