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Anticoagulation for Patients with Heparin-induced Thrombocytopenia Using Recombinant Hirudin During Cardiopulmonary Bypass

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Heparin-induced thrombocytopenia (HIT) is a common complication of heparin therapy. There are three types of HIT. In the majority of patients, thrombocytopenia is modest and resolves without sequelae (HIT I). In a smaller number of patients, the thrombocytopenia is severe (HIT II), and in still others, the thrombocytopenia is also associated with thrombosis (HITT). Administration of heparin to this latter group of patients causes platelet aggregation, thromboembolism, and thrombocytopenia. It is advisable that heparin not be administered in any form to patients with documented or suspected HIT II or HITT. This situation, of course, poses a problem for those patients requiring cardiopulmonary bypass (CPB) surgery. In this report, we summarize our experience with Lepirudin (Hoechst, Frankfurt Ammain, Germany), which is a recombinant hirudin (r-hirudin), as an alternative to heparin for systemic anticoagulation, as well as the use of the ecarine clotting time (ECT) for monitoring anticoagulation status during CPB.

Keywords: Anticoagulation; cardiopulmonary bypass; heparin; hirudin; recombinant; thrombocytopenia.

Case Report

Case #1

A 78-year-old male with a history of coronary artery disease (CAD) and coronary artery bypass graft (CABG) surgery 10 years prior to admission presented to a local hospital after 24 hours of intermittent chest pain unrelieved by rest. A diagnosis of myocardial infarction (MI) was made. The patient was treated with heparin, a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor, and aspirin, and transferred to our hospital the next day for further treatment. Past medical history included CAD, hypercholesterolemia, hypertension, and peripheral vascular disease. Past surgical history included CABG 10 years ago and left cervical endarterectomy 5 years ago. The patient had a history of cigarette smoking and a family history of CAD. On arrival, the patient's medications included metoprolol, atenolol, simvastatin, aspirin, and nitroglycerin. He had

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no known drug allergies. Coronary angiography showed triple vessel disease. The patient was scheduled for CABG surgery 4 days after admission. The patient's initial platelet was 129,000/mL but decreased to 89,000/mL 1 day after heparin therapy was initiated. Because of this decrease in platelet count, the heparin was discontinued and heparin-induced antibody tests were sent to the laboratory. The platelet count continued to decrease to 48,000/mL prior to surgery even after the heparin was discontinued. R-hirudin was initiated for anticoagulation, and the activated partial thromboplastin time (aPTT) was maintained between 1.5 to 2.5 times the normal values. The heparin-induced antibody test (ELISA test) was positive, and a diagnosis of HIT II was made.

The patient was brought to the operating room (OR) after standard preoperative medications were given. Standard monitors were placed, including radial and pulmonary arterial catheters. (All the pulmonary arterial catheters used in this report were heparin-coated, and the invasive catheters had no heparin or other anticoagulant in the solution.) General anesthesia was induced with midazolam (2 mg), sufentanil (210 ug), and vecuronim (7 mg). The r-hirudin infusion was continued. Anticoagulation for CPB was achieved with an additional bolus dose of 0.25 mg/kg r-hirudin 10 minutes prior to CPB followed by an infusion (0.15 mg/kg/hr). In addition, 0.20 mg/kg r-hirudin was added to the prime solution for the CPB circuit. During CPB, the ecarine clotting time was used to monitor anticoagulation. Intermittent r-hirudin bolus doses (15 mg) were necessary to maintain the ECT between 200 and 300 seconds. At the same time, activated clotting time (ACT) and aPTT were greater than 999 and 200 seconds, respectively. The r-hirudin infusion was discontinued after releasing the aortic cross-clamp. Total CPB time was 205 minutes. The patient tolerated separation from CPB with minimal inotropic support. The ECT returned to baseline 40 minutes after separation from CPB. Because this procedure was a redo CABG, intravenous (IV) low-dose regimen aprotinin (1.4 mg IV test dose, followed by loading dose of 140 mg IV over 20 min, 140 mg were added to CPB as "pump prime" dose, then 35 mg/hour IV constant infusion throughout the case) was used to minimize blood loss. No significant adverse effects were noted. The patient did not require r-hirudin administration after surgery. The total blood product utilization during the surgery were packed red blood cell (PRBC; 1200 mL), platelets (400 mL), cryoprecipitate (60 mL), and fresh-frozen plasma (FFP; 1200 mL). The total postoperative blood loss was 1,035 mL. The postoperative coagulation status was monitored using the aPTT, which returned to normal on postoperative day #2. The platelet value was 140,000/mL on postoperative day 7.

