Case Report

Challenges encountered with argatroban anticoagulation during cardiopulmonary bypass

Shvetank Agarwal, Beth Ullom, Yasser Al-Baghdadi, Michael Okumura

Department of Anesthesiology, Wayne State University/Detroit Medical Center, Detroit, MI, USA

Abstract

Use of argatroban as an alternative to heparin during cardiopulmonary bypass (CPB) in patients with heparin-induced thrombocytopenia has gained some attention in the past two decades. Dosing of argatroban during CPB is complex due to lack of complete understanding of its pharmacokinetic profile and the various elements during CPB that may alter its plasma levels. We report a case where the challenges in dosing argatroban led to failure to provide adequate anticoagulation during CPB, as evidenced by clot formation in the oxygenator, and extensive bleeding in the postoperative period.

Key words: Anti-coagulation, argatroban, cardio-pulmonary bypass, heparin induced thrombocytopenia, heparin alternative

Introduction

Cardiopulmonary bypass (CPB) in patients with heparin-induced thrombocytopenia (HIT) is challenging as heparin use in these patients can have devastating effects. In the past two decades, several alternatives to heparin have been developed. Argatroban is one alternative drug which has gained increased attention. Due to the lack of a reversal agent, dosing of argatroban during CPB is complex, secondary to the need to achieve adequate anticoagulation to prevent clot formation in the extracorporeal circuit while simultaneously preventing excessive anticoagulation, which could potentially lead to extensive postoperative bleeding. Activated clotting time (ACT) has been reported to be a reliable measure of the degree of anticoagulation during argatroban therapy.[1] Furthermore, it has been proposed that ACT levels should be maintained between 500 and 600 s during CPB.[2] We report a case where the challenges in dosing argatroban led to failure to provide adequate anticoagulation, as evidenced by clot formation in the oxygenator, and extensive bleeding in the postoperative period.

Address for correspondence: Dr. Shvetank Agarwal, Department of Anesthesiology, Wayne State University/Detroit Medical Center, 3990 John R., Box 162, Detroit, MI 48201, USA.
E-mail: shvetank_agarwal@yahoo.com

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Case Report

A 65-year-old woman with a medical history significant for diabetes mellitus, hypertension, peripheral vascular disease, and stage IV chronic kidney disease was scheduled for urgent coronary artery bypass grafting surgery (CABG). She was found to have severe triple vessel coronary artery disease after she sustained a non-ST elevation myocardial infarction three days postoperatively from a left lower extremity revascularization procedure. She had had a prior revascularization procedure on the left lower extremity for which she was taking clopidogrel. The clopidogrel was stopped 5 days prior to her most recent revascularization procedure.

The postoperative myocardial infarction was initially managed medically and therapy included a heparin infusion. On day 3 of heparin therapy, her platelet count dropped greater than 50% from a baseline of 197,000/cmm reaching a nadir of 36,000/cmm on day 4 of therapy. At this point HIT was suspected and heparin therapy was discontinued. Argatroban was selected for continued anticoagulation therapy because the patient had significant renal disease. Argatroban infusion was started at 0.8 mcg/kg/min and kept between 0.8 and 1.5 mcg/kg/min to maintain a target aPTT of 48–78 s.

The patient was brought to the operating room where she

underwent an uneventful induction of general endotracheal anesthesia. Her baseline lab work included the following: aPTT 42.1 s, PT 14.7 s, and INR 1.4. Her ACT measured using a Hepcon® HMS Plus System (Medtronic Inc., Minneapolis, MN) was 161 s. Aminocaproic acid (Amicar®, American Reagent Inc., Shirley, NC) bolus of 5 mg was given on skin incision, followed by infusion of 1 gm per hour for the duration of the surgery. In preparation for CPB, an initial bolus of 6.5 mg argatroban (0.1 mg/kg) was administered, followed by the commencement of a 5 mcg/kg/min infusion with a goal ACT greater than 500 s. Thirty minutes after the initial bolus, the ACT was found to be 313 s, prompting an additional 3 mg argatroban bolus and an upward adjustment of the infusion to 7.5 mcg/kg/min. A sample drawn 20 min after the second bolus returned an ACT of 765. At this point, retrograde arterial and venous autologous priming of the CPB was done and CPB was started.

