The Heart Surgery Forum #2009-1085
12 (6), 2009 [Epub December 2009]
doi: 10.1532/HSF98.20091085

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Hirudin for Management of Heparin-Induced Thrombocytopenia Type II in a Patient with Biventricular Assist Device Support

Ferdinand Vogt,[1] Andres Beiras-Fernandez,[1] Marion Weis,[2] Ralf Sodian,[1] Bruno Reichart,[1] Florian Weis[2]

Departments of [1]Cardiac Surgery and [2]Anesthesiology, University Hospital Grosshadern, Ludwig-Maximilians-University, Munich, Germany

ABSTRACT

A patient with severe dilated cardiomyopathy developed heparin-induced thrombocytopenia type II (HIT II) after implantation of a biventricular assist device (biVAD). Because the patient showed mild renal dysfunction but severe hepatic impairment, the management of anticoagulation was switched from heparin to the direct thrombin inhibitor hirudin, which was administered by continuous infusion of 0.6 to 1 mg/h. This protocol was monitored by measuring the plasma hirudin level, which ranged from 0.5 to 1.5 µg/mL. Unfortunately, the patient died on day 22 after implantation from fulminant sepsis caused by *Aspergillus fumigatus*. Neither thromboembolic events nor thrombocytopenia was observed after hirudin administration. The explanted biVAD showed no thrombotic material in the arterial/venous lines or on the polyurethane valves. We discuss the challenges posed by HIT II complicating VAD support as well as its clinical management with direct thrombin inhibitors.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a frequent complication (up to 7.8%) in patients undergoing ventricular assist device (VAD) implantation [Warkentin 2009]. This complication is associated with an extremely worse outcome, especially when it is diagnosed after the operative procedure [Christiansen 2000]. Thromboembolic events are a major complication in patients with VADs. Standard long-term anticoagulation protocols are usually based on a combination of coumarin and antiplatelet agents to reduce these effects [Christiansen 2000]. During the immediate perioperative period, however, continuous systemic administration of unfractionated heparin is still the mainstay of anticoagulation treatment. It is the most commonly used treatment for reasons of low cost, a short half-life, rapid neutralization (with protamine), and well-established monitoring of the activated clotting time or the activated partial thromboplastin time (APTT) [Christiansen 2000]. The use of heparin, however, is associated with a risk for developing antibodies against heparin/platelet factor 4 (HPF4) that can cause an immune-mediated thrombocytopenia known as HIT type II (HIT II). The clinical characteristics of HIT II are potentially life-threatening arterial and venous thromboembolic complications and bleeding [Koster 2007].

Argatroban, lepirudin, and recently bivalirudin are alternative therapeutic options in patients with HIT II. The differential therapeutic decision is usually based on the organ function of the liver and kidneys, taking into account the metabolic pathways of the respective drug [Nocera 2008]. Although argatroban is preferred for patients with a preserved liver function, the dosing regimen of hirudin has to be adapted to the patient's renal function. Because renal failure is a common sequela after VAD implantation, reports about the use of hirudin in this setting are scarce. APTT can be used for monitoring its anticoagulatory effects, but at APTT values greater than approximately 60 to 70 seconds (depending on the reagent), the hirudin concentration–APTT curve flattens, and even major increases in plasma levels cause only a minor change in the APTT [Tandler 2000].

The presented case describes the successful use of hirudin in a patient with preserved renal function and HIT II after implantation of a VAD. This case is documented not only by measurements of laboratory parameters but also by observation of the VAD chambers and valves after explantation and the absence of clinical thromboembolism.

