

Case Report

The Use of r-Hirudin During Cardiopulmonary Bypass in a Patient with Heparin Induced Thrombocytopenia

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ABSTRACT

Heparin-induced thrombocytopenia and its related complications can be life-threatening in patients undergoing cardiopulmonary bypass (CPB) with heparin exposure. While the literature illustrates many different techniques which might be employed in this situation, most are used infrequently. This case report provides an overview of the successful use of r-Hirudin, and associated monitoring techniques, in a high-risk patient undergoing cardiac surgery utilizing CPB.

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INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immunological response that occurs when specific heparin-dependent IgG antibodies found in the plasma bind to heparin and the platelet membrane (1, 2, 3). This IgG binding causes aggregation and degranulation of platelets resulting in a variety of clinical scenarios ranging from profound asymptomatic thrombocytopenia to catastrophic intravascular coagulation (4, 5). The incidence of HIT is estimated to occur in about 1.3% of all cardiac surgery patients, although the appearance of detectable antibodies is thought to be more frequent (4, 5). It therefore requires careful consideration, particularly since many patients receive repeated exposure to heparin during multiple interventions prior to having cardiac surgery utilizing cardiopulmonary bypass (CPB). If not recognized and treated appropriately, HIT can be lethal (4, 6). Also, consideration should be given to the possibility of anticoagulating patients with known HIT with alternatives to heparin (6, 7).

Hirudin is an antithrombotic substance found in the salivary gland of the medicinal leech (8, 9). It is a potent and specific inhibitor of thrombin, thereby affecting all thrombin-dependent coagulation assays. Unlike heparin, it works independent of antithrombin III, and is little affected by platelet factor 4 (8, 9). Recombinant hirudin (r-Hirudin) is cultured from yeast cells, and has a molecular weight of 6979.5 daltons. The elimination half-life is 30–60 mins. provided renal function is normal, and may be augmented by hemofiltration (5, 9). The volume of distribution is 9–17 L, and it is primarily confined to the extracellular space following intravenous administration (8, 9). Clearance is 170–2230 ml/min with the anticoagulant effect lasting approximately 40 mins. (8, 9). R-meizothrombin can be used as a reversal agent if overdosing occurs (10).

While the literature documents many possible alternative methods to conduct CPB on a patient with HIT, r-Hirudin is a practical option due to its unique properties.

CASE DESCRIPTION

A 56 year-old male with chronic coronary artery and obstructive pulmonary disease underwent coronary artery bypass in 1991. Subsequently he presented with intermittent angina pectoris after suffering an acute myocardial infarction. A cardiac catheterization was performed which demonstrated compromised left ventricular function with an ejection fraction of 25% and extensive coronary artery disease, with all previous bypass grafts occluded. The anterior descending coronary graft was reopened and stented. A heparin drip was initiated, and his platelet count dropped to 5000/ μ L. Due to the rapid decline in platelet number, the diagnosis of HIT was considered and the heparin drip was discontinued. He then underwent a bone marrow biopsy to rule out a possible stem cell proliferation de-

range, and the bone marrow examination was negative. After his platelet count gradually returned to normal he was evaluated for possible repeat coronary artery bypass grafting.

The patient's preoperative evaluation documented the following: Hgb 11.1 g/dL; Hct 33.0%; BUN 17 mg/dL; CREAT 1.1 mg/dL; Plt 312 thou/ μ L; activated partial thromboplastin time (aPTT) 26.2 sec; prothrombin time (PT) 14.0 sec; international normalized ratio (INR) 1.0; activated clotting time (ACT) 123 sec; glucose 92 mg/dL; Na⁺ 136 mEq/L; K⁺ 4.9 mEq/L; Cl⁻ 105 mEq/L. The patient's physical attributes the morning of operation were as follows: Ht 180 cm; Wt 75 Kg; BSA 1.95 m².

CASE MANAGEMENT

The extracorporeal circuit and priming solution had to be modified from the standard set-up in order to prevent any of the patient's blood from coming into contact with heparin or heparin-bonded components. These modifications included a non-heparin bonded A-V loop, oxygenator,^a and removal of the arterial line filter. Due to unavailability, the decision was made not to replace the arterial line filter with one that was non-heparin bonded. It was our opinion that the possible consequences of using a heparin bonded arterial line filter outweighed the potential benefit. The priming solution consisted of 2400 ml plasmalyte-A, 1 g CaCl, and 500 mg solu-medrol. This is our standard prime to which we normally add 2000 IU bovine heparin.

The patient was transferred to the operating suite in relatively stable condition. After induction of satisfactory general anesthesia and insertion of monitoring lines (all of which were flushed with normal saline), the chest, groins, and legs were prepped and draped in a routine sterile fashion. A repeat sternotomy incision was performed. The heart was carefully dissected, and the left internal mammary artery was taken down for grafting. Purse string sutures were inserted in the ascending aorta, superior vena cava, and lower right atrium. The patient was then given r-Hirudin 0.4 mg/kg as a bolus infusion, and he was started on a continuous infusion at 0.15 mg/kg/h to establish systemic anticoagulation. The infusion was adjusted to keep the aPTT between 2.5–3.5 times normal. Simultaneously, ACT's were measured in the operating room with the Hemocron JR,^b and the aPTT's were measured in the medical laboratory (Table 1).

