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The dosing and monitoring of argatroban for heparin-induced thrombocytopenia during extracorporeal membrane oxygenation: a word of caution

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SUMMARY

Heparin-induced thrombocytopenia is a serious complication of heparin use. Treatment includes discontinuation of heparin and initiation of alternative anticoagulation therapy. In extracorporeal membrane oxygenation anticoagulation is mandatory, and direct thrombin inhibitors (DTIs) have been approved in these cases. However, the use and monitoring of DTIs in extracorporeal membrane oxygenation patients is not well described. DTI use is also complicated by the imprecision of available monitoring tests and currently recommended dosing has been shown to result in a supratherapeutic anticoagulative state. This case report describes the successful use of the DTI argatroban as an alternative anticoagulant in a patient with heparin-induced thrombocytopenia requiring extracorporeal membrane oxygenation support.

Keywords

argatroban; heparin-induced thrombocytopenia; extracorporal membrane oxygenation

Heparin-induced thrombocytopenia (HIT) is a hypercoagulable disorder caused by antibodies to platelet factor 4 and heparin, and is associated with a 50% decrease in platelet count, with or without thrombotic complications[1]. HIT is diagnosed by the presence of anti-platelet factor 4–heparin antibodies and confirmed by heparin-induced platelet activation. The management of HIT includes withdrawal of heparin and the institution of alternative anticoagulation, as 40% to 50% of patients develop thrombosis without further anticoagulation[2]. In patients with HIT requiring extracorporeal membrane oxygenation (ECMO), alternative anticoagulation is required to prevent thrombotic complications and maintain circuit patency.

Argatroban is a synthetic, rapid-acting, non-immunogenic direct thrombin inhibitor (DTI) that binds the catalytic site of thrombin[3]. The United States Food and Drug Administration

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has approved argatroban for the treatment of HIT; however, the use and monitoring of argatroban in critically ill patients requiring ECMO support is not well described and recommended doses may lead to supratherapeutic drug levels.

CASE REPORT

Our patient was a 44-year-old obese female who presented with acute hypoxic respiratory failure, requiring intubation. She was placed on mechanical ventilation and prophylaxis for venous thromboembolism was initiated with heparin. Her respiratory function worsened and she met criteria for ECMO support (PaO_2/FiO_2=56).

Twelve hours after cannulation, the patient's platelet count dropped from 235×10^9/l to 32×10^9/l and she became hypercoagulable. Thrombosis developed in the circuit and on ECMO day (ED) one the oxygenator was changed. The patient received multiple platelet transfusions, a HIT panel was sent and heparin was discontinued. Argatroban infusion was initiated at 0.1 μg/kg/minute and titrated throughout the period of transition from heparin to argatroban and during the ECMO period to maintain a goal activated clotting time (ACT) level of 170 to 200 or activated partial thromboplastin time (aPTT) of 60. Titration was based on laboratory values for ACT and aPTT; however, the patient also continued to be clinically hypercoagulable (as noted by microthrombi within the circuit). This clinical hypercoagulability guided our decision-making. Platelet transfusions were initiated based on thrombocytopenia, cannula site bleeding and the patient's ongoing risk of haemorrhage with a goal platelet count of 50×10^9/l. On ED three, the patient required additional platelet transfusions, HIT was confirmed and argatroban was increased to 0.45 μg/kg/minute. late on ED four, the argatroban infusion was increased to 0.65 μg/kg/minute, at which dose the patient was adequately anticoagulated until decannulation on ED seven. The patient survived to discharge and there were no haemorrhagic or thrombotic complications during the patient's ECMO course, regardless of the anticoagulant used.

DISCUSSION

HIT is a serious complication of heparin use, with a mortality of 10% to 30%[4,5]. Anticoagulation with a DTI may be necessary in patients on ECMO; however, the recommended argatroban dose for patients with HIT is 2 to 10 μg/kg/minute, titrated until the aPTT is between 50 and 60 seconds (not to exceed 100 seconds). A small series suggests that doses of 2 μg/kg/minute lead to significant bleeding and a starting dose of 0.2 μg/kg/minute has been suggested for patients on ECMO[6]. Our patient was therapeutically anticoagulated at argatroban doses between 0.1 and 0.65 μg/kg/minute. However, the time necessary to transition to stable therapeutic levels of argatroban was related to uncertainty associated with indirect argatroban monitoring (which is vulnerable to interference) and the lack of an available DTI reversal agent[7].

Other studies have suggested possible factors associated with the need for lower doses of argatroban in critically ill patients[8] and patients receiving ECMO support[6]. In critically ill patients, univariate analysis showed that surgery prior to ECMO cannulation, dosing weight >90 kg, bilirubin >51.3 μmol/l, and platelet count $<70\times10^9$/l were associated with increased

risk of major and minor bleeding complications[8]. Multi-organ system failure and hyperbilirubinaemia, leading to decreased hepatic clearance of argatroban, may contribute to the need for lower dosing of patients receiving argatroban while on ECMO[6]. Additionally, other studies have examined the effects of the extracorporeal circuit on the coagulation cascade and noted that exposure to the ECMO circuit leads to both procoagulant and anticoagulant pathways, resulting in consumption and activation of clotting factors[9]. This consumptive coagulopathy leads to factor deficiencies, platelet dysfunction, thrombocytopenia and fibrinolysis[9]. In our case, the patient was 146 kg with hyperbilirubinaemia (peak of 39.3 μmol/l), platelet counts $<70\times10^9$/l, and multi-organ system failure which all placed her at a higher risk of bleeding complications with argatroban therapy. While not measured, the consumption and activation of existing clotting factors are also likely to have contributed to the need for lower argatroban dosing than the current recommendations.

DTI manufacturers recommend monitoring argatroban activity with aPTT; however, the most commonly used method of monitoring anticoagulation during ECMO support is ACT. Both aPTT and ACT are not directly influenced by DTIs, leading to poor correlation between test results and clinical response to anticoagulation. aPTT and ACT correlation with increasing doses of DTIs is nonlinear and, while accurate at low doses, neither is accurate at increasing doses[10,11]. In our case, the use of aPTT and ACT did not correlate with clinical evidence of ECMO circuit thrombosis. Based on this case, we recommend a starting dose of argatroban between 0.1 and 0.2 μg/kg/minute and then titrating the dose based on a combination of aPTT, ACT and clinical evidence of early thrombi formation. This pharmaco-therapeutic strategy resulted in sufficient anticoagulation without thrombotic or haemorrhagic complications of DTIs.

Written consent was obtained from the patient's next of kin to publish this case report.

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