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Joe Kin-Tong Lee
Kin-Lam Tsui
Ho-Nam Wong
Bonnie Chi-Shan Kho

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Dabigatran as Alternative Anticoagulant for Intra-Aortic Balloon Pump in a Patient with Suspected Heparin-Induced Thrombocytopenia

JOE KIN-TONG LEE,1 KIN-LAM TSUI,1 HO-NAM WONG,2 BONNIE CHI-SHAN KHO,2 HERMAN SUNG-YU LIU,2 KWOK-KEUNG CHAN,1 SHU-KIN LI1

From 1Division of Cardiology; 2Division of Haematology, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong

LEE ET AL.: Dabigatran as Alternative Anticoagulant for Intra-Aortic Balloon Pump in a Patient with Suspected Heparin-Induced Thrombocytopenia. Heparin induced thrombocytopenia (HIT) is an uncommon condition but can result in devastating outcomes. Alternative anticoagulants are recommended for HIT patients with on-going needs of anticoagulation. We report a case of cardiogenic shock treated with intra-aortic balloon pump. The patient was complicated with isolated HIT after administration of low-molecular-weight heparin, and was successfully managed with dabigatran, an oral direct thrombin inhibitor, as an alternative anticoagulant. (J HK Coll Cardiol 2013;21: 15-20)

Anticoagulation, Dabigatran, Heparin, Heparin-induced thrombocytopenia, Intra-aortic balloon pump

Introduction

Two types of heparin-induced thrombocytopenia (HIT) have been described. Type 1 HIT is a non-immunogenic form of HIT and occurs more commonly. It usually occurs within the first 2 days after heparin administration and platelet counts often return to normal despite continuation of heparin. The immune-mediated (type 2) HIT is of clinical importance. In the rest of the article, the term HIT refers to immune-mediated HIT unless otherwise specified. In susceptible patients receiving heparin, HIT antibodies are formed and bind to heparin-platelet factor 4 (PF4) complexes. Such an interaction triggers platelets activation and aggregation, and therefore leads to thrombocytopenia and thrombotic phenomenon in HIT. Patients who are using unfractionated heparin have an absolute risk of 2.6% to develop HIT, although the use of low-molecular-weight heparin may reduce the risk by ten-fold.1 Among patients with acute coronary syndrome using heparin, a similar incidence rate of 1.6% is reported.2 The occurrence is uncommon but the clinical consequence can be severe. Therefore heparin, being a substrate to cause HIT, should be discontinued in these
DABIGATRAN FOR HIT

patients. However it is frequently compelling to continue anticoagulation for the initial indications of heparinization, for examples, in patients requiring haemodynamic support from intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation. Anticoagulation should also be continued in patients with HIT, as thrombosis prophylaxis or as treatment of established thrombosis if any. Different classes of anticoagulants other than heparin, including direct thrombin inhibitors (lepirudin, bivalirudin, argatroban), synthetic pentasaccharide (fondaparinux), and direct factor-Xa inhibitor (danaparoid) have been shown to be useful alternatives in such patients who are contraindicated to heparin.3-8 Unfortunately, these agents are not readily available in some parts of the world, including in our locality. We report the use of dabigatran, an oral direct thrombin inhibitor (DTI), as an alternative anticoagulant in a patient on IABP who developed isolated HIT after administration of low-molecular-weight heparin. To our knowledge, the clinical evidence describing the use of dabigatran in patients with HIT is scarce. Dabigatran may have both advantages and disadvantages over other anticoagulants in managing patients with HIT.