Once it was established that the patient was adequately anticoagulated, cannulae were inserted. Two 24 Fr. venous cannulas^c were inserted into the right atrium to access the superior

a Maxima PRF, Medtronic Cardiopulmonary Inc. Anaheim, CA 92807

b ITC Corp. Edison, NJ 08820

c DLP, Grand Rapids, MI 49501

Table 1. Chronology of events during cardiopulmonary bypass

Time	pH	PCO ₂ (mmHg)	pO ₂ (mmHg)	BE (mEq/L)	PCV (%)	BSL (mg/dL)	K ⁺ (mEq/L)	Plt (thou/uL)	ACT (sec)	aPTT (sec)	× N
1145									219	80	2.8
1200	Initiation of cardiopulmonary bypass										
1205	7.39	37	373	-2.1	19				208	79	2.8
1220									225	99	3.5
1223	Aorta cross clamped										
1235									238	118	4.2
1243	Aortic cross clamp removed										
1245	7.42	38	276	-0.6					238	118	4.2
1300	7.39	40	351	-0.7	21	108	4.9		251	102	3.6
1315								164	225	92	3.2
1333	Termination of cardiopulmonary bypass										

BE, base excess, PVC, primary cell volume, BSL, blood sugar level, Plt, platelet, × N, times normal aPTT.

and inferior venae cavae, a 19.5 Fr. arterial cannula^d was inserted in the ascending aorta. An attempt to cannulate the coronary sinus proved unsuccessful. CPB was then initiated, and the patient was cooled to a nasopharyngeal temperature of 28°C. Pump flow rates ranged from a cardiac index of 1.7–2.3. A left ventricular vent was inserted through the right superior pulmonary vein. The aorta was then cross clamped, and 1200 ml. of 4:1 blood:crystalliod cardioplegia was administered through the aortic root at 10°C. The heart was cooled further with cold topical slush, retracted, and the left anterior descending artery was bypassed with the left internal mammary artery graft.

Arterial blood gases samples were drawn periodically while on bypass (Table 1). Minor adjustments in the FiO₂, sweep gas, and blood flow were made accordingly.

The aorta was cross clamped for a total of 20 min. Near the termination of CPB the patient's platelet count was measured and found to be within normal limits (Table 1). Once the patient was warmed to 37°C. low dose inotropic support was

initiated. The patient was successfully weaned from CPB after a total bypass time of 94 min.

The entire CPB circuit, oxygenator, and integrated cardiotomy reservoir^e were closely monitored for clot formation throughout the entire surgical procedure and were inspected afterwards. A small amount of clot in the silastic portion of the tubing in the raceway of the cardiotomy sucker was noted after the termination of CPB. The day following the operation the patient's platelet count was 173 thou/μL. The patient recovered without complication and was discharged five days post-operatively.

DISCUSSION

HIT is a rare condition that can create serious complexities in a very common surgical procedure when full systemic anticoagulation is required. The literature presents several options including the following: plasmapheresis to remove the antibodies prior to CPB; low molecular weight heparin; platelet inhibition; ancrod; and traditional heparin with full autologous platelet replacement post bypass (2, 5, 11). After carefully considering each of these options and their limitations, r-Hirudin seemed to be the most reasonable due to simplicity.

Despite r-Hirudin's notable characteristics and promising results, it has not been used frequently for CPB due to the precarious monitoring techniques required. While the ACT and aPTT can both be monitored (Table 2), there is not a true linear relationship between prolongation of these values and the r-Hirudin plasma concentration that has been shown with the ecarin clotting time (ECT) (12, 13, 14).

ECT is an alternative approach in monitoring the anticoagu-

^d Sarns, Ann Arbor, MI 48103

Table 2. Descriptive statistics^b

ACT and aPTT comparison from Table 1				
Variable	N	Mean	Median	SD
ACT	7	229.14	225.00	14.25
aPTT	7	98.66	99.00	16.13
Correlations (Pearson)				
Correlation of ACT and aPTT = 0.760, <i>p</i> -value = .047				

The ACT showed less variability than the aPTT as evidenced by a smaller standard deviation (SD).

^bMinitab Inc, Release 12, State College, PA 16801

^e Filtered Hardshell Venous Reservoir, Medtronic Cardiopulmonary Inc., Anaheim, CA 92807

lant effect of r-Hirudin using the prothrombin-activating enzyme ecarin. Ecarin is a metalloproteinase that activates the conversion of prothrombin to meizothrombin (15, 16). Meizothrombin by itself has only moderate clotting activity, but it becomes fully reactive in the presence of r-Hirudin, forming stable 1:1 complexes (15, 16). Upon neutralization of r-Hirudin clotting is initiated by meizothrombin itself, and by alpha-thrombin (FIIa) which is rapidly generated from meizothrombin in the presence of factors Xa and Va, or by autocatalytic activation (15, 16). On-line monitoring of ECT, thought to be the ideal way to monitor r-Hirudin during CPB, could allow minute-by-minute modulation of the r-Hirudin plasma concentrations, thus optimizing patient safety.

With the increased frequency of heparin usage for many medical therapies and/or procedures, it is likely cardiac surgical teams will be faced with HIT patients more often. r-Hirudin, having recently been approved for use in the United States by the FDA in March, 1998, may provide a safe alternative to traditional heparin. While on-line ECT monitoring is not widely available, it could prove useful to maximize patient safety during r-Hirudin administration and CPB.

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