Journal of Anesthesia & Clinical Research

Saito, et al., J Anesth Clin Res 2015, 6:4
http://dx.doi.org/10.4172/2155-6148.1000525

Case Report Open Access

# Anticoagulant Managements of Left Ventricular Assist Device Implantation in Two Patients with Heparin-Induced Thrombocytopenia (HIT): Use of Argatroban as an Anticoagulant for Cardiopulmonary Bypass

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**Received date:** March 24, 2015; **Accepted date:** April 23, 2015; **Published date:** April 29, 2015



## Abstract

Heparin-induced thrombocytopenia (HIT) can cause fatal arterial or venous thrombosis/thromboembolism. In high-risk cases, heparin should be immediately discontinued and an alternative administered; the only alternative permitted in Japan is argatroban, a direct thrombin inhibitor. Anticoagulation in patients with recent HIT requiring cardiopulmonary bypass (CPB) surgery is challenging, because it is sometimes difficult to find out appropriate dosage of argatroban using ACT based monitoring calculation.

Two dilated cardiomyopathy patients with HIT were administered argatroban as the anticoagulant for the CPB in left ventricular assist device (LVAD) implantation. After discontinuing argatroban, blood coagulopathy persisted beyond its expected half-life, leading to abnormal haemostasis. Because of severe intraoperative and postoperative bleeding, both patients required massive transfusion support, despite the case 2 performed plasmapheresis to eliminate argatroban at the weaning from CPB. However, blood loss in case 2 (18,159 ml) was significantly lower than that in case 1 (31,292 ml), which might be contributed by the smaller dosage of argatroban (242 mg in case 2 vs. 489 mg in case 1) and plasmapheresis.

Prolongation of ACT is multifactorial and affected by platelet count, fibrinogen concentration and, particularly total dose of argatroban. Furthermore, literatures and our experienses revealed that the recovery time to baseline ACT after stopping argatroban was significantly correlated with the total dose of argatroban (r=0.927). But, we could not authenticate the potency of plasmapheresis to eliminate argatroban and HIT antibodies.

Because no specific antidotes are available for argatroban, surgical teams should carefully monitor timing of argatroban administration and the total dosage.

**Keywords:** Heparin-induced thrombocytopenia; Left ventricular assist device; Argatroban; Cardiopulmonary bypass; Plasmapheresis

## Introduction

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication potentially associated with heparin treatment and reported to occur in 0.2% to 5% of heparin-treated adults [1]. HIT is an immune-mediated disorder that can lead to lethal arterial or venous thrombosis/thromboembolism, resulting in conditions such as myocardial infarction, cerebral infarction, and/or pulmonary embolism [2]. If HIT is strongly suspected, heparin should be immediately discontinued and an alternative anticoagulant (direct thrombin inhibitor or heparinoid) initiated before laboratory confirmation of HIT [3,4]. In Japan, only argatroban, a direct thrombin inhibitor, is permitted for use as a non-heparin alternative anticoagulant in patients with a history of HIT. The Food and Drug Administration (FDA) recommends that an argatroban infusion adjusted to an activated partial thromboplastin time (APTT) ratio of 1.5–3.0 (but not exceeding 100 seconds) is a suitable alternative anticoagulant for the treatment of patients with HIT. Some reports have indicated that argatroban can be used safely by monitoring the activated clotting time (ACT) instead of APTT during CPB or haemodialysis [5]. Anticoagulation management of patients with a recent history of HIT requiring CPB surgery is a serious challenge. In this report, we present the case of 2 patients with HIT who were administered argatroban as anticoagulant therapy for CPB in left ventricular assist device (LVAD) implantation.

## Case 1

A 59-year-old Japanese man was diagnosed with dilated cardiomyopathy (DCM) in 2002. His medical history included chronic heart failure, arrhythmia, and alcohol-related liver injury. He underwent cardiac resynchronization therapy with defibrillator in 2010, but did not respond. The patient was then placed on intra-aortic balloon pumping (IABP) support for severe heart failure and transferred to our hospital in 2012. Continuous infusion of heparin was started for anticoagulation. On day 7 of heparin treatment, his platelet count gradually decreased from $137 \times 10^9$/L to $51 \times 10^9$/L. HIT was strongly suspected, after ruling out the possibility of drug allergy, disseminated intravascular coagulation (DIC), multiple organ failure,

and severe infection. Heparin was immediately discontinued. A heparin-associated platelet antibody test was performed, and argatroban was infused as an alternative anticoagulant. After initiating argatroban infusion at 0.33 mg/kg/min, his ACT was maintained at approximately 250 seconds, and the platelet count recovered gradually. Argatroban was continuously administered during IABP application.

