Bivalirudin as an Alternative Anticoagulant in Cardiopulmonary Bypass in Patients with Heparin-Induced Thrombocytopenia (HIT)

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Background

Heparin is an anticoagulant commonly used for the prevention of thrombosis in interventional cardiology procedures, acute coronary syndrome, renal dialysis, and surgical procedures (including cardiac, vascular, and plastic surgery). The quick onset and rapid reversibility of its anticoagulant effect, in addition to its low cost make it the current anticoagulant of choice for short-term anticoagulation.

Heparin-induce thrombocytopenia (HIT) is an antibody-mediated reaction, which can result in arterial-venous thrombosis. The true incidence of HIT is unknown but is estimated to be around 3% (higher incidence with bovine lung versus porcine intestinal preparations). The diagnosis requires a high index of suspicion and depends on the following criteria: (1) thrombocytopenia (decrease ≥ 50%) on heparin therapy, (2) absence of other causes of thrombocytopenia (drugs, infection, etc.), (3) confirmation of heparin-dependent platelet antibody (IgG), and (4) resolution of the thrombocytopenia after discontinuation of heparin. The pathogenesis of HIT involves the binding of a heparin-platelet factor epitope to the HIT antibody (figure 1). This complex activates platelets to release procoagulant particles and induce endothelial tissue cells to produce clots. Diagnostic tests for HIT involve detecting antibodies against the heparin-platelet factor complex and the platelet activation assay. The typical onset of thrombocytopenia occurs within 4 days of initiating heparin but can be as rapid as 10 hours in patients with the HIT antibody who are re-exposed to heparin. HIT antibody is present for a mean of 85 days after a thrombocytopenic episode and is virtually undetectable after 100 days (figure 2). Because of the transient nature of this antibody, HIT does not recur more quickly or more often in a patient with previous HIT who is re-exposed to heparin if the antibody and activation assay are negative.

Thrombocytopenia and thrombosis within the arterial-venous system are the main clinical features of HIT. The high morbidity (40-80%) and mortality (>20%) mandates immediate treatment to include stopping heparin and avoiding heparin re-exposure (i.e. flush solutions, heparin-coated lines, etc.), giving a rapidly acting non-heparin anticoagulant to reduce thrombotic complications (low molecular weight heparin cross-reacts with the HIT antibody), and adjunctive therapies in specific situations (e.g. surgical thrombectomy).
Alternatives to heparin anticoagulation have included low molecular weight heparin, non-heparin anticoagulants (e.g. ancrod and danaparoid), and direct thrombin inhibitors (e.g. hirudin, lepirudin, bivalirudin, argatroban).

Thrombin is involved in multiple biological activities (e.g. coagulation, fibrin formation, platelet activation, and endothelial effects) and was targeted to prevent its cascade effect. **Hirudin** is an irreversibly binding direct thrombin inhibitor (DTI) isolated from the medicinal leech. The lack of a reversing agent, a characteristic of all direct thrombin inhibitors, and its antigenic potential led to the creation of lepirudin using recombinant yeast technology. **Lepirudin** interacts with both the fibrinogen-binding and catalytic sites of thrombin (completely inhibits all procoagulant actions of thrombin). Lepirudin undergoes renal elimination. Ecarin clotting time (ECT) is used to measure lepirudin effect instead of activated clotting time (ACT) because ECT reflects lepirudin concentration during CPB more accurately than ACT. ECT is not routinely performed and a special FDA humanitarian device exemption is needed.

Unlike hirudin/lepirudin, **argatroban** is a reversible-binding direct thrombin inhibitor synthetically derived from L-arginine. It has a short half-life (<50 min), undergoes hepatobiliary excretion (better suited for patients with renal insufficiency), and has a dose-dependent effect on aPTT and ACT. Because of its predictable pharmacokinetic and pharmacodynamic profile, argatroban has been used successfully in antithrombin deficient and HIT patients undergoing heart surgery. As with all thrombin inhibitors, no specific agent exists for reversal of anticoagulation.

**Bivalirudin** is a 20 amino acid synthetic peptide modeled after hirudin. It has a short half-life (<25 minutes) in patients with normal renal function and undergoes enzymatic degradation by proteolytic enzymes in the plasma (slowed with hypothermia). The enzymatic degradation in plasma presents a potential problem during surgery since stagnant blood in the surgical field or extracorporeal circuits can clot due to local bivalirudin metabolism (protease metabolism → decrease local bivalirudin levels → clot formation). Clearance of bivalirudin is reduced by about 80% in dialysis-dependent patients. Hemofiltration can remove up to 70% of circulating bivalirudin from treated blood and can be employed in patients with renal insufficiency. Monitoring of bivalirudin is challenging as neither the ACT or PTT are suitable monitoring tests at the relatively high bivalirudin concentrations needed for CPB. A plasma bivalirudin level of 10 – 15 µg/ml adequately suppresses fibrin formation and fibrinopeptide A formation within the CPB pump. ECT monitoring is preferred but the use of the kaolin ACT appears to correlate well with plasma levels and is unaffected by aprotinin. As with all current DTI, there is no known reversal agent. For this reason, it is expected that patients may experience more than the usual amount of post-operative bleeding. It is also not possible to monitor the PT/PTT/INR while the patient is still anticoagulated with bivalirudin.

