

Tirofiban-Induced Coronary Thrombolysis

Timothy G. Jayasundera, MD, Dmitriy N. Feldman, BA, Jonathan D. Marmur, MD

The use of platelet glycoprotein (GP) IIb/IIIa receptor antagonists during coronary angioplasty has become more widespread due to several trials demonstrating clinical benefit during and after the procedure.¹⁻³ These agents act by blocking the GP IIb/IIIa receptor on the surface of the platelet. The GP IIb/IIIa receptor binds circulating adhesive macromolecules and cross-links with the receptors of surrounding platelets, resulting in platelet aggregation. Tirofiban (Aggrastat™; Merck, Inc., West Point, Pennsylvania), a new non-peptide platelet GP IIb/IIIa receptor blocker, has demonstrated efficacy when used in the context of percutaneous coronary interventions (PCI) and acute coronary syndromes.^{4,5} Like other GP IIb/IIIa antagonists, tirofiban is primarily used to prevent vessel closure in the setting of PCI and unstable angina. We report a case in which tirofiban acted as a thrombolytic agent to achieve reperfusion following acute vessel closure.

Case Report. A 54-year-old male with a history of hypertension and depression presented to a referral

hospital with chest pain radiating to his left arm and neck, associated with shortness of breath and diaphoresis. The patient was diagnosed with an inferior wall myocardial infarction and was treated with r-PA (Retavase™; Centocor, Inc., Malvern, Pennsylvania), heparin, aspirin and nitrates. Subsequently, the patient developed recurrent chest pain and underwent coronary angiography, which revealed a 90% stenosis of the distal right coronary artery (RCA). The patient was then transferred to Mount Sinai Medical Center in New York for coronary angioplasty of the RCA.

On arrival, the patient was pain free with sinus bradycardia and inverted T-waves in the inferior leads. Physical exam was unremarkable. The patient subsequently developed chest pain associated with acute ST-segment elevation in the inferior leads and was immediately transferred to the cardiac catheterization laboratory. Angiography of the RCA revealed a total occlusion of the distal vessel with TIMI 0 flow (Figure 1A). Based on the dosing established in the RESTORE trial, the patient received a bolus dose of tirofiban (10 µg/kg over three minutes) followed by a 0.15 µg/kg/min infusion.⁴ As has become our practice in patients undergoing PCI with tirofiban, adjunctive heparin (40 U/kg bolus) was administered and subsequent boluses of heparin 10 U/kg were injected to maintain a target activated clotting time (ACT) between 200–220 seconds. After the completion of the tirofiban bolus (administered over 3 minutes), the ST-segments normalized and the patient reported that his chest pain had resolved. Repeat angiography 2 minutes after completion of the tirofiban bolus revealed

From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York.

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Address reprint requests to: Timothy G. Jayasundera, MD, Mount Sinai Medical Center, Cardiovascular Institute, Box 1030, One Gustave L. Levy Place, New York, NY 10029.



Figure 1. Right coronary artery (RCA) angiography before and after intravenous tirofiban and following stent implantation. (A) Left anterior oblique view of the RCA showing total occlusion in the distal portion of the vessel (arrow). (B) Restoration of TIMI 3 flow five minutes after the initiation of tirofiban. (C) Final angiographic result after balloon angioplasty and stent placement.

resolution of the total occlusion and restoration of TIMI 3 flow (Figure 1B). Balloon angioplasty with stent placement was then performed successfully (Figure 1C). The patient had an uneventful recovery with no elevation of his cardiac enzymes and was discharged home the following day.

