

## Case Report

# *The Emergency Use of Recombinant Hirudin in Cardiopulmonary Bypass*

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### ABSTRACT

The most common anticoagulant used for cardiopulmonary bypass is heparin. An alternate form of anticoagulant therapy is needed for patients who have immune-mediated heparin-associated thrombocytopenia (HIT). Thrombocytopenia causes bleeding and may lead to serious arterial and venous thrombosis. HIT or heparin-induced thrombocytopenia with thrombosis type II (HITT) are both described as adverse reactions to heparin. They are diagnosed with a platelet count less than a 100,000/mcl for 2 consecutive days. HITT, the severe form, is characterized with the thrombocytopenia in combination with thromboembolic complications, such as strokes, myocardial infarctions, and limb ischemia. Two cases are presented in which r-hirudin was used for anticoagulation for aortocoronary bypass surgery and mitral valve replacement. The activated partial prothrombin time (aPTT) was used to monitor coagulation. In the first case, the aPTT was maintained greater than 100 seconds, and at the termination of cardiopulmonary bypass, some clot was noted in the cardiopulmonary bypass circuit. In the second case, a longer cardiopulmonary bypass run was anticipated, the hirudin bolus and infusion rate were increased, and the aPTT was maintained at greater than 200 sec. Adequate coagulation resulted, and, at the end of bypass, no clot was noted. These case studies seem to suggest a higher dosage of r-hirudin may be required for the use of cardiopulmonary bypass and a need to maintain aPTT values greater than 200 sec to help monitor anticoagulation.

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## INTRODUCTION

Complications derived from the use of heparin are immune-mediated heparin associated thrombocytopenia (HIT) and heparin-induced thrombocytopenia type II (HITT). HIT occurs when the patient has been previously exposed to heparin or on chronic heparin therapy. Heparin binds to platelets and may inhibit platelet aggregation or may function as a platelet aggregating antagonist (1). HITT, type II, is present in the plasma as antiheparin immunoglobulin G (IgG). The IgG binds to repeating antigenic determinants of heparin and to the platelet surface epitopes (2). The IgG binding brings forth a platelet-release reaction, and subsequent aggregation contributes to profound thrombocytopenia and thrombosis (2). The differentiating symptoms between HIT and HITT are that type II is less at risk of bleeding than of having thromboembolic complications, exposing the patient to crippling disabilities or even death (3).

Recombinant(r) hirudin is a potent thrombin inhibitor, developed from the leech (*Hirudo medicinalis*) salivary gland (4). Hirudins are small anticoagulant proteins of 65 to 66 amino acids that inhibit thrombin (5). Their short duration restricts their use to intravenous therapy only. The major risk in using r-hirudin is hemorrhage, because there is no available antagonist (6). The biosynthetic molecule lepirudin is identical to natural hirudin except for 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. R-hirudin is a direct thrombin inhibitor and, in contrast to heparin, does not require antithrombin III as a cofactor (7). One molecule of r-hirudin binds to one molecule of thrombin and blocks the thrombogenic activity of thrombin, thus affecting all thrombin-dependent coagulation assays, making the celite-induced activated clotting time ineffective. An alternative approach to monitoring the coagulant effect of r-hirudin is required. Current literature suggests monitoring r-hirudin with a plasma-based ecarin clotting time (ECT), and in addition, or by itself, an aPTT (8). It has also been suggested, in addition to these tests, to obtain lepirudin plasma concentrations with a therapeutic range of 4.0 and 5.0  $\mu\text{g/ml}$  (9, 10).

Refludan<sup>a</sup> (lepirudin), an r-hirudin used in these patients, is approved by the U.S. Food and Drug Administration for use as an anticoagulant for patients with heparin-induced thrombocytopenia and associated thromboembolic disease to prevent further thromboembolic complications. R-hirudin is not indicated as an anticoagulant during cardiac surgery, although several published articles refer to the use of r-hirudin as an anticoagulant during coronary artery bypass surgery and aortic valve replacement (3, 9, 11). The dosage for r-hirudin suggests an initial intravenous bolus of 0.4 mg/kg with a continuous infusion of 0.15/kg per hour (Refludan drug insert). The drug insert

literature suggests the infusion rate should be adjusted to keep the aPTT at 90–150 sec. In cardiac surgeries, r-hirudin dosing includes priming of the heart–lung bypass machine with 0.25–50 mg/kg, with additional bolus doses to maintain r-hirudin plasma levels above 2.0 to 2.5  $\mu\text{g/ml}$  (3, 8, 9).