Case Report

A 70-year-old man was admitted to the hospital for anterior ST elevation myocardial infarction, with the presenting symptom of chest pain. He developed an episode of witnessed cardiac arrest due to ventricular fibrillation in the Emergency Department and the arrhythmia was promptly aborted by external defibrillation. The patient developed shock with blood pressure of 77/62 mmHg. He was also intubated and mechanically ventilated for respiratory failure. Electrocardiogram showed sinus rhythm and 2 mm ST segment elevation over the anterior chest leads. Severe pulmonary congestion was noted on chest X-ray. The patient was started on dopamine and an IABP was inserted for haemodynamic support. An urgent coronary angiogram showed a total thrombotic occlusion at the left main coronary artery. Primary PCI was performed, with a drug-eluting stent implanted to the left main artery. In view of the high thrombus load, a bolus dose of intra-coronary eptifibatide was given, followed by intravenous infusion over the next 24 hours. The patient was started on double antiplatelet agents, by loading aspirin 320 mg and clopidogrel 600 mg, followed by regular doses of aspirin 80 mg daily and clopidogrel 75 mg daily. He was also started on intravenous furosemide for diuresis, intravenous amoxicillin-clavulanate for possible secondary chest infection, intravenous ranitidine as prophylaxis for stress peptic ulcer, and subcutaneous tinzaparin 12,000 anti-Xa units every 24 hours (based on the patient's body weight 63 kg) as anticoagulant for the IABP. Subsequent blood tests showed a sudden and remarkable drop of platelet counts, from 166x10^9/L on admission, to a trough level of 59x10^9/L on the fifth day of hospitalization (Figure 1). The red and white cell counts, prothrombin time and activated partial thromboplastin time (aPTT) were unremarkable. His renal function was normal, with creatinine level of 63 umol/L (estimated creatinine clearance 85.8 mL/min).

Such a late drop of platelet counts was considered unlikely due to IABP-related thrombocytopenia or the use of glycoprotein IIb/IIIa inhibitor. Because of the timing (on day 5 after the administration of low-molecular-weight heparin) and the degree of drop in platelet counts (more than 50% drop than baseline level) with no obvious alternative explanation, a diagnosis of isolated HIT was suspected. Clinically there was no overt bleeding, skin necrosis or thromboembolic event, although doppler ultrasound had not been performed to detect any clinically silent deep vein thrombosis. The 4T's score for HIT was 5 (2 points for thrombocytopenia, 2 points for timing of platelet count fall, 0 points for thrombosis or other sequelae, 1 point for other causes for thrombocytopenia present, as the use of IABP and eptifibatide may cause thrombocytopenia but less likely in this case), indicating the intermediate probability of HIT. Functional assay for platelet activation, or immunoassay for heparin-PF4 antibodies were not performed as confirmatory tests because they were not readily available in our hospital. Therefore tinzaparin was taken off and dabigatran (PRADAXA®, Boehringer Ingelheim, Germany) 110 mg was given every 12 hours via the feeding tube.
as an alternative anticoagulant for the IABP. Clotting profile was checked 4.5 hours after initiation of dabigatran and the aPTT prolonged from the baseline 24 seconds to 42 seconds (reference: 24-38 seconds), which was believed due to the anticoagulation effect from dabigatran. The aPTT remained prolonged in the following few days when the patient was still on dabigatran. The continuous heparin saline flush through the IABP was also switched to normal saline. The platelet counts gradually improved and normalized on the fifty day after putting on dabigatran. The patient showed clinical improvement and was able to wean off

Figure 1. The list of medications administered, in conjoint with the trend of platelet counts in the first 12 days of hospitalization.

*Loading dose 600 mg on Day 1
†Loading dose 320 mg on Day 1
‡Intra-coronary bolus 12 mg during PCI, followed by 8 mg/hr iv infusion
Abbreviation: q8h (every 8 hours); iv (intravenous); QD (daily); po (per oral); BD (twice daily); sc (subcutaneous)
the IABP on day 9. Dabigatran was stopped once the IABP was taken off. Further anticoagulation was not contemplated, in view of absence of clinical thrombotic event and the bleeding risk associated with the concomitant use of double antiplatelet agents after implantation of a drug eluting stent. He was wean off the mechanical ventilation soon afterwards. He made good progress in rehabilitation and was discharged after 32 days of hospitalization. No clinical thrombotic event was noted during the disease course and recovery period.