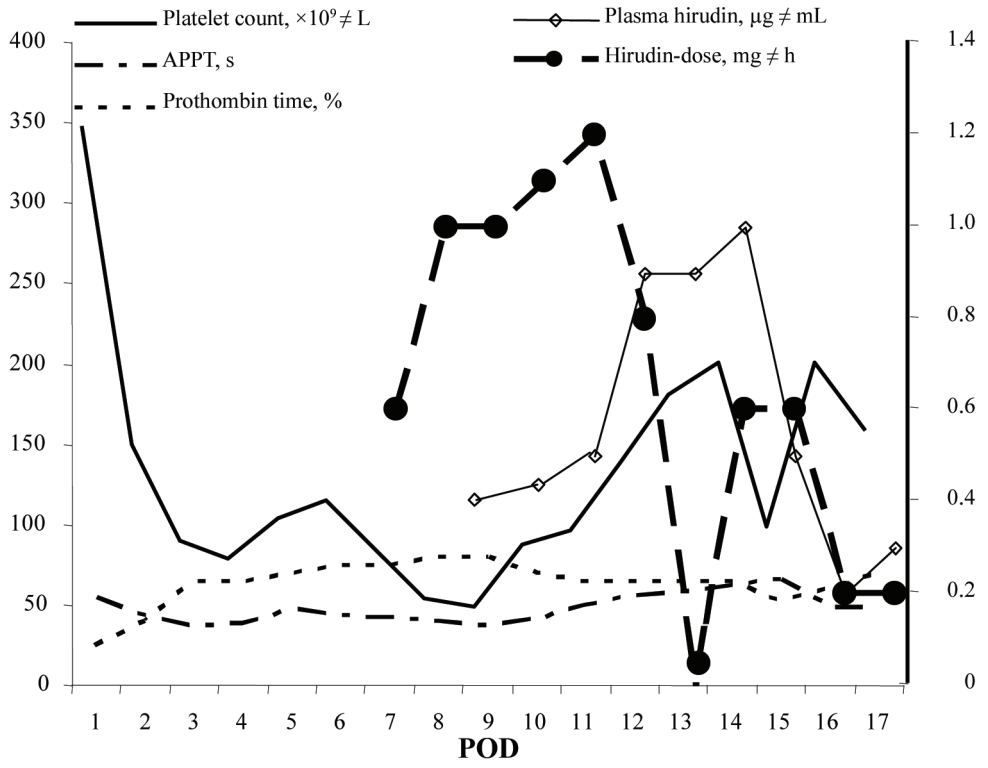
CASE REPORT

A 25-year-old man (175 cm, 120 kg) with severe dilated cardiomyopathy was transferred to our institution because of acute hemodynamic deterioration accompanied by beginning liver failure. A biventricular assist device (biVAD) (EXCOR®; Berlin Heart, Berlin, Germany) was uneventfully implanted. Intraoperative anticoagulation was established with heparin and was reversed with protamine after weaning the patient from cardiopulmonary bypass. Continuous intravenous heparinization was started 12 hours after surgery to achieve a target activated clotting time of 160 to 180 seconds in the absence of bleeding.

F.V. and A.B.-F. contributed equally to this work.

Received June 6, 2009; received in revised form August 10, 2009; accepted August 24, 2009.

Correspondence: Andres Beiras-Fernandez, MD, Department of Cardiac Surgery, University Hospital Grosshadern, Ludwig-Maximilians-University, Marchioninistraße 15, 81377 Munich, Germany; 0049-89-70975074; fax: 0049-89-70952365 (e-mail: abeiras@med.uni-muenchen.de).



Monitoring of hirudin administration, including the platelet count (left *y* axis), hirudin doses (right *y* axis), plasma hirudin levels (right *y* axis), the prothrombin time (left *y* axis), and the activated partial thromboplastin time (APTT) (left *y* axis). POD indicates postoperative day.