We present the utilization of r-hirudin on an emergent basis to analyze the recurring situation of HITT patients requiring cardiac surgery. This dire event calls for immediate therapy; however, options available are not standardized. Currently, only a few reports exist on use of the thrombin inhibitor r-hirudin. This article addresses a clinically feasible management approach while reviewing anticoagulation and anticoagulation monitoring for the challenging HITT patient requiring cardiopulmonary bypass.

## MATERIALS AND METHODS

### PATIENT HISTORIES

Two patients requiring urgent cardiac surgery presented to our institution with the diagnosis of HITT. The first case study is a 59-year-old, 103 kg male with unstable angina, peripheral vascular disease, and hyperlipidemia. Catheter studies showed a three-vessel coronary artery disease. The patient had a history significant for HITT, which he developed after aortobifemoral bypass graft surgery. Treatment with heparin ended when thrombosis resulted in a left below the knee amputation.

The second patient is 62-year-old, 143 kg male with severe mitral valve regurgitation. The patient had undergone a previous coronary artery bypass grafting/mitral valve replacement 71 days before this operation. The earlier surgery required two periods of circulatory arrest and deep hypothermia. The post-operative period with this surgery was complicated by renal insufficiency, prolonged mechanical ventilation requiring tracheostomy, and inotropic support. During this period, the patient's platelets decreased, reaching 36,000/  $\text{mcl}$ . He also developed signs of deep vein thrombosis, and therapeutically was put on heparin. Continued thrombi occurred in the left axillary subclavian and popliteal and common femoral veins. Heparin was discontinued, and the diagnosis of HITT was established.

### ANTICOAGULATION PROTOCOL

The drug r-hirudin was used as an anticoagulant in these patients. In both cases, an initial intravenous bolus of hirudin was given, and the cardiopulmonary bypass circuit was primed with 25 mg of r-hirudin. Intravenous maintenance drips of r-hirudin were given to keep the aPTT within anticoagulant range. In the first case, an initial bolus of 25 mg was given before cardiopulmonary bypass, and an intravenous infusion drip of 0.15 mg/kg/h was given throughout cardiopulmonary bypass. Follow-up boluses of r-hirudin were not given. The infusion drip of r-hirudin was stopped at the end of cardiopulmonary bypass, and the r-hirudin was allowed to wear off.

In the second case, the patient had renal failure with a creatinine of 2.2. In accordance with product information, a pa-

a Hoechst Marion Roussel, Inc., Kansas City MO

tient with renal impairment (creatinine of 2.1–3.0), the bolus dose should be reduced to 0.2 mg/kg body weight. An initial bolus of 25 mg was given. This dose approximated the recommended 143 kg man dose by weight with a 70% reduction for renal insufficiency. An intravenous infusion drip of 0.05 mg/kg/h of r-hirudin was started (30% reduction for renal impairment). Then, 15 minutes after the onset of cardiopulmonary bypass, an additional bolus of 5 mg of r-hirudin was given because of an aPTT of 143 sec. The cardiopulmonary bypass run required no further boluses of r-hirudin. Two hours and fifteen minutes after the initial bolus of r-hirudin, the infusion drip was decreased to 0.02 mg/kg/h. This was done to aid with decreasing the blood levels of r-hirudin, because the end of the bypass was approaching. As in the first case, the infusion drip was stopped at the end of cardiopulmonary bypass, and the hirudin was allowed to wear off.

To prevent the patients from receiving pump prime with r-hirudin, no extracorporeal prime was given to the patients at the end of cardiopulmonary bypass.

#### **ANTICOAGULATION MONITORING**

The use of the cardiopulmonary bypass machine in cardiovascular surgery requires an anticoagulation monitoring system that is easy to use and reliable. Based on the results of several study trials, the aPTT has been introduced to measure the anticoagulant effect of r-hirudin; however, it has been shown that the aPTT is not adequately sensitive to provide accurate measurement of r-hirudin in larger doses (12). Accurate measurement of r-hirudin can be obtained with thrombin-based chromogenic assays (8). These tests require special laboratory equipment and presently are not available commercially. An alternative clotting assay, the ECT assay, has been shown to be suitable for r-hirudin measurement within a range of 0.2 and 2  $\mu\text{g/ml}$  (13). Unfortunately, this test is not available at all institutions, and in life-saving circumstances, the facilities available dictate the tests used. The aPTT was used to monitor the anticoagulation effect of r-hirudin in these cases. Necessary equipment to perform such other tests as the ECT or lepirudin plasma concentrations were unavailable. In both cases, the aPTT was run in 15-min intervals. In the first case, the aPTT results were read in the range greater than 100 sec.