**Discussion**

Non-heparin anticoagulants, including lepirudin, bivalirudin, argatroban, fondaparinux, and danaparoid, are used to treat HIT. However there is not much clinical evidence describing the use of novel oral anticoagulants for this indication. Fieland and Taylor have reported the use of dabigatran for stroke prevention in a patient with non-valvular atrial fibrillation who developed thrombocytopenia after coronary artery bypass graft surgery. The patient was subsequently found to have heparin-PF4 antibodies. However the clinical diagnosis of HIT in this case was not established, in view of the absence of thrombotic event, low probability of HIT as defined by the 4T's score, and the possible confounding effects on thrombocytopenia and heparin-PF4 antibodies by cardiopulmonary bypass. In our case report, we describe the use of dabigatran as an alternative anticoagulation regimen in a patient with clinically diagnosed isolated HIT and yet required ongoing anticoagulation for the IABP. We endorsed the 110 mg twice daily dosage as we took reference from the RELY trial that this dosage was non-inferior to warfarin for stroke prevention in patients with non-valvular atrial fibrillation. We avoided the 150 mg twice daily dose in view of the bleeding risk associated with the concomitant use of double antiplatelet agents. Another reason to use the 110 mg, instead of 150 mg, twice daily dose is that administration of crushed dabigatran pellets without the capsule shell increases the oral bioavailability by 75%, which can precipitate bleeding complication. For this reason the manufacturer advises against taking the drug with the capsule broken, chewed or opened. We still decided to give crushed dabigatran pellets via the feeding tube in this patient because we were left with no treatment option, as those non-heparin parental anticoagulants were not available in our unit.

Dabigatran has the properties of reversible, rapid and selective inhibition of thrombin. It is rapidly absorbed from oral route and once absorbed, the pro-drug dabigatran etexilate is converted to the biologically active form dabigatran. Dabigatran is approved for the use of stroke prevention in non-valvular atrial fibrillation, and deep vein thrombosis prophylaxis after orthopaedic surgery. We believe that dabigatran, being an univalent DTI, can act like other parenteral DTIs to exert an anticoagulation effect, and at the same time not precipitating or aggravating the pathological process of HIT. It is supported by the fact that the molecular structures of dabigatran and other parenteral DTIs are dissimilar to that of heparin, making the DTI unlikely to form complexes with PF4 and then to trigger platelet activation. The parenteral DTIs have not been shown to cause the pathological processes of HIT. Similarly, a recent in-vitro study also demonstrated that dabigatran does not potentiate the interactions of PF4 or anti-heparin-PF4 antibodies with platelets, supporting its practical use in patients with acute or history of HIT.

Compared with other non-heparin anticoagulants which have established roles in HIT, dabigatran has several potential advantages: dabigatran has predictable pharmacokinetic and pharmacodynamic profiles, and at the same time it provides therapeutic anticoagulation effect with large safety margin. Therefore it can be taken with a fixed dosage, and blood tests for the purpose of drug titration is non-essential for approved indications. The property of reversible binding to thrombin may also provide a better side effect profile when compared with other DTIs with irreversible thrombin binding, such as lepirudin. DTI with reversible thrombin binding leaves a small amount of free, enzymatically active thrombin available for control of haemostasis. The better risk-benefit ratio is seen in an experimental model, in which melagatran, also a reversible thrombin binder, provides a lower bleeding risk than irreversible thrombin binder hirudin. Nevertheless, an effective antidote of dabigatran has not yet been established. Ongoing anticoagulation for
certain duration is usually required after the initial thrombocytopenic phase in HIT, and these patients are usually managed by switching the parental anticoagulants to warfarin. The use of dabigatran can omit this medication transition, and at the same time offering benefit over warfarin by not requiring drug titration.

