

Managing Argatroban in Non-Obstructive Thrombosis of Mechanical Mitral Valve in Heparin Induced Thrombocytopenia Type II: A Case Report

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Abstract

We describe the successful management of argatroban in non-obstructive mechanical heart valve thrombosis in a context of heparin induced thrombocytopenia (HIT) type II. A 77-year-old female with permanent atrial fibrillation and mechanical heart valve developed an asymptomatic non obstructive thrombus of mechanical mitral heart valve diagnosed while she was under argatroban for acute HIT type II. Total disappearance of thrombus was achieved with a medical antithrombotic strategy combining increase of argatroban and VKA dosages and implementation of an antiplatelet treatment with aspirin.

Keywords: Heparin induced Thrombocytopenia; Argatroban; Mechanical heart valve; Heparin

Background

Heparin induced thrombocytopenia type 2 (HIT) is a serious adverse effect of heparin administration and requires alternative anticoagulant therapy. Management of patients with mechanical heart valves is particularly challenging in this context. We describe the management of an asymptomatic non obstructive thrombus of mechanical mitral heart valve in a context of acute HIT type II.

Case Report

A 77-year-old female with permanent atrial fibrillation and mechanical heart valve was recently admitted to our hospital for a total left hip replacement. She had a previous history of rheumatic mitral and aortic stenosis and of three cardiac surgeries: a bio prosthetic aortic and mitral valve replacement at 45-year-old, a mechanical valves replacement ten years later for deterioration of both biological prosthesis, and finally a replacement of the mitral mechanical valve. She was under vitamin K antagonists (VKA) with a target INR between 3 and 4 to prevent thromboembolic events. Six days before total hip replacement, VKA were stopped and unfractionated heparin (UFH) was used during perioperative period. Three days after surgery, she presented with severe bleeding and hypotension, due to a compressive hematoma of her left thigh, which required emergency surgery and transfusion of 6 Red Blood Cell units. UFH had to be temporarily stopped and gradually re-introduced. Seven days after the initial surgery, the patient presented a thrombocytopenia at 33 G/L. Heparin induced thrombocytopenia (HIT) type 2 was confirmed with positive laboratory tests (positive anti-PF4 IgG antibody with a high optical density) and a positive platelet aggregation test. The 4Ts Score was at 5. UFH was immediately stopped. As the patient had just experienced severe bleeding, argatroban was initiated as anticoagulation therapy, using the lower dose regiment of 0.5 µg/kg/min, with a target aPTT ratio of 1.5 to 3 times baseline. APTT ratio (STA-PTTA Reagent, Diagnostica Stago, Asnières, France) raised from 0.93 before treatment to 2.35 4 hours after starting argatroban. Concomitantly, platelet count rapidly increased from 33 G/L (Day 1) to 163 G/L (Day 3) and to 250 G/L (Day 7). At Day 7, Coumadin (4 mg) was introduced in addition to argatroban, as thrombocytopenia was corrected and the bleeding risk controlled.

At day 9, transthoracic echocardiogram (TTE) showed an increase in mitral trans-prosthesis diastolic pressure gradient from 3 mmHg to 7 mmHg. Transoesophageal echocardiogram (TOE) identified an

8 mm non-mobile non-obstructive thrombus on the lateral side of the mechanical mitral valve and thrombus with sludge in left atrial appendage (Figure 1). As the patient was asymptomatic, it was decided to optimize antithrombotic therapy rather than propose a 4th mitral valve replacement. Thus, argatroban dose was increased to 1.5 µg/kg/min (Figure 2) to get an aPTT ratio of 3, VKA dosage was also increased from 4 mg to 6 mg daily (INR 1,6), and 160 mg o.d. aspirin was added. TOE on Day 15, showed disappearance of the mitral thrombus and regression of the left atrial appendage thrombus. TOE on day 22, showed a complete regression of thrombi.

