Tirofiban Hydrochloride – Platelet GP IIb/IIIa Inhibitor

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ABSTRACT

Published on 29th March 2010

Tirofiban is a peptidomimetic (nonpeptide) platelet glycoprotein IIb/IIIa inhibitor. Clinical studies have shown that tirofiban plus heparin is more effective than heparin alone in patients with acute coronary syndromes. Tirofiban has also been shown to be effective in reducing ischemic complications associated with percutaneous coronary intervention. Tirofiban (in combination with aspirin, clopidogrel and heparin) is indicated for use in patients undergoing PCI as well as for the treatment of unstable angina or non-Q-wave myocardial infarction.

Tirofiban is a competitive inhibitor of glycoprotein (GP) IIb/IIIa preventing the binding of fibrinogen, von Willebrand factor (vWF), and other adhesive ligands to the GP IIb/IIIa receptor on activated platelets.

Tirofiban is administered intravenously. The recommended regimen of 0.4 mcg/kg/min IV for 30 minutes followed by 0.1 mcg/kg/min IV thereafter produces a peak tirofiban plasma concentration that is similar to the steady state concentration during the infusion.

Keywords: Tirofiban, Platelet aggregation inhibitor, Mechanism of action, indications, Contra indications, Adverse reactions.

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Regardless of the stimulus for their activation, platelet activation depends on their membrane binding sites for fibrinogen and vWF in the GP IIb/IIIa complex. This mechanism provides the rationale for pharmacological intervention directed against the platelet GP IIb/IIIa complex. Because GP IIb/IIIa antagonists do not block TXA_2 production by activated platelets, concomitant use of aspirin may enhance their antithrombotic efficacy.

Platelet GP IIb/IIIa antagonists generally belong to one of the following classes:[1] monoclonal antibody against GP IIb/IIIa;[2] peptide (peptidomimetic) antagonists, many of which contain the RGD sequence that can compete with fibrinogen for its GP IIb/IIIa binding site; and[3]nonpeptide (nonpeptide-mimetic) antagonists of GP IIb/IIIa. Three intravenous drugs currently available for percutaneous coronary intervention or acute coronary syndromes represent the prototypes for these groups: abciximab, a monoclonal antibody; eptifibatide, a peptide antagonist; and tirofiban, a nonpeptide mimetic.

DESCRIPTION

Tirofiban is a peptidomimetic (nonpeptide) platelet glycoprotein IIb/IIIa inhibitor. Clinical studies have shown that tirofiban plus heparin is more effective than heparin alone in patients with acute coronary syndromes. Tirofiban has also been shown to be effective in reducing ischemic complications associated with percutaneous coronary intervention. Tirofiban (in combination with aspirin, clopidogrel and heparin) is indicated for use in patients undergoing PCI as well as for the treatment of unstable angina or non-Q-wave myocardial infarction.

MECHANISM OF ACTION

Tirofiban is a competitive inhibitor of glycoprotein (GP) IIb/IIIa preventing the binding of fibrinogen, von Willebrand factor (vWF), and other adhesive ligands to the GP IIb/IIIa receptor on activated platelets. "Integrins", which are found on virtually all cell types, are a family of adhesion molecules that mediate many physiologic responses. Unlike many of the other integrins, GP IIb/IIIa is platelet specific and is also the most abundant receptor found on activated platelets, with about 50,000 copies/cell. Fibrinogen is the principal ligand to bind to the GP IIb/IIIa receptor. The binding of fibrinogen and, to a lesser extent other ligands such as vWF, to the GP IIb/IIIa receptor results in cross- linking between platelets and is the final common pathway of platelet aggregation, which ultimately leads to thrombus formation. Glycoprotein IIb/IIIa inhibitors can prevent platelet aggregation regardless of the agonist involved; thus, tirofiban will

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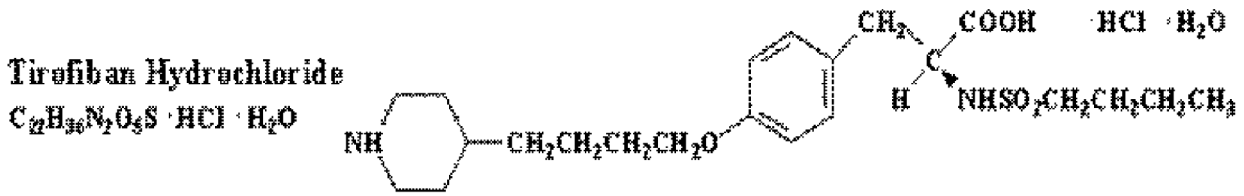

Figure 1. **Molecular structure of Tirofiban Hydrochloride**

block thrombin-induced platelet aggregation while aspirin will not.