Despite circulatory assist by IABP, the patient's cardiac function deteriorated further; therefore, he was scheduled for LVAD implantation. Since the patient had a recent history of HIT, we decided that argatroban would be used as an alternative anticoagulant during CPB.

An argatroban bolus of 0.3 mg/kg (15 mg) was administered before the skin incision was made; subsequently, 5 mg/kg/min of argatroban was started. The ACT showed the insufficient value (250 seconds) for CPB 89 minutes after the administration of argatroban started; therefore, a second bolus of 15 mg argatroban was administered, and the infusion rate increased to 10 mg/kg/min. However, ACT did not exceed beyond 400 seconds. Moreover, argatroban boluses were administered three times, and the infusion rate increased up to 15 mg/kg/min. 250 minutes after the administration of the first bolus of argatroban, the patient's ACT finally reached 400 seconds, and CPB was initiated. During CPB, ACT was maintained above 400 seconds by administering argatroban at an infusion rate of 15–20 mg/kg/min and as 4 boluses of 15 mg. However, even when ACT was greater than 700 seconds, we noted thrombus formation in the reservoir of the extra-corporeal circuit. The peak ACT was 871 seconds after CPB. Immediately after the completion of external cardiopulmonary circulation, continuous infusion of argatroban was stopped. The total dose of argatroban was 489 mg. The relationship between argatroban dose and ACT in Case 1 is shown in Figure 1.

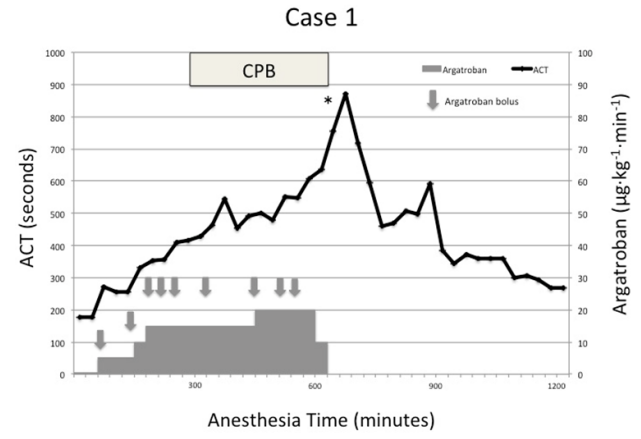


**Figure 1:** The clinical course of activated clotting time (ACT), infusion rate of argatroban and timing of argatroban bolus administration (grey arrow) during the operative period in Case 1. Thrombus formation was found in the extra-corporeal circuit at '*'. CPB = Cardiopulmonary Bypass.

The patient required massive transfusion support (13,440 ml of concentrated red cells, 17,280 ml of fresh-frozen plasma, 1,100 ml of platelet concentrates, and 3 g of fibrinogens) for severe intraoperative and postoperative bleeding. Finally, the total amount of blood loss was 31,292 ml. Forty-nine hours later, ACT was restored to the preoperative level.

## Case 2

A 30-year-old Japanese man was transferred to our hospital for the management of familial DCM accompanied with severe heart failure in 2012. Inotropic agents, diuretics, and an anticoagulation drug (heparin) were immediately administered. However, his condition progressively worsened. Invasive mechanical ventilation was started on the fifth day, and IABP was initiated for cardiogenic shock on the 11th day. However, on the 12th day, his platelet counts decreased drastically from 185 × $10^9$/L to 61 × $10^9$/L. Therefore, HIT was strongly suspected. A heparin-associated platelet antibody test was performed, and heparin was replaced with argatroban. Infusion of argatroban at 0.05–0.15 μg/kg/min was initiated; subsequently, ACT reached approximately 250 seconds, and the platelet count normalized a few days later. Argatroban was continuously administered during IABP application.

He responded poorly to medical treatment, therefore, he was scheduled for LVAD implantation. We decided to use argatroban for anticoagulant during CPB.