Discussion. The use of GP IIb/IIIa antagonists in the setting of coronary interventions and acute coronary syndromes is increasing due to demonstrated efficacy in several clinical trials. The first of these agents to be introduced into clinical practice was abciximab (ReoPro™; Centocor, Inc., Malvern, Pennsylvania and Eli Lilly, Indianapolis, Indiana), which showed a benefit in the 30-day composite endpoint of death, myocardial infarction (MI) and urgent repeat revascularization in the setting of PCI in patients with acute coronary syndromes and high risk lesion morphology.¹ Initial enthusiasm was tempered because of the higher rate of bleeding in patients treated with abciximab. Subsequent trials showed that the incidence of bleeding could be reduced by lowering the dose of heparin without reducing the clinical benefit of GP IIb/IIIa inhibition.²

Two recently-introduced agents, tirofiban (Aggrastat™; Merck, Inc.) and eptifibatide (Integrilin™; Cor Therapeutics/Key Pharmaceuticals, Inc., Kenilworth New Jersey), were approved based on clinical trials demonstrating efficacy in the setting of acute coronary syndromes and PCI.⁴⁻⁷ Tirofiban with heparin was shown to reduce the composite endpoint of death, MI and refractory ischemia at 7 days, 30 days and 6 months compared to heparin alone in patients presenting with unstable angina.⁵ The efficacy of tirofiban in the context of planned intervention was tested in the Restore trial, wherein the composite endpoint of MI, death, and any revascularization was statistically significant at 2 and 7 days, but was not significant at 30 days.⁴ However, unlike virtually every interventional trial testing other IIb/IIIa inhibitors, the primary endpoint in the RESTORE trial included any elective revascularization event. When the more appropriate composite endpoint of death, MI, or urgent revascularization is used, the risk reduction achieved by tirofiban is statistically significant at the 30-day endpoint. The marked difference in statistical significance between

analyses that use urgent intervention versus any intervention has also been noted for abciximab. The efficacy of abciximab in primary PCI for acute MI was tested in the RAPPORT trial.⁸ This study demonstrated that if results were measured by the composite endpoint of death, reinfarction, and any intervention, abciximab is ineffective at 6-months in acute MI treated with primary angioplasty. However, when the more appropriate endpoint of death, reinfarction, and urgent intervention is used, abciximab reduces the risks of intervention in acute MI in a highly significant manner.

In this case, tirofiban given pre-PCI resulted in reperfusion of an acutely thrombosed vessel. Data from the TIMI 14 study demonstrate that abciximab is able to achieve reperfusion in a significant number of patients presenting with acute coronary occlusion.⁹ Thus, it would appear that GP IIb/IIIa inhibitors are able to achieve thrombolysis as a class effect. The mechanism through which GP IIb/IIIa inhibitors achieve thrombolysis is not completely understood. One possible mechanism is that effective inhibition of platelet aggregation arrests further thrombus growth, thereby allowing the intrinsic lytic system to dominate and achieve reperfusion.

It is also noteworthy that our patient's artery reperfused in the setting of a relatively low ACT (210 seconds). Preliminary data from TIMI 14 suggest that reperfusion with a combination of abciximab and t-PA can be achieved with a low dose of heparin (30 U/kg).⁹ The EPILOG study showed that reduced doses of heparin resulted in the reduction of bleeding events without loss of efficacy.² Preliminary data from *ex vivo* experiments using the Badimon perfusion chamber indicated that combining heparin with the GP IIb/IIIa inhibitor (abciximab) does not add any additional antithrombotic effect to abciximab alone.¹⁰ Based on these observations, it is our belief that reduced doses of heparin are appropriate in the context of GP IIb/IIIa inhibition. Therefore, we advocate a low dose of heparin (30 U/kg) and suggest a target ACT of 180–200 seconds in patients undergoing PCI treated with abciximab. We would recommend a slightly higher dose of heparin (40 U/kg) with a target ACT of 200–220 in patients treated with tirofiban. We believe that a higher dose of heparin is appropriate when using tirofiban versus abciximab because the non-specificity of abciximab

(inhibition of vitronectin and MAC-3) confers heparin-like effects to abciximab.¹¹ In the case of tirofiban, the inhibition of GP IIb/IIIa is highly specific; therefore, an adjunctive heparin effect may be useful. In situations associated with a high degree of platelet activation, e.g., rotational atherectomy, abciximab has been proven to inhibit platelet aggregation.¹² The efficacy of tirofiban in this situation is under investigation at the present time.

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