The CPB circuit consisted of a Sarns disposable centrifugal pump with Capiox® RX25RW hollow fiber oxygenator and hardshell venous reservoir, arterial filter, and tubing. All of these listed components were X-coated™ from Terumo (Terumo Cardiovascular Systems, Ann Arbor, MI, USA). The circuit was primed with 1000cc of Normosol®-R (Hospira, Inc., Lake Forest, IL, USA), 12.5G/250cc albumin (Telecris Biotherapeutics, Inc., Research Triangle Park, NC, USA), and 50meq $NaHCO_3$. Hypothermia was permitted to 32.5°C measured rectally. After about 15 min of CPB, a clot was noted to be forming on the mesh sock of the venous reservoir. At the same time, the ACT results on the blood that was drawn earlier came back at 409 s, which prompted administration of a 3 mg bolus of argatroban. About 12 min later, blood was redrawn to check the ACT and other labs. The hematocrit values had fallen to 20% from the initial bypass hematocrit of 24%; so, two units of packed red blood cells were added to the CPB circuit. The repeat ACT values after the 3 mg argatroban bolus had increased only marginally to 499 s; so, another bolus of 1.5 mg was given followed by an upward adjustment of the infusion to 10 mcg/kg/min. This increased the ACT to 605 when measured 20 min later.

As there was no further evidence of a compromised CPB circuit, and because of the risks of changing the CPB circuit including the need for circulatory arrest, a decision was made to continue with the present CPB circuit while carefully monitoring the clot in the reservoir and other CPB circuit parameters that would indicate further problems. After the clot discovery, another ACT machine was brought into the room, and the two machines were run in a staggered fashion to prevent the delay in obtaining results. Additionally, given that clot formed with an ACT between 409 and 499 s, the remainder of the bypass run was carried out with an ACT greater than 600 s with a peak of 775 s. Ultrafiltration was started midway through the case, followed by zero balance ultrafiltration with Hemoflow F50NR Fresenius Polysulfone® Capillary Dialyzer (Fresenius Medical Care, Inc, Waukegan, IL) and a total of about 1200 cc of ultrafiltrate was removed by the end of bypass. Anastomosis of the grafts proceeded uneventfully. In order to avoid prolonged coagulopathy in the postoperative period and because of ACTs consistently staying above 600 s, we decided not to continue the argatroban infusion until the termination of bypass. Thus, the argatroban infusion was stopped about 15 min after removal of aortic cross clamp and recovery of patient's native rhythm. CPB was continued for another 40 min after cessation of the argatroban infusion because of trouble in achieving hemostasis by the surgeon. The subsequent separation from CPB was successful on first attempt with a total bypass time of 150 min. BRAT 2® Autologous Transfusion System (Sorin Group USA, Inc., Arvada, CO) was employed during the case for recovery of shed blood, using acid citrate dextrose solution as anticoagulant instead of heparin, but a decision was made to not reinfuse the processed blood. During the latter half of the CPB, relatively lower hematocrit levels were deliberately tolerated in order to preserve packed cells for after bypass. The hematocrit at the time of CPB termination was 20%; so, two units of banked packed cells were transfused immediately thereafter by the anesthesiologist. In the postbypass period, there was considerable difficulty in achieving hemostasis, which required further transfusion of 6 units of fresh frozen plasma, 5 units of platelets, and 8 more units of packed red cells. The last ACT before leaving the OR was 447 s. Drainage of the bypass circuit revealed no visible clots in the circuit other than the original one in the hardshell venous reservoir which appeared attached to the mesh material [Figure 1].

