Vascular Surgery Using Argatroban in a Patient With a History of Heparin-Induced Thrombocytopenia

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For patients with a history of heparin-induced thrombocytopenia (HIT) who undergo cardiac or vascular surgery, the optimal anticoagulation substitute for heparin has yet to be established. Recombinant hirudin has been recommended; however, this agent is unsuitable for patients with renal dysfunction. Argatroban was used in the present patient who had a history of HIT and renal dysfunction and required peripheral vascular surgery. Argatroban was easy to monitor and control, regardless of renal function, and has advantages over other anticoagulants for such patients. (*Circ J* 2003; 67: 889–890)

Key Words: Argatroban; Heparin-induced thrombocytopenia; Vascular surgery

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated thrombocytopenia that often, paradoxically, causes thrombosis.¹ Thus, heparin should be avoided in patients with a history of HIT who require anticoagulation to undergo cardiac or vascular surgery. However, the optimal alternative anticoagulation agent has yet to be established. Argatroban has been reported to be a good anticoagulant in the field of cardiovascular surgery;² however, its use as a substitute for heparin in HIT patients is not well documented. We present a case of a patient with a history of HIT undergoing peripheral vascular surgery using argatroban for anticoagulation.

Case Report

A 68-year-old male who complained of left intermittent claudication was admitted to hospital. His platelet count was 147,000/ μ l at the time of admission. Arteriography demonstrated severe narrowing of the left external iliac artery and balloon angioplasty was performed. Repeat arteriography revealed a patent left external iliac artery and to prevent acute arterial obstruction after the procedure, continuous intravenous heparin (10,000 U/day) was administered for 4 days. Six days later, the patient developed diffuse purpura; his platelet count had decreased to 15,000/ μ l, fibrinogen was normal at 180 mg/dl, fibrinogen-derived product (FDP) had increased to 184 μ g/ml and bleeding time was prolonged to 10 min. The platelet-rich plasma aggregation to small-dose heparin assay confirmed the diagnosis of HIT. The patient complained of sudden calf pain and physical examination revealed arterial obstruction of the right posterior tibial artery, most likely from HIT-associated thrombosis. Heparin was stopped and nafamostat mesilate was administered to prevent further thrombo-

sis. His platelet count gradually increased and normalized after cessation of heparin.

Five years after that HIT episode, he developed right lower leg ischemic necrosis and was again admitted to hospital. Laboratory tests showed his serum creatinine level had elevated to 1.6 mg/dl and creatinine clearance had decreased to 43 ml/min. Arteriography revealed complete occlusion of both common iliac arteries, and consequently he underwent axillobifemoral bypass surgery using an expanded polytetrafluoroethylene graft. In the operating room, 30 min prior to the arterial clamp, continuous intravenous infusion of argatroban was started. An activated clotting time of 150 s was achieved using 2.7 μ g $\cdot$ kg⁻¹ $\cdot$ min⁻¹ of argatroban. He received 10 mg in total of argatroban in 1 h, before and during the arterial clamp. The bypass surgery was successfully performed in 3 h without any thromboembolic or bleeding complications. He was started on a permanent warfarin regimen, beginning after surgery. The postoperative course was uneventful and his ischemic symptoms improved.

Discussion

HIT is a rare but lethal syndrome caused by antibodies against complexes of platelet factor 4 and heparin (HIT antibodies).¹ Patients with HIT have profound thrombocytopenia, sometimes associated with thrombosis. Thrombotic events are most frequently venous, but arterial thrombosis leading to myocardial infarction and ischemic limb damage requiring amputation also occur. The mortality rate can reach 20–30%.¹

No consensus currently exists on the best alternative anticoagulant for patients with a history of HIT who must undergo cardiac or vascular surgery. Recent reports recommend the use of recombinant hirudin (Lepirudin),³ which is a direct thrombin inhibitor; however, this agent is not available in Japan and furthermore, patients with renal dysfunction (creatinine >1.5 mg/dl) have a greater risk of postoperative bleeding.⁴ Another report favors danaparoid (Orgaran), but it also carries the risk of life-threatening hemorrhage because of its variable elimination half-life.⁵ In addition, the

(Received January 28, 2002; revised manuscript received April 15, 2002; accepted May 2, 2002)

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activated clotting time does not correlate with the plasma concentration of Orgaran.⁵ Low molecular weight heparin has been used but was abandoned because of cross-reactivity with HIT antibodies.⁶ More recently, Potzsch et al reported that antibody-negative patients with a history of HIT undergoing cardiopulmonary bypass have been safely treated with heparin.⁷ Certainly, in some cases, HIT antibodies become undetectable a few months after the cessation of heparin therapy;¹ however, the assay for the antibodies against complexes of platelet factor 4 and heparin is not widely available in Japan. Furthermore, the number of patients in the Potzsch et al report was small,⁷ so we believe the use of heparin in such patients should be restricted because the risk of recurrent HIT is unknown.

Argatroban, which is also a direct thrombin inhibitor, may be a good alternative intraoperative anticoagulant for patients with HIT. It has been safely used as an anticoagulant in a variety of cardiovascular operations,² and because it does not resemble heparin, there is no cross-reactivity with HIT antibodies.⁸ Pharmacokinetic evaluation suggests that argatroban is easy to monitor and control, with little potential for overdosing or underdosing, regardless of age or renal function.⁹ The efficacy of argatroban is easily monitored by measuring activated clotting times, as was done in the present case. The dosages of argatroban required to achieve a variety of target activated clotting times have been documented² and more importantly, because argatroban has little potential for overdosing regardless of renal function, it can be safely used even in patients with renal dysfunction. In addition, it has been recently reported that argatroban anticoagulation can be used as treatment during an acute HIT episode.¹⁰ In that study, argatroban reduced new thromboses and achieved a more rapid rise in platelet counts in patients who were developing HIT, without increasing the bleeding risk. These findings support the safety of argatroban for HIT patients and indicate its

advantages over other anticoagulants.

In summary, when patients with a history of HIT undergo peripheral vascular surgery, argatroban, at a dose determined by titration of activated clotting times, is a viable anticoagulation substitute for heparin.

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