Prolonged argatroban clearance in a critically ill patient with heparin-induced thrombocytopaenia

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ABSTRACT

This is a case of argatroban use in a critically ill patient with heparin-induced thrombocytopaenia (HIT), presenting with unexpectedly prolonged drug clearance possibly secondary to hepatic congestion due to reduced cardiac contractility.

A 63-year-old woman from Asia with end-stage renal failure was hospitalised in the critical care unit with non-ST elevation myocardial infarction with underlying triple vessel disease. She was subsequently started on intravenous unfractionated heparin infusion after an intra-aortic balloon pump was inserted. Six days after the initiation of heparin, she developed HIT and argatroban was started for treatment of HIT. Despite starting on the recommended dose of 2 µg/kg/min, she developed significantly prolonged activated partial thromboplastin time (aPTT) with delayed clearance. Argatroban was stopped 14 hours after time of initiation in view of the markedly prolonged aPTT (in the range of 145 s), and levels only normalised at approximately 60 hours after argatroban was stopped.

BACKGROUND

Heparin-induced thrombocytopaenia (HIT) is a life-threatening, immune-mediated adverse drug reaction with an estimated mortality rate of 20%.¹ It leads to the generation of thrombin that results in thromboembolic events. The treatment of HIT includes prompt discontinuation of heparin and initiation of alternative anticoagulants.

Inhibition of thrombin generation is achieved with the use of direct thrombin inhibitors (DTIs) such as lepirudin, desirudin, argatroban, bivalirudin or indirect factor Xa inhibitors such as danaparoid or fondaparinux.²

In patients with renal failure, the recommended DTI is argatroban as it has minimal renal excretion.³ Argatroban is metabolised in the liver and has a half-life of approximately 50 mins. The recommended starting dose is 2 µg/kg/min, with a target activated partial thromboplastin time (aPTT) of 1.5–3 times the initial value (approximately 60–80 s) and an upper limit of 100 s. In patients with heart failure, multiorgan failure, severe anasarca or postcardiac surgery, it is recommended that the initial starting dose be reduced to less than 2 µg/kg/min.^{2,4}

We report our experience with a patient who had received argatroban for HIT in the cardiology critical care unit. The patient did not have the risk factors as listed above, but developed significantly prolonged aPTT with delayed clearance, despite being started at the recommended dose.

This case is important for hospital pharmacy practice as the pharmacokinetic profile of argatroban presented in an unexpected manner in our patient.

CASE PRESENTATION

Our patient, a 63-year-old Chinese woman, had first presented to another institution with a non-ST elevation myocardial infarction. Her significant medical conditions included end-stage renal failure on regular haemodialysis, type II diabetes mellitus, dyslipidaemia and iron-deficiency anaemia.

The patient was diagnosed with triple vessel disease. She was started on enoxaparin 3 days prior to the transfer. On the day of transfer, the patient developed unstable angina that was refractory to nitroglycerin. An intra-aortic balloon pump (IABP) was inserted just prior to the transfer and she was started on intravenous unfractionated heparin infusion.

On transfer, the patient was placed on continuous renal replacement therapy (CRRT). Unfractionated heparin infusion was continued in view of the IABP in situ. ECG done showed mild left ventricular dysfunction with an ejection fraction of 50% and normal right ventricular function.

Six days after the patient was first started on heparin, her platelet count had dropped from a baseline of $192 \times 10^9/L$ to $67 \times 10^9/L$. She did not have any obvious arterial or venous thrombosis but she was scored intermediate probability on HIT 4T score with a positive ELISA heparin antibody test. A provisional diagnosis of HIT was made and the unfractionated heparin was stopped. She still required anticoagulation as the IABP was still in situ and argatroban was chosen as the anticoagulant of choice in view of the patient's renal function. Prior to the initiation of argatroban, her baseline liver function tests were within normal limits.

The dosing and titration of argatroban based on aPTT in this patient was managed by both the haematologist and the pharmacist.

INVESTIGATIONS

The 4T score of the patient was 5 which is an intermediate clinical probability score. She had a platelet count fall of more than 50% with a platelet fall at day 7 and platelet nadir of $63 \times 10^9/L$. She had no prior exposure to heparin, no clinical signs of thrombosis nor any skin necrosis or other skin reactions. She also did not have any systemic reaction to postintravenous unfractionated heparin. She was having a concurrent infection and was critically ill, factors which may have contributed to the drop in platelet counts as well.