Case #2

An 80-year-old female with a history of atrial fibrillation and hypertension, was admitted to the hospital with bradycardia after a fall. After initial evaluation, a pacemaker was placed. In addition, an echocardiogram showed 3+ mitral valve regurgitation, and blood cultures were positive for *Staphylococcus aureus*. The patient was treated with ampicillin and gentamycin, and discharged to a skilled nursing facility for continued antibiotic treatment. She presented to the hospital 10 days later with shortness of breath, paroxysmal nocturnal dyspnea, and orthopnea. The admitting diagnosis was congestive heart failure (CHF) with pulmonary edema, atrial fibrillation, acute renal failure, anemia, urinary tract infection, and septicemia. During her hospital course, she developed bilateral DVT and she was treated with heparin. Her platelet count was noticed to decrease from 420,000/mL prior to heparin therapy to 47,000/mL 3 days later. HIT was suspected and heparin was discontinued. Because of the DVT, r-hirudin treatment was initiated. Coronary angiography showed occlusions of the right coronary artery (60%) and left anterior descending artery (30%). A repeat echocardiogram showed 3+ mitral valve regurgitation with posterior leaflet dysfunction and tricuspid valve regurgitation. Endocarditis was diagnosed and the patient was treated with vancomycin. Additional medications at that time included metoprolol, digoxin, lansoprozole, and lorazepam (Ativan). The patient was allergic to penicillin, atenolol, diltiazem, verapamil, and ciprofloxacin. Because of worsening CHF, an intra-aortic balloon pump was inserted. After the blood cultures were negative, the patient was taken to the OR for CABG and mitral valve replacement.

Patient was brought to the OR with her continuous r-hirudin infusion. After induction of general anesthesia, anticoagulation for CPB was achieved with a bolus dose of 0.25 mg/kg r-hirudin given 10 minutes prior to CPB followed by an infusion of 0.15 mg/kg/hr. R-hirudin (0.20 mg/kg) was added to the prime solution for the CPB circuit. During CPB, the ecarine clotting time was used to monitor anticoagulation. Additional r-hirudin boluses (5 mg) were necessary to maintain the ecarine clotting time between 200 and 300 seconds. At the same time the ACT and aPTT were greater than 999 and 200 seconds, respectively. The r-hirudin infusion was discontinued 1 hour prior to separation from CPB. The total CPB time was 129 minutes. The patient tolerated separation from CPB with minimal inotropic support. The postoperative coagulation status was monitored using the aPTT, which returned to normal on postoperative day 3. The total blood loss was 2,800 mL. The total blood product utilization during the surgery included PRBCs 1200 mL, platelets 400 mL, cryoprecipitate 30 mL, and FFP 1800 mL. The total postoperative blood loss was 1,175 mL. The patient's platelet count was 107,000/mL on postoperative day #1 and 161,000/mL on postoperative day 7.