**The Procedure**

**Preoperative Preparation**

The attending surgeon and/or chief cardiothoracic surgical fellow will notify the attending anesthesiologist, *Terry Gernsheimer* (or if unavailable, the attending hematologist on call), and the scheduled perfusionist that a HIT patient is scheduled for cardiac surgery AS SOON AS POSSIBLE. The laboratory medicine resident in the clinical coagulation lab at UWMC (598.6242) should be notified that bivalirudin levels should be needed to follow bivalirudin anticoagulation.
Preoperative blood order – the surgical team will order 10 units packed red blood cells and 6 units fresh frozen plasma. The anesthetic team should verify the presence, or imminent arrival, of the products at UW prior to anticoagulation.

Bivalirudin availability – the anesthetic team should contact OR Pharmacy regarding the use of bivalirudin for CPB. During satellite pharmacy hours (0600 – 1800), contact the pharmacist (206.598.4194) and inform them that bivalirudin is requested. During nights and weekends, contact the main hospital pharmacy (206.598.4999) and request “Bivalirudin for OR” to be mixed (250 mg bivalirudin in 250 ml normal saline) and delivered as soon as possible.

Perfusion should be reminded not to use heparin-bonded circuits and to remove all heparin from their cart prior to the patient entering the room.

All heparin should be removed from the anesthesia syringe pack and cart prior to bringing the patient into the room (all flush lines for monitoring are heparin-free). Additionally a standard heparin coated pulmonary artery catheter should NOT be used.

**Anticoagulation Protocol**

Before initiation of CPB, the perfusionist is to add 50 mg of bivalirudin to the CPB circuit regardless of patient weight or the pump prime volume.

The anesthesiologist will administer bivalirudin according to the following:

- 1.0 mg/kg intravenous (IV) bolus
- 2.5 mg/kg/hr IV infusion immediately following bolus
- infusion rates may be increased or decreased in 0.25 mg/kg/hr increments and/or boluses of 0.25 mg/kg may be administered to maintain a bivalirudin level of 10-15 µg/ml

The bivalirudin infusion shall be discontinued when it is estimated that 15 minutes remain prior to the discontinuation of cardiopulmonary bypass (CPB). If CPB is not terminated within 20 minutes following discontinuation of the infusion, an additional bolus of 0.5 mg/kg of bivalirudin is to be delivered and the infusion restarted at 2.5 mg/kg/hr until CPB is terminated.

At the termination of CPB, a bivalirudin bolus of 50 mg will be added to the pump and the pump will be kept in a “recirculation mode” with an infusion of 50 mg/hr.

**Hemostasis Monitoring and Transfusion**

After delivery of the bivalirudin bolus, the perfusionist will monitor bivalirudin levels at 5 minutes and then every 30 minutes throughout CPB (bivalirudin monitoring shall be performed by the OR satellite lab and the results faxed to the OR directly). The perfusionist will monitor the ACT every 15 minutes.

An emergency hemostasis panel and thromboelastogram (TEG) will be performed 30 minutes prior to coming off CPB. For platelet counts <100,000 per µl or anticipated to be <100,000 per µl, order 1 unit of apheresis (preferred) or 6 units pooled platelets. The platelet count will be maintained at
>100,000 per µl until the bivalirudin level has dropped to less than 1 µg/ml and the ACT has returned to normal values.

The platelet count should be rechecked every 30-60 minutes while there is continued bleeding.

It should be noted that blood stagnation in the surgical field will lead to localized breakdown of bivalirudin and clot formation may occur. This does not indicate subtherapeutic bivalirudin levels and ACT values. The half-life of bivalirudin is roughly 20-25 minutes but can be prolonged in patients with renal insufficiency or hypothermia.

Transfusion for bleeding diathesis is no different than other CPB procedures utilizing heparin anticoagulation. Platelets should be maintained >100,000 per µl or higher if microvascular bleeding (“oozing”) is present. Notification of the transfusion attending is important to maintain open lines of communication.

When transferring the patient to the CTICU, notify the nurse and CTICU resident on-call that bivalirudin was utilized and to be especially vigilant of the chest tube drainage. Additionally, inform the staff of the amount of blood and blood products available in transfusion support services.

### Bibliography


Illustrations

Figure 1. Pathogenesis of HIT

Figure 2. Temporal Aspect of Heparin/Platelet Factor 4 (IgG) Antibody