In the second case, the aPTT results were read at a higher range of greater than 200 sec. Notifying the laboratory of the need for a higher range accomplished this. The laboratory uses the instrument MLA 1600 to run the aPTTs. If values greater than 200 sec are required, the instrument will automatically redo tests reading greater than 100 sec; if the results are between 100 and 200 sec, a number will be reported. If the results are greater than 200 sec, the term, long no clot detected (LNCD) will be reported. This will automatically receive a greater than 200 sec result. If the laboratory is not notified of the need for a greater than 200 sec result, all results will be reported greater than 100 sec regardless of whether they are greater than 100 sec or greater than 200 sec.

## **RESULTS**

In the first case, after the initial bolus of r-hirudin and the start of the infusion drip and the cardiopulmonary bypass, all aPTTs were greater than 100 sec, and no follow-up boluses were given. Changes in blood thickness or clot formation were not noted during the hypothermic period (28–32°C) of cardiopulmonary bypass. However, during the rewarming phase (temperature greater than 32°C), an increase in the blood thickness was noted by the perfusionist (e.g., as milk is to pudding), but there was no evidence of clot. The aPTTs at this time remained greater than 100 sec. After full rewarming, cardiopulmonary bypass was terminated as soon as possible. The patient tolerated removal from cardiopulmonary bypass on the first attempt without inotropic support. After termination, the extracorporeal circuit was examined, and there was clot throughout the circuit from the venous hardshell reservoir to the outlet of the membrane oxygenator. No visible clot was present in the arterial filter. Cardiopulmonary bypass time was 79 min. No sequelae occurred from the clots in the circuit after the patient came off cardiopulmonary bypass. Postoperatively, on arrival in the ICU, the patient's aPTT was 60.3 sec. The patient was discharged to home on postoperative day 9 in stable condition.

In the second case, because of the experience of clot in the bypass circuit post cardiopulmonary bypass, the aPTTs were set to run greater than 200 sec. Every 15 min, an aPTT was run, with results ranging greater than 200 sec. Cardiopulmonary bypass time was 297 min. The patient tolerated separation from cardiopulmonary bypass poorly; he required inotropic support for poor left ventricular function. Twenty minutes after removal of cardiopulmonary bypass, the aPTT was 150 sec (Figure 1).

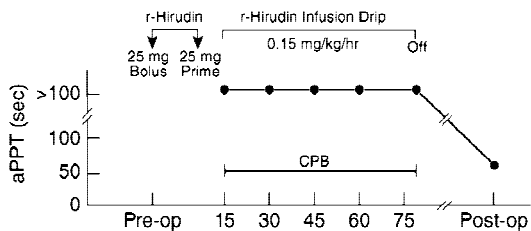
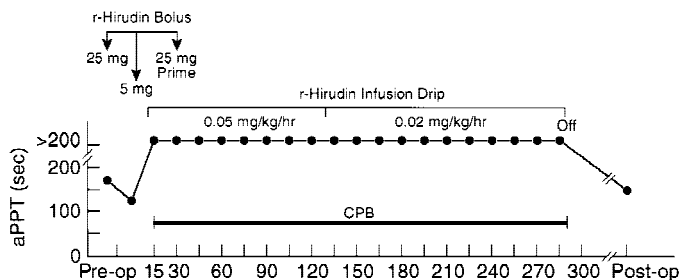
Postoperatively, there was no bleeding, but the patient continued to have cardiovascular compromise, hypotension, and inadequate end organ perfusion. The patient died 24 hours after surgery from profound cardiovascular failure, unrelated to bleeding complications or the use of r-hirudin.

## **DISCUSSION**

The use of r-hirudin in emergency cardiopulmonary bypass allows patients with HITT to have required surgery. Some guidelines can help the perfusionist administer patient care effectively when r-hirudin is used in cardiovascular surgery.