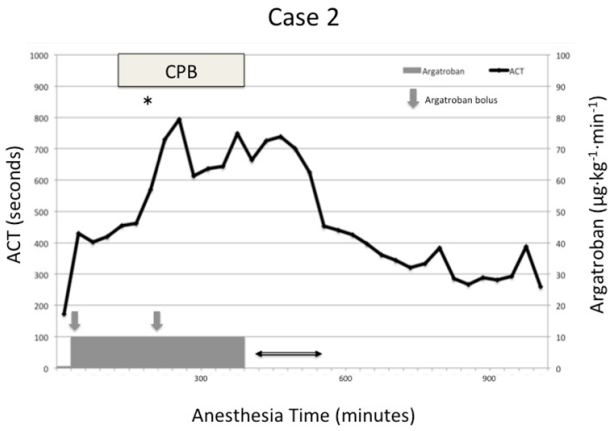


**Figure 2:** The clinical course of activated clotting time (ACT), infusion rate of argatroban, and timing of argatroban bolus administration (grey arrow) during the operative period of the second case. Thrombus formation was found in the right atrium and the reservoir of cardiopulmonary bypass (CPB) at '*'. Plasmapheresis was started at the time of weaning from CPB and performed during '⇔'. ACT : Activated Clotting Time, CPB : Cardiopulmonary Bypass.

Approximately 2 mg/kg (100 mg) of argatroban was administered before the skin incision, and infusion of 10 μg/kg/min argatroban was started. ACT rapidly reached more than 400 seconds, and CPB was initiated. During CPB, ACT was maintained above 400 seconds by infusion of 10 μg/kg/min argatroban. However, when ACT showed 569 seconds during CPB, thrombus formation was noted in the right atrium and the reservoir of CPB. Another bolus of 0.3 mg/kg (15 mg) of argatroban was administered. The peak ACT was 793 seconds during CPB. Immediately after completion of the external cardiopulmonary circulation, the continuous argatroban infusion was discontinued. The total dose of argatroban administered was 242 mg.

The relationship between the argatroban dose and ACT in the case 2 is shown in Figure 2. At the weaning from CPB, plasmapheresis was started to eliminate argatroban from the patient's blood. But the anticoagulation effect of argatroban was prolonged, and it was critically difficult to control bleeding. He required a considerable amount of transfusion support (9520 ml of concentrated red cells, 13,440 ml of fresh-frozen plasma, 1,100 ml of platelet concentrates, and 3 g of fibrinogens). The total amount of blood loss was 18,159 ml. ACT was restored to the preoperative level after nineteen hours.

## Discussion

HIT is a prothrombotic, immune-mediated adverse drug reaction to heparin therapy. It occurs because of the formation of platelet-activating antibodies against complexes of PF4 and heparin, and is characterized by thrombocytopenia and high risk for venous and arterial thrombosis [2]. The treatment of HIT requires immediate discontinuation of all heparin products, including heparin-containing fluids and catheters. Subsequently, prompt administration of an alternative anticoagulant is necessary for HIT treatment. On June 30th, 2000, argatroban was approved by the FDA for prophylaxis or treatment of thrombosis in patients with HIT. In Japan, since July 16th, 2008, only argatroban, a direct thrombin inhibitor, has been approved for use as a suitable alternative anticoagulant in patients with a history of HIT. Argatroban has been shown to be efficacious and safe for HIT with or without thrombosis in 2 prospective, nonrandomized, multicenter studies [6,7].

For argatroban, the volume of distribution is 174 ml/kg, elimination t1/2 is 39–51 minutes (>181 minutes with liver dysfunction), steady-state time-to-peak is 1 to 3 hours, and elimination percentages are 65% by faeces and 22% by urine. The liver metabolizes argatroban. Genzen and colleagues reported that a cardiac transplant patient with a suspected history of HIT had excessive anticoagulation and blood loss in the perioperative period when argatroban was used because the prolonged elevation of argatroban concentration after infusion may have been influenced by the patient's critical condition, cardiac output, and decreased postoperative hepatic function [8]. Therefore, in our patients, the anticoagulation effect of argatroban was prolonged, probably because of liver dysfunction accompanied by right-sided heart failure, leading to abnormality in haemostasis. Therefore, we suggest that when using argatroban in patients with liver dysfunction, increasing the initial dose and decreasing the continuous infusion rate might be suitable, because the volume of distribution of argatroban is high in patients with liver dysfunction and they have marked abnormalities in drug metabolism or excretion.