Case #3

The patient was a 49-year-old male with a history of a large left renal mass with a thrombus in the inferior vena cava (IVC) extending to the right atrium. The patient was treated with heparin to prevent embolism. On day #3 of heparin therapy, the patient's platelet decreased from 283,000/mL to 87,000/mL. Laboratory evaluations showed the presence of antibodies to unfractionated and

low-molecular weight heparin. The patient was then changed to r-hirudin for anticoagulation. The platelet count increased to 128,000/mL on the day of surgery for resection of renal mass and thrombus. General anesthesia was induced with sufentanil, etomidate, and pancuronium. Anticoagulation for CPB was achieved with a bolus dose of 0.25 mg/kg r-hirudin 10 minutes prior to CPB followed by a 0.15 mg/kg/hr infusion and 0.20 mg/kg added to the prime solution for the CPB circuit. During CPB, the ecarine clotting time was used to monitor anticoagulation. Intermittent r-hirudin bolus doses (25 mg) were necessary to maintain the ecarine clotting time between 200 and 300 seconds. At the same time, ACT and aPTT were greater than 999 and 200 seconds, respectively. The r-hirudin infusion was discontinued at the time of separation from CPB. The total CPB time was 234 minutes. The patient tolerated separation from CPB with minimal inotropic support. The aPTT returned to normal on postoperative day #1. The platelet count was 58,000/mL on postoperative day #1, 133,000/mL on postoperative day #2, and 209,000/mL on postoperative day #7. The total blood product utilization during surgery included PRBCs 1500 mL, platelets 400 mL, and FFP 1100 mL. Postoperatively, the case was complicated by abdominal surgical bleeding. The patient was returned to surgery to stop the bleeding. The total postoperative blood loss was 2,620 mL (chest-tube drainage: 600 mL). The patient developed fevers and arrhythmia postoperatively, and r-hirudin was again used for anticoagulation. The aPTT was used for monitoring. The patient died from a cardiac arrest on postoperative day #19 secondary to the refractory arrhythmia.

Discussion

Heparin-induced thrombocytopenia type II (HIT II) and heparin-induced thrombocytopenia with thrombosis (HITT) are life-threatening complications of heparin therapy.[1–6] This syndrome is immunoglobulin G (IgG)-mediated. After IgG binding, platelets aggregate and become activated, producing disseminated thrombosis, embolism, and profound thrombocytopenia. The diagnostic criteria for heparin-induced thrombocytopenia (HIT) include thrombocytopenia during heparin therapy, absence of other causes of thrombocytopenia, resolution of thrombocytopenia after discontinuation of heparin, and confirmation of a heparin-dependent platelet antibody by in vitro testing.[7] The reported incidence of HIT II varies from 1% to 30% of surgical patients.[8] An incidence of approximately 1% has been reported in patients undergoing cardiac surgery.[9] In contrast, HIT I, which is a process of heparin-induced microaggregation of platelets, is a clinical diagnosis and heparin-dependent platelet antibody studies are usually negative. There is no need to discontinue or avoid future heparin because the process is self-limited.[10] Patients with CAD and peripheral vascular diseases who are treated with heparin for anticoagulation may develope HIT II. For these patients, subsequent anticoagulation with heparin for CPB poses a problem. An alternative anticoagulant is required so as to prevent thromboembolism and bleeding in those patients.[1]

Recombinant hirudin is a yeast-derived recombinant form of the natural anticoagulant hirudin, a 65 amino acid compound produced in trace amounts by the European medicinal leech. Recombinant hirudin is identical to natural hirudin except for the substitution of leucine for isoleucine at the N-terminal end of the molecule, and the absence of a sulfate group on the tyrosine at position 63.[11] It is a highly specific direction inhibitor of thrombin.[1] Unlike heparin, its mechanism of action is independent of antithrombin III.[5] One molecule of r-hirudin forms a tight stoichiometric complex, with one molecule of thrombin including thrombin trapped within established clots, thus neutralizing its thrombogenic activity.[7] All thrombin-dependent coagulation assays are affected. The aPTT values increase in a dose-dependent fashion.