As argatroban also increased INR, guidelines recommend to stop argatroban when INR>4 for a desired therapeutic range of INR between 2-3 (under VKA alone). INR target was between 3-4 due to the two mechanical valves. INR reached 5.08 on day 14, with both



Figure 1: Non-obstructive thrombus on the lateral side of the mechanical mitral valve (TOE).

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Received October 15, 2016; Accepted November 22, 2016; Published November 26, 2016

Citation: Bouchot O, Vanzetto G, Casset C, Marlu R (2016) Managing Argatroban in Non-Obstructive Thrombosis of Mechanical Mitral Valve in Heparin Induced Thrombocytopenia Type II: A Case Report. J Clin Case Rep 6: 886. doi: 10.4172/2165-7920.1000886

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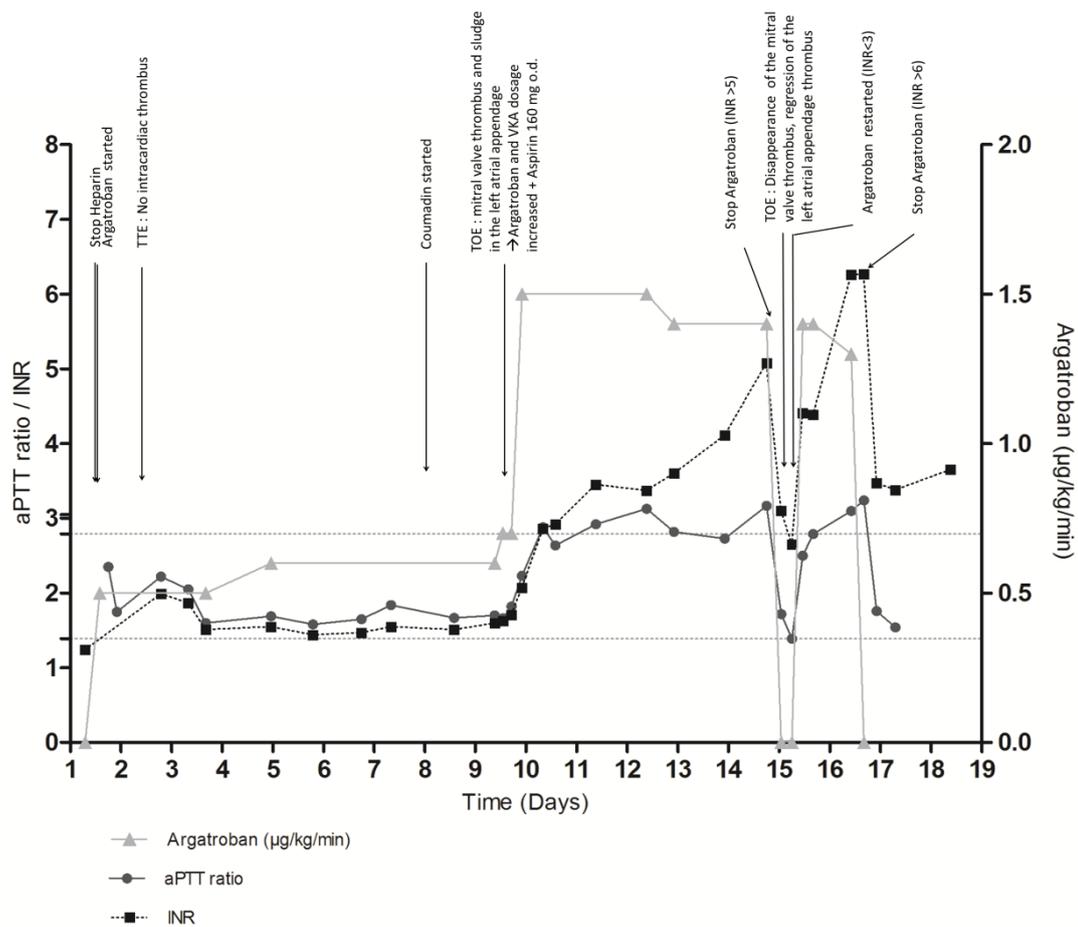


Figure 2: Course of activated partial thromboplastin time (aPTT) and international normalized (INR) during monotherapy by argatroban and cotherapy argatroban and coumadin. The horizontal dotted lines correspond to the aPTT ratio goal range (1.5 to 3.0 times baseline value).

coumadin and argatroban, thus argatroban was stopped; INR was 3.1, 4 hours later. As INR decreased to 2.65 the following day, argatroban was reintroduced on day 15 and 16. Argatroban was finally stopped when INR reached 6.27 on day 16, allowing for target INR without argatroban (3.47 on day 16).