Pharmacokinetics

Tirofiban is administered intravenously. The recommended regimen of 0.4 mcg/kg/min IV for 30 minutes followed by 0.1 mcg/ kg/min IV thereafter produces a peak tirofiban plasma concentration that is similar to the steady state concentration during the infusion. Metabolism of tirofiban appears to be limited. In patients with coronary artery disease, the plasma clearance of tirofiban ranges 152—267 mL/ min. Plasma clearance is about 19—26% lower in elderly patients (> 65 years) than in younger patients. Plasma clearance is also significantly decreased (>50%) in patients with a CrCl< 30 mL/min, including patients requiring hemodialysis. Mild to moderate hepatic insufficiency does not affect the plasma clearance of tirofiban. Renal clearance accounts for about 39% of plasma clearance. About 65% of a dose of tirofiban is excreted in urine and about 25% in feces, both largely as unchanged drug. The elimination half-life of tirofiban is approximately 2 hours (range: 1.7—2 hours).

Tirofiban inhibits platelet function, as demonstrated by its ability to inhibit ex vivo adenosine phosphate (ADP)-induced platelet aggregation and prolong bleeding time. An IV infusion regimen of tirofiban0.4 mcg/kg/min for 30 min, followed by 0.1 mcg/ kg/ min for up to 48 hours in the presence of heparin and aspirin, produces > 90% inhibition of ex vivo ADP-induced platelet aggregation with a 2.9-fold prolongation of bleeding time during the loading infusion. Platelet inhibition persists over the duration of the maintenance infusion . Following discontinuation of the infusion, ex vivo platelet aggregation returns to near baseline in about 90% of patients within 4—8 hours.

Indications and Clinical use

Tirofiban hydrochloride, in combination with heparin and aspirin (&clopidogrel) is indicated in the management of patients with unstable angina or non-Q-wave myocardial infarction, including patients who may subsequently undergo PTCA, to decrease the rate of refractory ischemic conditions, new myocardial infarction and death.[1,2]

Contraindications

Tirofiban hydrochloride is contraindicated in patients with:

- known hypersensitivity to any component of the product
- active internal bleeding or a history of bleeding diathesis
- a history of intracranial hemorrhage or neoplasm, arteriovenous malformation, or aneurysm
- who developed thrombocytopenia following prior exposure to tirofiban
- known coagulopathy, platelet disorder or history of thrombocytopenia
- stroke within 30 days prior to hospitalization or any history of hemorrhagic stroke
- major surgical procedure or severe physical trauma within the previous month
- history, symptoms or findings suggestive of aortic dissection
- severe uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure of >110 mmHg

Warnings

Tirofiban hydrochloride inhibits platelet aggregation and therefore caution should be employed when used with other drugs affecting hemostasis

Adverse Reactions

Tirofiban should be used with caution in the following patients:

- recent (<1 year) bleeding, including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance
- platelet count <150,000 cells/mm3
- history of cerebrovascular disease within 1 year
- hemorrhagic retinopathy

- chronic hemodialysis

Use in Pregnancy

Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. However, there are no adequate and well controlled studies in pregnant women. Tirofiban should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether tirofiban is excreted in human milk. However, significant levels of tirofiban are excreted in rat milk. Therefore, nursing should be discontinued during the period of drug administration and the milk discarded. Nursing may resume 24 hours after cessation of treatment with tirofiban.

PRECAUTIONS

Bleeding Precautions

Tirofiban hydrochloride inhibits platelet aggregation and therefore caution should be employed when it is used with other drugs that affect hemostasis (e.g., warfarin).

During therapy with tirofiban, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of tirofiban and heparin should be discontinued. Transfusions maybe given if required. Fatal bleedings have been reported Tirofiban is associated with minor increases in bleeding rates particularly at the site of arterial access for femoral sheath placement.

Laboratory Monitoring

Baseline evaluation: Should be performed on platelet count, hematocrit, hemoglobin and activated partial thromboplastin time (aPTT) prior to treatment.

Following the loading infusion: Monitor platelet count within 6 hours following the loading infusion and at least daily thereafter (or more frequently if there is evidence of significant decline).

In patients previously exposed to GP IIb/IIIa receptor antagonists: Monitor platelet count

Monitor aPTT: Monitor aPTT frequently and adjust the dose of heparin accordingly. Potentially lifethreatening bleeding may occur especially when heparin is administered with other products affecting hemostasis, such as GP IIb/IIIa receptor antagonists

Renal Insufficiency

Patients with moderate (creatinine clearance <60 mL/ min) and severe (creatinine clearance <30 mL/ min) renal insufficiency should be monitored for bleeding complications. Since clinical studies showed a decreased plasma clearance of tirofiban in patients with severe renal insufficiency, the dosage should be reduced in these patients

Adverse Reactions

The most common drug-related adverse event reported during therapy with tirofiban hydrochloride when used concomitantly with heparin and ASA was bleeding.

END NOTE

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Conflict of Interest: None declared

Cite this article as: Jayakumar B. Tirofiban Hydrochloride – Platelet GP IIb/IIIa Inhibitor. Kerala Medical Journal. 2010 Mar 29;3(1):25-27

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