Unlike heparin, r-hirudins are not inhibited by platelet factor 4. No antagonists to direct thrombin inhibitors are known. R-hirudin is administered intravenously. The initial dose for CPB is 0.25 mg/kg[3,5] followed by an infusion of 0.15 mg/kg/hr.[7] The pharmacokinetic properties of r-hirudin can be described by a two-compartment model. Its distribution is confined to extracellular fluids, with an initial distribution half-life of approximately 10 minutes. The metabolic pathway of r-hirudin has not been firmly established to date. It is thought that catabolic hydrolysis of the parent drug causes release of amino acids. Systemic clearance is proportional to the glomerular filtration rate. Clearance is approximately 25% lower in women than in men, and approximately 20% lower in the elderly when compared with young adults. About 48% of an r-hirudin bolus is excreted in the urine, of which 35% is unchanged drug. Elimination of r-hirudin follows first-order process. The elimination half-life is approximately 1.3 hours in young healthy volunteers and can be prolonged up to 2 days for patients with renal failure.[2,12,13]

Three different methods have been used to monitor anticoagulation by r-hirudin during CPB: ACT, aPTT, and ECT.[3,14] The ecarine clotting time is based on the fact that the snake venom enzyme, ecarin, converts prothrombin to meizothrombin, which has a weak coagulant activity. Meizothrombin is neutralized by hirudin, resulting in a dose-dependent prolongation of clotting time. Studies have demonstrated that the ECT has a linear correlation with plasma hirudin concentrations, whereas both the ACT and aPTT had poor correlations.[3] The method we used was a standardized ECT test using Pharmanetics (Morrisville, NC). Although this method has not been approved by the U.S. Food and Drug Administration (FDA), it has been suggested for compassionate use in certain situations. In order to validate this method, we correlated our results with recovery studies using *in vitro* spiked plasma with hirudin to determine whether there is a linear response with this method, and whether there is a correlation between the "therapeutic level" of hirudin and ecarine clotting time results. The answers to the two questions were yes. This method has also been tested and shown to have a correlation with r-hirudin level.[15] In our cases, ecarine clotting time was maintained between 200

and 300 seconds during CPB. At the same time, the ACT and aPTT were greater than 999 and 200 seconds, respectively. Recombinant hirudin combined with monitoring of ECT was a safe, effective, and easily managed anticoagulant technique in the cases reported here. Although there are no documented interactions between the ECT and aprotinin usage, aprotinin has been used in combination with r-hirudin during CPB, with no significant adverse effects noted in our cases.

Bleeding is the major risk associated with use of lepirudin, including intracranial, retroperitoneal, and gastrointestinal bleeding. The preexistance of such bleeding is an absolute contraindication for the use of r-hirudin. Other relative contraindications include cerebral aneurysm, coagulopathy, diverticulitis, hemophilia, lumbar puncture, peptic ulcer disease, spinal anesthesia, stroke, and thrombolytic therapy.*,†,[16,17] Before initiation of therapy, coagulopathy should be ruled out. Formation of antibodies against r-hirudin is observed in approximately 56% to 74% of treated patients.[18,19] This action has not been associated with allergic reactions or neutralization of its activity. However, it may increase the anticoagulant effect of r-hirudin due to delayed renal elimination of active hirudin-antihirudin complexes. It is important that the dosage be adjusted according to the aPTT and/or ecarine clotting time. In this report, the blood product use was greater than is seen in our usual cases. This finding can be explained by the nature of the diseases, the length of bypass time, and the transfusion protocol of this institution (the transfusion protocol at the end of CPB surgery was Hct: 30%, platelet: 100,000/mm^3, and fibrinogen: 200 mg%).

In our limited experience, we consider that r-hirudin combined with ecarine clotting time monitoring is a safe and effective method in the management of anticoagulation during CPB for all three patients with HIT II described in this report. ACT and aPTT were also used during CPB to monitor the anticoagulant status, but gave less accurate readings. Aprotinin can be used in combination with hirudin with no noticeable adverse effects in the patient in this report who received aprotinin. The aPTT is an effective method for monitoring the patient's coagulation status postoperatively.

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†Product information Refludan®, lepirudin. Kansas City, MO: Hoechst Marion Roussel, 1998.