No hemorrhagic events were reported during treatment with argatroban, argatroban + coumadin or with the intensive antithrombotic strategy argatroban + coumadin + aspirin.

Discussion

HIT II is a serious adverse effect of UFH that may cause severe venous or arterial thrombotic complications. Treatment modalities include replacing heparin by an alternative anticoagulant. In case of HIT, two treatments are available in France: sodium danaparoid, whose activity is predominantly anti-Xa, and argatroban, a direct anti-IIa. The pharmacokinetic profile of argatroban is particularly interesting for patients at high risk of bleeding, especially in post-operative care because of its short half-life (~one hour) compared to that of danaparoid (~25 hours). Accordingly, anticoagulation by argatroban can be rapidly reversed after stopping continuous intravenous infusion. Argatroban is also a safer option compared to danaparoid in case of renal failure, this was not the case of our patient.

A few cases of valvular thrombosis secondary to HIT have been reported. Ricom et al. published a case of an asymptomatic valvular

thrombosis after mechanical valve replacement surgery, revealed by routine TTE. Successful treatment with total thrombus disappearance was achieved with intravenous danaparoid [1]. Successful use of danaparoid in 2 pregnant women with previous HIT and prosthetic heart valve has also been reported [2]. Fondaparinux has already been successfully used in post-operative care in patients with former HIT, who underwent mechanical heart valve replacement [3,4]. Finally, lepirudin, which is no longer labelled in our country, has also been successfully used in a patient with early post-operative prosthetic mitral valve thrombosis in a context of HIT [5]. An *in vitro* study [6] which compared argatroban to UFH in preventing thrombus formation on mechanical heart valves suggests that continuous infusion of argatroban could be an efficient option for patients developing HIT after mechanical heart valve replacement. To our knowledge, we are the first to report the use of argatroban in a patient with mechanical heart valve presenting HIT.

Guidelines recommend to initiate treatment at 0.5 µg/kg/min in case of moderate liver failure, after cardiac surgery or in critically severe patients, and at 2 µg/kg/min in other patients. As our patient had recently experienced severe bleeding, argatroban was started at 0.5 µg/kg/min and dosage was adjusted according to usual guidelines (aPTT ratio 1.5 to 3.0 times baseline value, determined without heparin or argatroban). Our patient developed a mitral mechanical valve thrombus when the aPTT ratio was between 1.7 and 2.0 times baseline during day 3 to day 9. This highlights that target was insufficient to avoid

valve thrombosis. Increasing aPTT ratio to 3 times baseline, adding aspirin and pursuing with VKA overlapping until reaching the target INR, allowed for total thrombus regression.

The present case suggests that when using argatroban, the aPTT ratio target should be nearer to the upper limit of the goal range for patients with a mitral mechanical valve. Determination of plasma Argatroban levels might also help to determine the optimal dosage, while aPTT cephalin reagents may have different sensibility to argatroban and inflammation may influence aPTT values.

Surgery was not considered as a therapeutic option in our patient. The surgical risk was high with three prior cardiac surgeries. As recommended in ESC 2012 [7] guidelines, in case of small thrombus <10 mm, anticoagulation must be optimized. Surgery is only considered if thrombus persists or embolism event occurs. Fibrinolysis may be considered if surgery is at high risk and should only be used in absolute necessity (risk of bleeding or thromboembolism).

In conclusion, managing a patient with a mechanical valve and HIT is particularly challenging and associated with a high thrombotic risk. As demonstrated here, argatroban could be an efficient option with a aPTT target ratio in the upper limit of the usual defined goal range.

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