For dabigatran being a drug in oral preparation, the alterations of pharmacokinetics in critically ill patients may make it less effective. Reduced gut motility and diminished gastrointestinal tract perfusion due to blood shunting occur in patients who are critically ill, in shock or using inotropes. In general, such physiological responses impede drugs absorption from the gastrointestinal tract, and therefore lead to a delay in achieving peak serum concentration, and possibly lower total drugs exposure, i.e. smaller area under curve for time and drugs concentration.\(^{20}\) As dabigatran is administered twice daily, the trough plasma drug level and therefore its anticoagulation effect are particularly vulnerable to reach the subtherapeutic range when drug absorption is impeded. In contrast, such a phenomenon is less likely to occur in most of the parental anticoagulants used for HIT treatment, which are administered by continuous infusion with titration of dosage according to the clotting profile. Acute kidney injury is not uncommon in these critically ill patients and can lead to diminished renal clearance of dabigatran, which in turn increases the risk of adverse drug effects such as bleeding. Although there is a lack of study working specifically on the dabigatran pharmacokinetics in critically ill patients, we may have some clues from studies investigated on subjects who have undergone orthopaedic surgery and have received dabigatran as prophylaxis for deep vein thrombosis. The postoperative physiological changes may resemble that of a critically ill patient to some extent: Lower peak plasma dabigatran level and a delay in reaching the plasma peak level are found during the early postoperative period, when compared with the healthy control subjects.\(^ {21,22}\) Such findings are considered due to reduced gastric motility and gastric pH following surgery. We had not checked the plasma dabigatran level or the ecarin clotting time in our case to confirm adequate drug absorption and therapeutic anticoagulation effect during the critically ill status. Having acknowledged the limitation of non-linear relationship between aPTT and plasma dabigatran level, we believe certain anticoagulation effect had been exerted as suggested by the prolonged aPTT.

Eptifibatide can also cause thrombocytopenia. The incidence of eptifibatide-induced moderate thrombocytopenia (<100x10^9/L) is 3.8%, while severe thrombocytopenia (<50x10^9/L) occurs uncommonly, with an incidence of 0.6%\(^ {23}\). In the presented case, eptifibatide had been used on day 1 and 2, and the onset of thrombocytopenia was on day 5. The use of eptifibatide was unlikely the cause of thrombocytopenia, as glycoprotein IIb/IIIa inhibitors-induced thrombocytopenia occurs early, typically within 24 hours from the initiation of treatment. The use of IABP is commonly associated with thrombocytopenia. It appears that the occurrence of thrombocytopenia is independent of the use of heparin, but instead the mechanical force of IABP takes into account.\(^ {24}\) IABP-related thrombocytopenia usually takes place right after the administration of IABP and the platelet counts drop gradually to a nadir on day 3 to day 4.\(^ {24-26}\) In our reported patient, the pattern of stable platelet counts initially with a sudden drop on day 5 was more compatible with HIT instead of IABP-related thrombocytopenia. Although the use of beta-lactam antibiotic can also cause thrombocytopenia, the normalized platelet counts despite continuation of amoxicillin-clavulanate rejected the diagnosis of antibiotic-induced thrombocytopenia. We did not performed any functional or antibodies assay to ascertain the immune-mediated mechanism of HIT, as patients having non-immune-mediated HIT (type 1) usually do well when heparin is continued and need not to have alternative anticoagulant. Nevertheless, the molecular dissimilarity of dabigatran with heparin, and the results of in-vitro molecular studies make dabigatran a potential option in patients with HIT.\(^ {15,16}\) More clinical studies are required to prove its efficacy and safety in HIT.

**Conclusion**

Several alternative anticoagulants have established their roles in treating patients with HIT, but
the drug supplies are not always available. The novel oral DTI dabigatran has structural dissimilarity to heparin. Its lack of interaction in the pathological process of HIT makes it a feasible option in treating patients with HIT and a need of ongoing anticoagulation. Because of its pharmacokinetic and pharmacodynamic properties, dabigatran has both potential advantages and disadvantages to the other anticoagulants.

References