As regarding anticoagulation management of patients with a recent history of HIT requiring CPB surgery, it has been reported that argatroban should be administered as an initial bolus of 0.1–0.3 mg/kg, followed by continuous infusion at 5–10 μg/kg/min for initiating CPB [9]. However, several reports indicate that this dose is inappropriate for initiating CPB and that additional boluses or an increased infusion rate is required [10,11]. In Case 1, as recommended by Martin and colleagues [9], we administered argatroban 0.3 mg/kg (15 mg) as a bolus dose and subsequently started continuous infusion at 5 μg/kg/min. However, a long waiting time and several additional low-dose (0.3 mg/kg) boluses of argatroban were required to reach the target ACT (above 400 seconds) before starting CPB. Therefore, in Case 2, we administered argatroban at an initial bolus dose of 2 mg/kg (100 mg) and subsequently started continuous infusion at 10 μg/kg/min. ACT rapidly increased to above 400 seconds. However, even when ACT was maintained at more than 400 seconds during CPB, clot formations in the right atrium and the reservoir of CPB circuit were found in both cases. Some studies have suggested that during CPB using argatroban, ACT should be maintained at a level higher than that targeted when using heparin [12-14]. It is advisable that ACT should be maintained at 500 seconds or higher and that particular attention should be paid to detect clot formation in the area of static blood flow during CPB when argatroban is used. Monitoring of the anticoagulatory effect of argatroban during CPB needs further investigation.

The total dose of argatroban administered in Cases 1 and 2 were 489 mg and 242 mg, respectively. And the recovery period of ACT to the preoperative level in Cases 1 and 2 were 49 hours and 19 hours, respectively. Although appropriate dose of argatroban during CPB has not been established, several previous case reports and our experiences about administration of argatroban during CPB (table 1), limited in sample size, suggested that the recovery period to the baseline ACT after stopping argatroban was significantly correlated with the total dose of argatroban (r=0.927) (Figure 3). Prolongation of ACT is multifactorial and may be affected by platelet count, fibrinogen concentration and, particularly, the increase in the total dose of argatroban. The findings in the present cases suggest that anticoagulation management during CPB using argatroban for patients with a history of HIT poses a serious challenge in maintaining adequate anticoagulation and preventing excessive bleeding after CPB.

| Reference | Age/sex | ARG total dose (mg) | CPB time (minute) | Recovery time to baseline ACT after stopping ARG (hour) |
|---|---|---|---|---|
| [17] | 72/M | 66 | 260 | 4 |
| [18] | 47/M | 155 | 176 | 5 |
| | 23/F | 22 | 136 | 5 |
| | 23/F | 103 | 136 | 7 |
| | 74/M | 250 | 466 | 10 |
| [present report] | 59/M | 489 | 195 | 49 |

| | | | | |
|---|---|---|---|---|
| | 30/M | 242 | 260 | 19 |

**Table1:** Case reports about administration of argatroban during cardiopulmonary bypass (CPB): Comparing argatroban (ARG) total dose with recovery time to baseline activated clotting time (ACT) after stopping ARG.

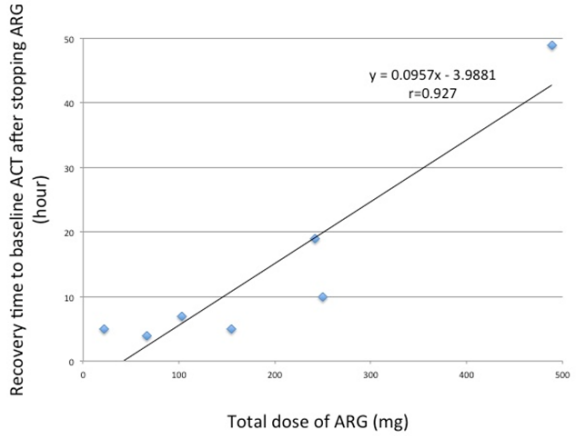


**Figure 3:** Recovery time to baseline activated clotting time (ACT) after stopping argatroban was significantly correlated with total dose of argatroban (r=0.927). ARG : Argatroban.

Despite careful management, haemorrhagic complications can occur when using argatroban as an anticoagulant. Unfortunately, very few options are available for the management of haemorrhagic complications, and no specific antagonist is available for argatroban. Studies have examined the usefulness of plasmaphaeresis as a therapeutic alternative for patients with HIT. According to Brady and colleagues, plasmaphaeresis can be a valuable adjunct in the successful management of patients with HIT and thrombosis [15]. We administered plasmapherasis only in Case 2, aiming to eliminate argatroban. Although both the patients had very similar backgrounds and required massive transfusion support for severe intraoperative and postoperative bleeding, the blood loss in Case 2 was much lesser than that in Case 1. Welsby et al. reported that an alternative management strategy using intraoperative plasmaphaeresis for patients scheduled for cardiac surgery with acute or subacute HIT can reduce antibody load and decrease the thrombotic risk associated with high anti-HPF4 titers [16]. But we are not convinced that plasmapheresis may be effective in the removal of argatroban because of no blood concentration measurement for argatroban at all.

