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Dabigatran as a Treatment Option for Heparin-Induced Thrombocytopenia

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Abstract

Heparin-induced thrombocytopenia (HIT) is a potentially serious adverse drug reaction that can result in lethal vascular thrombosis. Dabigatran is a direct thrombin inhibitor that might be useful in the management of HIT. This study evaluated the efficacy and safety of dabigatran in patients with HIT. We included 43 patients in the study who received dabigatran for the management of suspected HIT, based on 4Ts (thrombocytopenia, timing of platelet count drop, thrombosis or other sequelae, and other causes of thrombocytopenia) scores. Three patients were excluded because they had received dabigatran with a creatinine clearance <15 mL/min. Patients' records were analyzed longitudinally, with 12 months follow-up from the time of initiation of dabigatran, for occurrence of thrombosis, dabigatran-related complications, and outcome. Patients with chronic kidney disease, hepatic impairment, mechanical heart valves, active bleeding, and extremes of weights (<50 and >120 kg) were excluded from the study. Arterial thrombosis was not observed in any of our patients. The platelet counts normalized in all patients except for 2, which was attributed to the underlying comorbidities. We did not observe any hemorrhagic events or significant thrombosis during the follow-up period. Eight patients died from nonthrombotic causes, which were unrelated to adverse effects of dabigatran. Based on our findings, dabigatran could be considered a safe and effective agent in the management of HIT, particularly in the developing countries, where there could be issues with the cost and availability of other agents recommended for this condition. Further studies are needed to validate our findings.

Keywords

dabigatran, heparin-induced thrombocytopenia, HIT, thrombin inhibitor

Heparin-induced thrombocytopenia (HIT) is a potentially dangerous adverse drug reaction that is caused by binding of platelet-activating immunoglobulin G antibodies to platelet factor 4-heparin complexes on the surface of platelets elicited by exposure to heparin.[1–4] As a result, thrombin is produced, and a hypercoagulable state occurs that significantly increases the risk of developing venous and arterial thromboembolism in affected patients.[5]

According to the current guidelines, it is recommended to discontinue heparin in patients with moderate suspicion of HIT (4Ts score ≥ 4), and instead, a nonheparin anticoagulant is started as soon as possible.[6] Because low-molecular-weight heparin has a high affinity for HIT antibodies, it should not be used in patients with HIT.[7] According to the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, argatroban, lepirudin, or danaparoid are recommended over other nonheparin anticoagulants in patients with HIT with thrombosis or isolated HIT who have normal renal function.[8] These nonheparin anticoagulants, approved for the treatment of HIT, are costly and not readily available in low-income countries.

Dabigatran is a reversible and direct competitive thrombin inhibitor. This agent is a prodrug, dabigatran etexilate, which is converted to its active form after ingestion.[8] Dabigatran has a predictive pharmacokinetic and pharmacodynamic profile, does not need frequent laboratory monitoring, and allows

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simplified dosing regimens. Dabigatran has been effective in the management of venous and arterial thromboembolism[8,9] and has shown no effect on the fundamental pathway to the development of HIT (platelet activation via anti-PF4/heparin antibodies).[10,11]

There are only a few case reports in the literature evaluating the clinical use of dabigatran in HIT.[12–18] In our study, we identified patients with suspected HIT who were treated with dabigatran and followed them for 12 months for efficacy and safety.

Methods

We conducted this study at Firoozgar Hospital (one of the main teaching hospitals affiliated with the Iran University of Medical Sciences) from February 2014 to February 2016. This study was approved by the institutional review board of Iran University of Medical Sciences (IR.IUMS.REC 1395.119930).

The study was designed retrospectively in the adult patients who received unfractionated heparin or low-molecular-weight heparin for different prophylactic or therapeutic indications, such as coronary artery bypass surgery or other surgical procedures, atrial fibrillation, deep venous thrombosis (DVT), and pulmonary thromboembolism, who were suspected to have developed HIT and received dabigatran for its management.

