CLINICAL REPORT

Non-recovery of ACT in a patient with heparin-induced thrombocytopenia type II during mitral valve replacement using argatroban anticoagulation

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Abstract Argatroban was used as the anticoagulant during cardiopulmonary bypass (CPB) in a patient with heparin-induced thrombocytopenia (HIT) type II undergoing mitral valve replacement. Dosage was reduced because of preoperative congestive liver disorder. Perioperative coagulability was poor, and, ultimately, failure of hemostasis led to a fatal outcome. Although argatroban use as an anticoagulant for HIT is reported, the optimal dose has not been established. During long-term CPB, increasing the total dosage may extend anticoagulant ability, leading to dose dependence. Because no antagonist for argatroban exists, failure of hemostasis might occur.

Keywords Argatroban · CPB · Heparin-induced thrombocytopenia type II

Introduction

Use of argatroban, a thrombin inhibitor, as a heparin alternative has been reported in cases of heparin-induced thrombocytopenia (HIT) [1–3]. Argatroban is advantageous because its anticoagulation activity can be evaluated by activated coagulation time (ACT) or activated partial thromboplastin time (APTT). However, because its half-life in blood is short, argatroban must be administered

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continuously to prolong the ACT, although the correct dose has not yet been established. There is no neutralizer of argatroban, such as protamine sulfate against heparin, which is a major drawback of argatroban use. We report our experience with argatroban as a cardiopulmonary bypass (CPB) anticoagulant in a HIT-II patient in whom recovery of the ACT was unsuccessful after mitral valve reimplantation.

Case description

A 74-year-old Japanese woman had undergone mitral valve reimplantation (mechanical valve) and Maze procedure to treat mitral stenosis and atrial fibrillation, respectively, 3 years previously. She was referred to our hospital for treatment of sepsis from pneumonia and was admitted to the ICU. Her current treatment with oral potassium warfarin, discontinued because of a prothrombin time-international normalized ratio (PT-INR) >6, was changed to anticoagulant therapy with continuous intravenous infusion of heparin. Platelet count at admission (21.4×10^4/μl) was decreased considerably, to 3.4×10^4/μl on day 4 of heparin treatment. Because of other laboratory data (PT-INR 1.2, fibrin degradation products 6.6 μg/ml, fibrinogen 391 mg/dl) and not disseminating intravascular coagulation, potentially positive heparin-induced platelet agglutination was indicated. Thus, she was diagnosed as having HIT, and the anticoagulant was switched from heparin to argatroban, which was continuously infused at a rate of 0.3 μg/kg/min. The ACT was 160–200 s, PT-INR was 2.78, and APTT was approximately 2.2 times longer. Her Child–Pugh score for hepatic dysfunction was 9 (Class B). Transesophageal echocardiography on hospital day 10 revealed deviation of the posterior leaflet of the