## Conclusion

We presented two cases of HIT in DCM patients requiring LVAD implantation, wherein argatroban was administered as an anticoagulant during CPB and blood coagulopathy extended beyond the expected half-life of argatroban. A high total dose of argatroban is considered to prolong the time required for ACT to return to the preoperative level. We believe that prolongation of ACT may be affected by various factors such as platelet count, fibrinogen concentration and, probably, total dose of argatroban. Plasmapherasis was performed only in Case 2, and the blood loss in Case 2 was much lesser than that in Case 1. But we are not convinced that plasmapheresis may be effective in the removal of argatroban, since we did not measure the serum argatroban concentration at all. Because argatroban has no specific antagonist, unlike heparin, the total dose administered and timing of the drug administration should be carefully evaluated. Effectiveness of plasmapheresis in the removal of argatroban should be substantiated by further investigation.

## References

1. Warkentin TE, Greinacher A, Koster A, Lincoff AM (2008) Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 133: 340-380.
2. Amiral J, Bridey F, Dreyfus M, Vissoc AM, Fressinaud E, et al. (1992) Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 68: 95-96.
3. Warkentin TE, Kelton JG (1996) A 14-year study of heparin-induced thrombocytopenia. Am J Med 101: 502-507.
4. Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, et al. (1999) Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. Am J Med 106: 629-635.
5. Ohteki H, Furukawa K, Ohnishi H, Narita Y, Sakai M, et al. (2000) Clinical experience of Argatroban for anticoagulation in cardiovascular surgery. Jpn J Thorac Cardiovasc Surg 48: 39-46.
6. Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, et al. (2001) Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 103: 1838-1843.
7. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG; Argatroban-915 Investigators (2003) Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 163: 1849-1856.
8. Genzen JR, Fareed J, Hoppensteadt D, Kurup V, Barash P, et al. (2010) Prolonged elevation of plasma argatroban in a cardiac transplant patient with a suspected history of heparin-induced thrombocytopenia with thrombosis. Transfusion 50: 801-807.
9. Martin ME, Kloecker GH, Laber DA (2007) Argatroban for anticoagulation during cardiac surgery. Eur J Haematol 78: 161-166.
10. Edwards JT, Hamby JK, Worrall NK (2003) Successful use of Argatroban as a heparin substitute during cardiopulmonary bypass: heparin-induced thrombocytopenia in a high-risk cardiac surgical patient. Ann Thorac Surg 75: 1622-1624.
11. Azuma K, Maruyama K, Imanishi H, Nakagawa H, Kitamura A, et al. (2010) Difficult management of anticoagulation with argatroban in a patient undergoing on-pump cardiac surgery. J Cardiothorac Vasc Anesth 24: 831-833.
12. Ishida H, Yamazaki T (2009) Use of argatroban during cardiopulmonary bypass for atrial septal defect with heparin induced thrombocytopenia after introduction of dialysis. Kyobu Geka 62: 122-124.
13. Furukawa K, Ohteki H, Hirahara K, Narita Y, Koga S (2001) The use of argatroban as an anticoagulant for cardiopulmonary bypass in cardiac operations. J Thorac Cardiovasc Surg 122: 1255-1256.
14. Agarwal S, Ullom B, Al-Baghdadi Y, Okumura M (2012) Challenges encountered with argatroban anticoagulation during cardiopulmonary bypass. J Anaesthesiol Clin Pharmacol 28: 106-110.

15. Brady J, Riccio JA, Yumen OH, Makary AZ, Greenwood SM (1991) Plasmapheresis. A therapeutic option in the management of heparin-associated thrombocytopenia with thrombosis. Am J Clin Pathol 96: 394-397.

16. Welsby IJ, Um J, Milano CA, Ortel TL, Arepally G (2010) Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. Anesth Analg 110: 30-35.

17. Furukawa H1, Konishi T, Fukata M, Okada H, Sakagami N, et al. (2013) [Open heart surgery using cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia(HIT)]. Kyobu Geka 66: 383-386.

18. Yotuida H, Yamasaki Y, Nishigak T, et al. (2008) Impact of cardiopulmonary bypass for the patients with heparin induced thrombocytopenia. J extra-corporeal technology 34: 301-307.