The aPTT on arrival to the ICU was more than 200 s and the ACT done 2 h later was 227 s. The first 24 h of the ICU stay required transfusion of 9 units of packed red cells, 10 units of fresh frozen plasma, and 10 units of platelets in order to correct the coagulopathy. The coagulation parameters did stabilize by post-op day 1 and so did the bleeding. She was subsequently discharged home on post-op day 26 without any obvious neurological deficits. Her delayed hospital discharge was because other medical conditions unrelated to coagulopathy.

Discussion

HIT is an infrequent, but potentially serious complication of heparin therapy. The more severe form, Type II HIT or HIT-II, is an immune-mediated adverse drug reaction that is caused by IgG antibodies against platelet factor 4 (PF4) – heparin complexes.[1] Re-exposure to heparin can result in

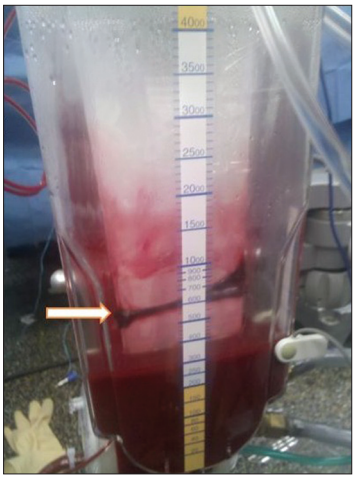

Figure 1: Postcardiopulmonary bypass picture showing thrombus in the venous reservoir attached to the mesh material

significant thrombocytopenia with potential venous and arterial thrombosis. These patients are particularly challenging to manage during CPB as it mandates use of heparin alternatives for anticoagulation.

Alternative agents to heparin include lepirudin, bivalirudin, ancrod, and argatroban. Among these agents, argatroban has gained considerable popularity and acceptance in the management of anticoagulation in patients with HIT. Argatroban was licensed by the Food and Drug Administration (FDA) for prophylaxis or treatment of thrombosis in patients with HIT on June 30th, 2000. It was subsequently approved for use during percutaneous coronary interventions in patients who have HIT or are at risk for developing HIT, on April 3rd, 2002. (personal communication: GSK, Research Triangle Park, NC). Its use in CPB is still off-label.

Argatroban is a low molecular weight arginine derivative that unlike heparin does not need antithrombin III as a cofactor. It exerts its anticoagulant effect by direct competitive thrombin inhibition. It virtually spares other serine proteases because of its high specificity for thrombin.[2] *In-vitro* thromboelastographic studies have demonstrated differential effects of argatroban on clot dynamics, delaying clot formation with lesser effect on clot strength.[3,4] It has a more favorable pharmacokinetic profile compared to lepirudin, which is also a direct thrombin inhibitor. Two advantages of argatroban include the lack of dependence on kidneys for elimination and its shorter duration (half-life of argatroban is 40–50 min versus 80 min for lepirudin).[5] Argatroban is also preferable to bivalirudin, a third direct thrombin inhibitor with short half-life of 25 min, as elimination of bivalirudin is temperature and renal based, both of which can be deranged during CPB.[5] Ancrod, a Malayan pit viper derived defibrinogenating agent, has been used successfully for CPB in patients with HIT. However, Ancrod's half-life of 3–5 h, renal elimination, and need of cryoprecipitates to reverse its effect, make it less popular.[5]

Other encouraging features of argatroban include its nonantigenicity, neutrality to heparin antibodies, and reliable and reproducible monitoring aPTT at low doses and with celite or kaolin ACT at higher doses.[6] Some disadvantages of argatroban are the slow onset of action (30 min), a delayed peak effect (approximately 2 h), and lack of a specific antidote. Argatroban's short half-life necessitates that it be administered as a continuous intravenous infusion to produce the anticoagulant effect needed during CPB.[7]