Fig. 1 Argatroban dose and time course of the activated clotting time (ACT), prothrombin time (PT), activated partial thromboplastin time (APTT), and transfused products during the operation. *CHDF* continuous hemodiafiltration, *CPB* cardiopulmonary bypass, *IABP* intraaortic balloon pump
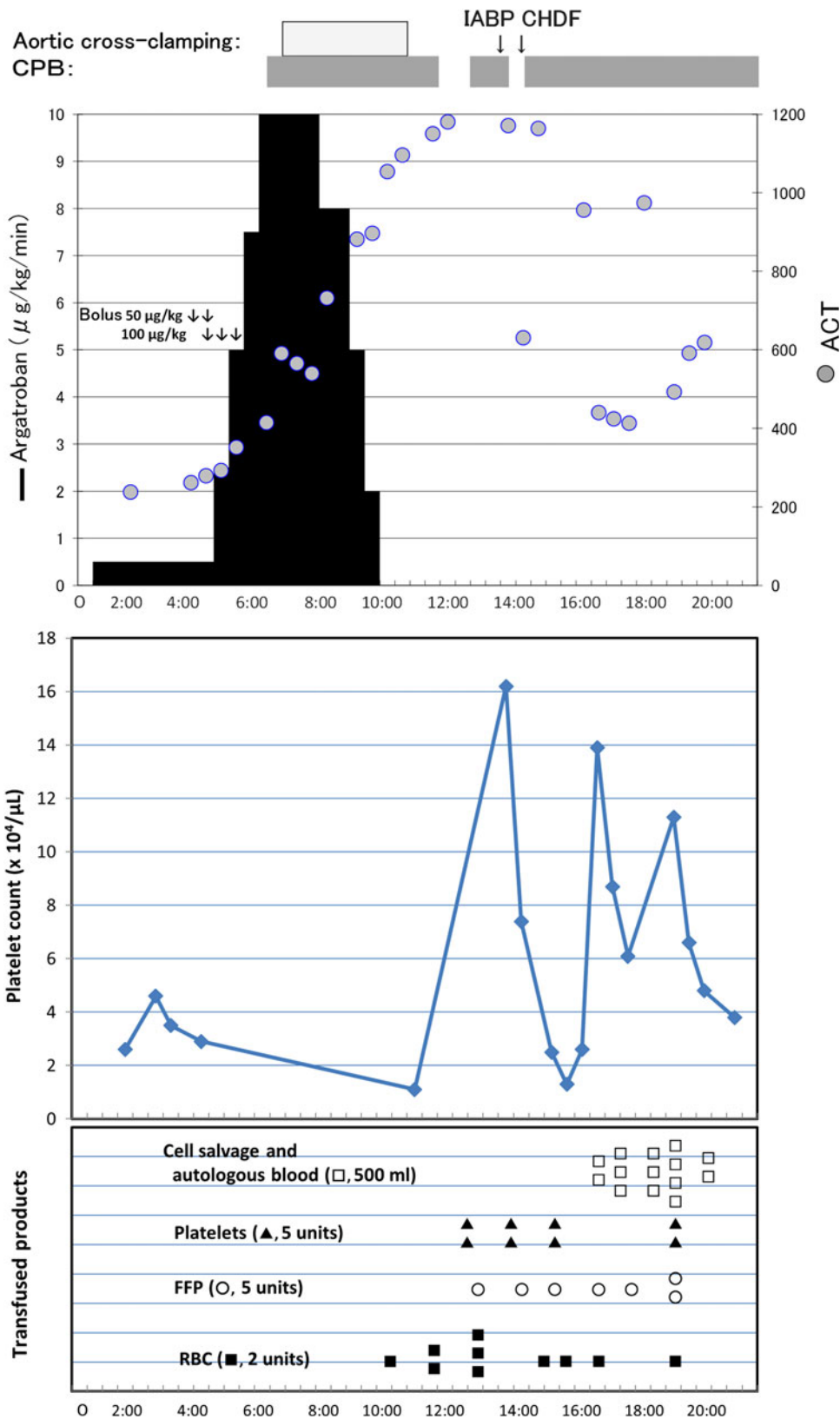
reimplanted mitral valve as the cause of cardiac failure. The patient underwent repeat mitral valve reimplantation on hospital day 13 (Fig. 1).

The intraarterial blood pressure monitoring line was primed with nonheparinized saline, and a heparin-coated pulmonary artery (PA) catheter was washed with saline to

remove the heparin. A CPB circuit and artificial lung (HPO-23 RHF-C; Mera, Tokyo, Japan) were used, and simultaneously, a heparin-free reservoir, centrifugal pump, and arterial filter were prepared. Pretreatment ACT was 238 s, and the target ACT was 400 s or more. Infusion of argatroban was started at a rate of 0.5 μg/kg/min, adding 2.0 mg each if necessary.