#### **DOSING**

Several studies have shown dosage options for a patient on cardiopulmonary bypass. One used an initial bolus of 0.2 mg/kg, with a maintenance intravenous drip of 0.1 mg/kg/h to maintain the aPTT between 60–80 sec (14). Once the desired aPTT was obtained, the infusion was stopped, and a bolus regimen of r-hirudin was used to avoid accumulation (14). The cardiopulmonary bypass circuit was primed with 5 mg of r-

**A. Patient 1****B. Patient 2**

**Figure 1: Patient 1 received the recommended dosage. All aPTTs were greater than 100 sec. At the end of cardiopulmonary bypass, there was clot in the circuit. Patient 2 received the recommended dosage for renal impairment. The patient came off bypass without clots in the circuit or increased postoperative bleeding even with the long pump run.**

hirudin, and additional boluses were given throughout surgery to maintain aPTT levels (9). Another case study reported a 50-mg IV bolus 20 min before cardiopulmonary bypass, with a secondary bolus of 5-mg IV bolus after 10 min of cardiopulmonary bypass (10). The cardiopulmonary bypass circuit was primed with 25 mg of r-hirudin, and the aPTT ranged from 150–500 sec (10). The appropriate dosing for cardiopulmonary bypass is unclear. Although a higher dose may be required to ensure adequate anticoagulation with exposure to cardiopulmonary bypass machine, underdosing may produce dangerous thrombotic results.

**HEPARIN-COATING**

In HITT, any form of patient–heparin contact, including use of heparin-bonded catheters and heparin-flush, will precipitate a thrombotic event (15). In our first case, all disposable equipment was examined to eliminate the use of heparin-coated products; inadvertently, an arterial filter coated with heparin was used. It appeared that no leeching out of the heparin occurred during the case, and the patient suffered no ill effects.

**aPTT USAGE**

Use of an accurate monitoring system to evaluate anticoagulation can be obtained with the ECT and measuring lepirudin plasma concentrations (8). aPTT in conjunction with ECT has also been a reliable form of monitoring (8). If availability of equipment permits the aPTT to be the only monitoring tool, then knowledge of the pitfalls of the aPTT might help to pro-

vide a less problematic cardiopulmonary bypass run. The aPTT may not give adequate information for overdosing, but would provide enough information to prevent underdosing. The initial bolus before cardiopulmonary bypass will start the anticoagulation process, and the priming dose in the circuit helps to maintain the levels. An intravenous infusion of r-hirudin helps to maintain levels. The use of subsequent boluses can increase lowering levels if a drop in the aPTT is noted.

**RENAL FUNCTION**

The short half-life of hirudin (1.3 h) and good kidney function of the patient will help the plasma concentrations fall rapidly at the end of cardiopulmonary bypass. To aid patients with renal failure, or, in the event of overdosing, it is possible to lower the r-hirudin plasma level quickly and effectively by means of hemofiltration (9). Use of diuretics can also aid with the decreasing of plasma levels of r-hirudin. Returning unused pump prime to the patient should be limited if plasma concentrations of r-hirudin are unknown.

**COMMUNICATION**

Communication can be vital in a case that varies widely from standard cardiovascular surgery. Preparation for such cases requires teamwork to address and diminish the difficulties that might occur in such a surgical case. The surgeon and the perfusionist must discuss the complexity of the surgery and the anticipated length of cardiopulmonary bypass. The pharmacy should be notified of the impending need for r-hirudin and ensure drug availability. The laboratory should be notified well in advance to be aware of the frequency of aPTT tests needed and the higher range of results required. Communication between team members is essential to ensure the patient will have the best possible care.

In conclusion, the treatment strategies for a patient using r-hirudin on cardiopulmonary bypass are as follows:

1. communication between key personnel to establish mode of care;
2. preparation for the patient with renal failure, including changing the dose of r-hirudin (appropriate for renal impairment) and utilizing the use of diuretics and/or the hemoconcentrator;
3. monitoring anticoagulation with the best option available to the hospital. If aPTTs are used run every 15 min at a higher range result; observe the blood for increased thickness and the circuit for clots, especially while rewarming;
4. use recommended dosage of r-hirudin, taking into account past reports of this drug in cardiac surgery; adjust dosing according to the patient's history and weight; use bolus doses to raise blood levels of r-hirudin and an infusion drip to maintain anticoagulation during cardiopulmonary bypass; stop intravenous infusion after bypass to aid plasma concentrations to drop; do not return unused pump prime to the patient; and

5. examine disposable equipment for heparin coating and eliminate such coating, if present.

The results of these case studies showed us that even with the recommended aPTT of greater than 100 sec, we had clot in the cardiopulmonary bypass circuit. A rise in the range of the aPTT results and an increase in the dosing of r-hirudin (taking into account the patient's renal impairment) enhanced our ability to maintain anticoagulation. Our experience in these cases helped us to broaden our scope of care with HITT patients.

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