The early postoperative course was uncomplicated (the patient was free of vasoactive drugs and had no further need for transfusions by postoperative day 4 [POD 4]). On POD 7, the platelet count had decreased from 111 × 10^9/L to 51 × 10^9/L, leading to the clinical suspicion of the development of HIT II, which was proved on POD 8 by detection of HPF4 antibodies with a HIT II enzyme-linked immunosorbent assay (PF4 Enhanced®; GTI Diagnostics, Waukesha, Wisconsin, USA). An absorbance value >1.0 was considered indicative of HIT. Therefore, heparin infusion was immediately stopped, and because the patient still showed laboratory signs of relevant liver dysfunction but had a calculated glomerular filtration rate of 60 mL/min per 1.73 m^2, we chose to administer hirudin (Refludan®; Schering, Berlin, Germany) to continue systemic anticoagulation therapy. The hirudin infusion was started at 0.6 mg/h without prior application of a bolus. The platelet count reached a nadir at 58 × 10^9/L on POD 8. After recovery of the platelet count (to >100 × 10^9/L), treatment with acetylsalicylic acid as a platelet-aggregation inhibitor was commenced on POD 10. The plasma hirudin level ranged between 0.5 and 1.5 µg/mL (therapeutic range, 0.5-1.5 µg/mL) under a continuous intravenous dosage of 0.8 to 1.0 mg/h during the next few days (Figure). The patient had neither postoperative bleeding events nor any clinical signs of thromboembolism. On POD 14, the patient developed a fulminating pneumonia that was proved on POD 16 to be caused by *Aspergillus fumigatus* by means of a computed tomography–guided biopsy of a suspected aspergilloma area. Despite triple therapy with caspofungin, voriconazole, and amphotericin B, the patient developed severe septic shock on POD 18 and died 4 days later. During that period, the platelet count again had decreased to <100 × 10^9/L, probably because of sepsis. Hirudin application therefore was stopped on POD 17, because the patient developed clinical signs of disseminated intravascular coagulation (DIC). The diagnosis of DIC was based on re-emerging bleeding from the insertion sites of intravenous catheters and the VAD cannulae. The values for coagulation variables deteriorated (see Figure), and antithrombin levels fell dramatically to 25%. Fibrinogen levels fell from 367 to 104 mg/dL. Thus, the coagulopathy and the DIC prompted transfusion of fresh frozen plasma. When the VAD was finally explanted, it showed no thrombotic material, in neither the left ventricular nor right ventricular pump and cannulae. The leaflets of the valves preventing blood reflux were also free of thrombotic material. Our approach shows an efficient management of HIT II in a patient with a biVAD.

COMMENT

The optimal anticoagulation treatment for patients with biVADs is still an issue of debate. Thromboembolism, which occurs in up to 24% of patients, and bleeding events are both common complications, with a potentially worsening outcome [Schmid 1998]. HIT II is a life-threatening disease and particularly difficult to diagnose and treat in VAD patients. Alternative options for systemic anticoagulation in

the perioperative period are argatroban, hirudin, and bivalirudin. Our case documents the rare clinical condition in which a patient experiences significant hepatic impairment after VAD implantation while having a preserved kidney function. Under these circumstances, hirudin is a valid option if the prerequisites for monitoring are fulfilled. In the lower range of anticoagulatory effects, monitoring may be accomplished with the APTT. At APTT values >60 seconds, however, the hirudin–APTT curve flattens, and even very high plasma levels of hirudin do not translate into further increases in APTT values. In this case, the ecarin clotting time may be used, because it correlates much better with anticoagulatory effects than the APTT; however, in patients with reduced concentrations of prothrombin and fibrinogen, which is a common finding in patients after VAD implantation, the ecarin clotting time is also often not correct [Warkentin 2004]. Thus, if therapeutic anticoagulation (ie, APTT >60 seconds) is to be achieved, monitoring of plasma hirudin levels is recommended [Greinacher 2008]. Tschudi et al [2009] very recently demonstrated that omitting the formerly recommended initial bolus and reducing the dosage provide both sufficient anticoagulation and safety. This approach corresponds with the regimen we used and may be of utmost importance in patients with only a mildly reduced renal function. Despite being a feasible option for the management of patients with a VAD, however, hirudin has to be compared with agents whose metabolism is less dependent on organ function and that are easier to titrate. Currently, bivalirudin seems to be the best option for patients with HIT given the aforementioned aspects and has been used successfully even for anticoagulation during cardiopulmonary bypass. Thus, anticoagulation management has to be tailored to the individual patient with HIT II with respect to organ function and the cost of the particular agent being considered [Warkentin 2004]. In conclusion, hirudin is a potential option for systemic anticoagulation in patients with biVADs and HIT II, if renal function is not severely impaired.

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