Anesthesia was induced with propofol, fentanyl, and vecuronium. Immediately after induction, infusion of argatroban was started at a rate of 0.5 μg/kg/min. Three hours after initiation of the operation, an arterial cannula was inserted into the ascending aorta and a venous cannula into the superior/inferior vena cava. However, because the ACT was not prolonged beyond the second half of the 200-s period, three doses of argatroban at 50 μg/kg and two doses at 100 μg/kg were administered intravenously in addition to increasing the continuous intravenous dose to 10 μg/kg/min. Upon confirmation of the ACT to be more than 400 s, extracorporeal circulation was started. Thereafter, however, the ACT exceeded 1,000 s, and the dose was tapered. Aortic cross-clamping was released after valve replacement along with simultaneous discontinuance of argatroban treatment. With confirmation of a restored heartbeat, CPB weaning was attempted, but cardiac arrest occurred suddenly while removing the cannula and was associated with an irregular rhythm, which required CPB restoration. When a regular rhythm was again restored, CPB weaning was repeated, but cardiac arrest resulted, requiring further CPB. The ACT fluctuated extensively from 400 to 900 s, and persistent bleeding occurred that was difficult to control. Moreover, the patient's blood pressure was low, and intraaortic balloon pumping was initiated. Hyperkalemia (6.5 mEq/l) and decreased urine volume were observed, and continuous hemodiafiltration (CHDF) was commenced during the operation. Thereafter, massive transfusions continued to be required, and it was difficult to stop bleeding without shortening the ACT. The chest was closed with the arterial and venous cannulae left inserted, and they were connected to a percutaneous cardiopulmonary support system (PCPS). Procedure totals included CPB time, 434 min; aortic cross-clamp time, 164 min; operation time, 17 h 56 min; bleeding volume, 30,369 ml; and total dose of argatroban, 50.1 mg. Blood pressure remained low regardless of massive transfusions, and the pacing became impossible. Thus, PCPS was started 2 h postoperatively. Unfortunately, uncontrollable bleeding continued, and the CPB circuit malfunctioned because of poor blood suction. After obtaining consent from the family, we discontinued PCPS 4 h after the operation, and the patient died 1 h later.

Discussion

In general, in HIT cases in which surgery requiring CPB is inevitable, the operation should be delayed as long as possible until the HIT antibody becomes negative, and then CPB should be established using heparin [4]. In emergency cases, however, an alternative anticoagulant to heparin is required. Lepirudin (Refludan), bivalirudin (Angiomax), danaparoid sodium, and argatroban were available [5]. Presently, for patients who require urgent cardiosurgery with acute HIT, the use of bivalirudin rather than other nonheparin anticoagulants and compared to heparin plus antiplatelet agents is suggested [6]. However, neither lepirudin nor bivalirudin is approved in Japan. Danaparoid sodium, with its potent anti-Xa action, makes monitoring of coagulation difficult; it shows cross-reactivity in 10–20 % of patients with HIT [7] and is therefore contraindicated. Thus, argatroban is the only option as an anticoagulant for CPB in Japan.

Argatroban is recommended as an anticoagulant for treatment of HIT complicated by thromboembolism, and evidence of effectiveness is reported [8]. Compared to heparin, argatroban is characterized by mild expression of anticoagulation activity, no prolongation of bleeding time, and freedom from platelet-stimulating action. Furthermore, its biological half-life is as short as 39–51 min, making modulation excellent [9]. Argatroban is metabolized primarily in the liver, and when considering the decrease in clearance in hepatic disorders classified as Child–Pugh Class B, a reduction in the initial dose to less than one fourth (0.5 μg/kg/min) of the usual dose is recommended [9–11].

In the present patient, deviation of the posterior leaflet of a previously implanted mitral valve was no longer preventing cardiac failure. Thus, it was not possible to delay the operation until the HIT antibody had become negative, and emergency surgery was conducted. In addition, because the patient had hepatic dysfunction apparently related to congestive hepatic failure resulting from cardiac failure, treatment was initiated with a decreased dose of argatroban as recommended above. However, the ACT did not prolong, requiring frequent intravenous injections and increased infusion doses. The above-recommended dose was determined from patients with hepatic cirrhosis and was thought not to be applicable to congestive hepatic failure as in the present case. Further, it has been reported that the time for the blood concentration of argatroban to reach a steady state is 1–3 h, and extension of the concentration in plasma and a half-life of argatroban in critically ill patients with low cardiac output and multiple organ dysfunction, as compared with healthy subjects, even if decreased argatroban is used [12]. Therefore, in patients such as this in whom the ACT does not prolong, closer observation of the clinical course and avoidance of simply increasing the dose of argatroban without monitoring are necessary.