The patient's albumin was normal at 35 g/L on admission but decreased to 25 g/L 3 days after argatroban was started, along with mild cholestasis of conjugated bilirubin 11 mmol/L with elevated liver enzymes LDH 1864 U/L, ALP 294 U/L, AST 82 U/L. Clinically there was no hepatomegaly or ascites.

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Figure 1 Trend of patient's coagulation parameters over time.

A CT abdomen performed did not reveal any enlarged inferior vena cava (IVC) which would be suggestive of right heart dysfunction.

The patient's aPTT was 38.1 s (upper limit 35.6 s) prior to initiation of argatroban, and baseline liver function tests were within normal limits.

TREATMENT

Argatroban was started at the recommended rate of 2 µg/kg/min, with a target aPTT of 60–100 s. Argatroban was stopped 14 hours after time of initiation in view of the markedly prolonged aPTT. Levels only normalised at approximately 60 hours after argatroban was stopped (figure 1).

This was complicated by a drop in the patient's haemoglobin from 9 to 6 g/dL. The patient was haemodynamically stable and did not have any overt signs of gastrointestinal bleed. An oesophagogastroduodenoscopy done showed multiple Forrest 2c duodenal ulcers and a Forrest 2a duodenal ulcer. There was no active bleeding seen. Her subsequent haemoglobin levels remained stable.

OUTCOME AND FOLLOW-UP

Her subsequent aPTT and haemoglobin levels remained stable with no clinical signs of bleeding. The patient eventually declined to have a coronary artery bypass graft and was discharged from our hospital.

DISCUSSION

There have been a few case reports with regards to using argatroban in the dialysis population, that is, in haemodialysis and in CRRT with mixed results. Argatroban was dosed at 2 µg/kg/min in a group of 47 CRRT patients with median aPTTs within range and few patients with bleeding episodes.⁵ As our patient had normal liver function tests with none of the risk factors stated earlier, a decision was made to initiate the starting dose at 2 µg/kg/min based on current dosing recommendations.^{2,4}

Her aPTT was 56 s after initial measurement 2 hours (approximately 3 half-lives) after initiation of argatroban. Five hours later, her aPTT was markedly prolonged at 144 s. Hence argatroban infusion dose was reduced and holding off the drug did not result in significant reduction of aPTT. In addition, based on the half-life of argatroban, the estimated clearance corresponding to a time span of 5 half-lives is approximately 4 hours. In our patient, it took 64 hours (approximately 77 half-lives) before argatroban was cleared, suggestive of possible drug accumulation and delayed hepatic clearance.

A possible explanation for the marked aPTT prolongation and delayed drug clearance could be that of hepatic congestion as a result of reduced cardiac contractility. From the increase in

the liver enzymes, it is suggestive that hepatic congestion led to reduced hepatic perfusion, impairing the metabolism and clearance of argatroban.⁶ Of note, patients with cardiovascular disease were not included in a published pharmacokinetics and pharmacodynamics study of argatroban. They reported an estimated half-life of 152 mins in patients with impaired hepatic function⁷; this would still equate to 25 half-lives for our patient. A second contributing factor may be race. It has been reported that Asians required a lesser median dose to other races to achieve comparable aPTT.⁸

There has been much better understanding in the pharmacokinetics and individualisation of the dosing of argatroban since it was first studied.⁶ However, this case report illustrates that there is room for further research and improvements in dosing and monitoring. Our patient has heart failure with likely occult liver dysfunction and consideration may be made to dose argatroban at a much lower starting dose in Asian patients to prevent over-anticoagulation. This case report underscores the importance of a high clinical suspicion and dosing for argatroban in a critically ill patient. Organ dysfunction often develops during critical illness and hence may affect pharmacokinetics of drugs used. Hence, initial aPTT and monitoring based on guidelines may not be sufficient, but must be individualised. More frequent monitoring of the liver function tests and aPTT should be advocated to minimise possible issues of prolonged argatroban clearance in the ICU population.

Learning points

- The efficacy and safety of the new direct-acting antiviral agents, when combined with biological patient populations.
- Reduced cardiac contractility can possibly lead to hepatic congestion which may affect the clearance of argatroban.
- More studies are required to ascertain the pharmacokinetic profile of argatroban in patients with different comorbidities.

Contributors ESY first identified this case to write as a case report, he is also the guarantor. Data collection and analyses were done by all authors. The first draft was written by CT, after which all authors participated in manuscript revisions/edits prior to our first submission. All authors approved the final version to be published.

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