Argatroban has been used in maintaining extracorporeal support not only in adults,[8-12] but in children,[13] infants,[14-16] and even neonates.[17] During CPB using argatroban, there have been concerns with inadequate anticoagulation resulting in clotting of the extracorporeal circuit and at the same time concerns about increased bleeding in the postoperative period because of the latency in normalization of the ACT. Clots in the oxygenator have been reported in the postbypass period after discontinuation of argatroban,[9-11] but more disconcerting is the fact that people have reported clot formation even during CPB at an ACT of 495 s.[18] Based on these reports, Follis *et al.* have recently proposed a strategy to keep the ACT between 500 and 600 s.[18]

In our patient, we were cognizant of these challenges and so were vigilant for any signs of coagulation in the extracorporeal circuit during bypass. CPB was initiated at therapeutic ACTs, but the drop in ACT immediately thereafter was probably due to decreasing plasma levels of argatroban as a result of hemodilution. Retrograde autologous priming was used to further reduce dilution of argatroban levels in the pump circuit prime. At the time when clot was discovered, the ACT was measured to be 499 s but had been as low as 409 s. We had not anticipated such a precipitous drop in ACT, otherwise we would have added argatroban to the prime and/or given another bolus just before initiation of bypass. Though the clots were not significant enough to warrant change of the CPB circuit and the patient had an uneventful CPB run, this raises questions to safety and efficacy of argatroban anticoagulation for CPB.

In the latter half of the CPB, the ACTs remained high and stable, which could represent a stable therapeutic plasma level of argatroban. This may either be because of its delayed onset or the relatively large total dose administered to the patient. The reduction in effective circulating volume caused by ultrafiltration could on one hand be a contributing factor in increasing the plasma levels of argatroban, while on the other hand, a fraction of argatroban may have been eliminated in

this process, as has been seen previously.[19-21] This complex interplay of factors leading to unpredictable argatroban concentration, in addition to the platelet dysfunction induced by the extracorporeal circuit, could be the cause of prolonged coagulopathy that was seen in our patient.

There are not many case reports describing use of argatroban in on-pump cardiac surgeries. Edwards *et al.* reported the use of argatroban on a 68-year-old woman for a quadruple coronary artery bypass grafting and tricuspid annuloplasty, where they did not have any clot formation in the CPB circuit, despite not adding argatroban to the pump prime, but the patient was coagulopathic after the surgery.[8] They had given an initial bolus of 0.1 mg/kg followed by a continuous infusion of 5–10 mcg/kg/min keeping the ACT between 400 and 500 s throughout the duration of CPB. Smith *et al.* required very high doses of argatroban (initial bolus of 0.3 mg/kg followed by infusion of 40 mcg/kg/min) to maintain ACTs above 400 s in their 70-year-old patient undergoing mitral valve replacement, despite adding 4.2 mg of argatroban into the pump prime.[11] The surgery was complicated with mild coagulopathy after discontinuation of argatroban, but no clots were seen in the CPB circuit. On the other hand, in the case reported by Furkukawa *et al.*, a small clot was seen in the reservoir upon termination of CPB.[9] They had used the standard dosing regimen of argatroban, but had not added argatroban to the pump prime and their target was to keep the ACT between 300 and 400 s. But the most notable and unfortunate of these case reports is the one described by Nielson *et al.*, where argatroban anticoagulation failed to prevent thrombosis in the CPB circuit, and also caused profound coagulopathy in a 12-year-old patient ultimately leading to death.[3]

In this case report, we have presented the challenges encountered in maintaining adequate anticoagulation using argatroban and preventing excessive bleeding after discontinuation of argatroban. This case report also brings into light the many probable factors which may have an effect on the plasma or the CPB concentration of argatroban during the perioperative period. There is definitely a paucity of data to guide the safe administration of drug in patients requiring CPB, especially in those requiring prolonged CPB runs, and till we have more information, we recommend adding argatroban to the pump prime and to maintain the ACTs between 500 and 600 s. Also, we cannot recommend off-pump over on-pump CABG as data regarding safety of argatroban in off-pump cases is also conflicting.[18-21] Though we agree that argatroban can be a good alternative to heparin in select patients, we propose the need for systematic pharmacokinetic studies to help guide argatroban dosing for cardiac surgery involving CPB.

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