In the present patient, failure of the ACT to recover even after withdrawal of argatroban made it difficult to achieve

hemostasis and eventually led to a lethal outcome. Use of CPB is reported to increase the hepatic enzymes [13], and we speculated that progression of congestive hepatic failure from prolonged CPB and the increased total dose resulting from dose escalation to prolong the ACT might have lowered argatroban metabolism in the liver, consequentially causing a fatal coagulation disorder. In addition, although conventional wisdom has considered the metabolism of argatroban to be unaffected by renal disorders [14], hepatic dysfunction complicated by acute renal failure requiring continuous hemodialysis has been reported to enhance the action of argatroban [15]. Also in our patient, although a decreased initial dose of argatoraban was performed for hepatic dysfunction because extension of ACT was poor, additional doses were administered, and it fell into the significant extension of ACT and serious hemorrhagic state. A strategy to keep the ACT between 500 and

600 s has recently been proposed [12]. However, especially in a critical condition, it was possible that the correlativity of the anticoagulant function of argatoraban and ACT decreased because of altered clearance of argatoraban [12, 16–18]. As a result, it was thought that excessive anticoagulation condition and an uncontrollable hemorrhagic state ensued.

The safe dose of argatroban is now being established for percutaneous transluminal coronary angioplasty and off-pump coronary artery bypass grafting without the application of CPB [19]. However, although use of argatroban as an anticoagulant for CPB has been reported (Table 1), the optimal dose is still being explored. Because formation of thrombus in a CPB circuit has been reported [20], simple dose reduction should be avoided. However, it is highly likely that overdosage of argatroban to compensate for the absence of acceptable antagonists prolongs coagulation,

Table 1 Case report of cardiopulmonary bypass (CPB) using argatroban (ARG): comparing argatroban dose, ACT times, CPB times, and blood products

Author [References]	Age/sex	Procedure	ARG in CPB	ARG loading (μg/kg)	ARG infusion (μg/kg/min)	ACT starting CPB	Peak ACT	CPB time (min)	Massive bleeding	Blood products	Clot in pump
Furukawa et al. [1]	44/Male	AVR	None	100	5–10	350	400	167	None	2uRBC	Yes
Edwards et al. [2]	68/Female	CABG + TVR	50 μg/kg	100	5–10	400	470	97	Yes	9uRBC 9uFFP 13uPLT 20uCryo	None
Martin et al. [3]	48/Male	MVR	None	100	3–6	253	753		None	3uRBC 5uFFP 1uPLT 1uCryo	None
Gasparovic et al. [21]	82/Male	AVR redo	None	None	10	350	745	169	Yes	26uRBC 24uFFP	None
Kurup et al. [18]	85/Female	AVR + CABG	None	100	5–15	>400	>700	127	Yes	20uRBC 18uFFP 30uPLT 5uCryo	None
Smith et al. [22]	70/Male	MVR + CABG	4,200 μg	350	25	320	476	90	None	2uRBC 6uFFP 2uPLT	None
Follis et al. [12]	66/Female	MVR	None	None	2.1–14	>495	>999	208	Yes	7uRBC 10uFFP 13uPLT	Yes
Yoshinori et al. [present report]	74/Female	MVR redo	None	50 × 3 100 × 2	0.5–10	>400	>999	434	Yes	30uRBC 40uFFP 40uPLT	None

CPB cardiopulmonary bypass, *ACT* activated clotting time, *AVR* aortic valve replacement, *CABG* coronary artery bypass, *TVR* tricuspid valve replacement, *MVR* mitral valve replacement, *uRBC* units of red blood cells, *uFFP* units of fresh frozen plasma, *uPLT* units of plateletes, *uCryo* units of cryoprecipitate

endangering hemostasis [12, 18, 21–23]. Moreover, in critical cases of hepatorenal disorder, low cardiac output, and cases of long-term treatment, argatroban clearance has a tendency to fluctuate. ACT is widely used, and use in the present case allowed rapid measurement. With our case, monitoring of coagulation was uncorrected by extensive fluctuation of the ACT. Therefore, it was thought that it fell into an uncontrollable hemorrhagic state. Argatroban has the possibility of unpredictable solidification and bleeding, and the point that is suitable for monitoring is not established. When use of argatroban cannot be avoided, we have to take the risk of a critical situation fully into consideration.

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