Medical records for these selected patients were reviewed and analyzed longitudinally for the efficacy and safety of dabigatran and their overall outcome for 12 months. The diagnosis of HIT was made based on a 4Ts score of 4 or higher.[6]

Patients were excluded if they had 1 or more of the following conditions: severe renal insufficiency (creatinine clearance <15 mL/min), inappropriately dose-adjusted based on renal function, hepatic impairment (Child-Pugh B and C), mechanical heart valves, active bleeding, and extremes of weight (<50 and >120 kg).

The 4Ts score was calculated by a hematologist or cardiologist. Neither the serotonin-release assay nor Fc receptor-blocking monoclonal antibody (to confirm the diagnosis of HIT) was available in our center at the time of the study. The patients with suspected HIT had received 110 mg dabigatran twice daily if they had normal renal function or 75 mg twice daily if kidney function was impaired (creatinine clearance, 15–30 mL/min). The duration of treatment with dabigatran was based on the initial indication, which was determined by the treating physician. Platelet count recovery was defined as a count ≥150 000 mL^{-1} (or back to the baseline if the baseline counts were less than 150 000 mL^{-1}).

The primary outcome measure was the incidence of new symptomatic and objectively confirmed venous or arterial thromboembolism. The secondary outcome was an assessment of drug safety, including the development of hemorrhagic events based on clinical findings.

Table 1. Clinical Characteristics of Patients and the Reason for Anticoagulant Therapy

Age (years), mean, SD		69.98 ± 13.14
Sex, n (%)	Male	16 (40%)
	Female	24 (60%)
Reason for anticoagulant therapy		
DVT prophylaxis		13 (32.5%)
Confirmed DVT		11 (27.5%)
Nonvalvular arterial fibrillation		9 (22.5%)
CABG		3 (7.5%)
Confirmed PTE		3 (7.5%)
Suspicion PTE		1 (2.5%)

DVT, deep vein thrombosis; CABG, coronary artery bypass graft; PTE, pulmonary thromboembolism.

Statistical Analysis

Clinical and laboratory data were extracted from the paper and electronic patient charts. SPSS 23 software was used for statistical analysis. The descriptive assessment is stated as mean ± standard deviation (SD) for numerical variables; number and percentage are expressed for nominal variables. The unpaired Student *t* test and Mann-Whitney *U* test were used to compare variables with normal and nonnormal distributions, respectively. For categorical variables, the chi-square test was used as appropriate. $P < .05$ was considered statistically significant in all cases.

Results

A total 134 patients received dabigatran during this study period; of these, 43 received dabigatran for suspected HIT, of whom 40 met the study inclusion criteria. Three patients were excluded because of receiving dabigatran with a creatinine clearance <15 mL/min. The clinical characteristics of study patients and the indications for anticoagulant therapy are shown in Table 1. Of the 40 patients selected for final analysis in the study, 31 received unfractionated heparin, and 9 had received low-molecular-weight heparin.

Thirty-three patients (82.5%) had high probability and 7 patients (17.5%) had moderate probability for HIT diagnosis based on 4Ts score of ≥6 and 4–6, respectively. All heparin products were discontinued in patients with suspected HIT, and dabigatran was initiated. Thirty-three patients (82.5%) received dabigatran 110 mg twice daily, and 7 (16.6%) received 75 mg twice daily, based on their creatinine clearance or the discretion of the treating physicians. Thirty-six patients had creatinine clearance more than 30 mL/min, and 4 had creatinine clearance between 15 and 30 mL/min.

The platelet counts (mean ± SD and range) at baseline and at the time of HIT diagnosis were 213 550 ± 75 733 (116 000–412 000) and 80 125 ± 28 824 (35 000–160 000), respectively. These counts recovered significantly to 157 550 ± 85 688 (32 000–432 000) after the administration of dabigatran ($P < .001$).

The mean time from the start of the unfractionated heparin or low-molecular-weight heparin to the possible diagnosis of HIT was 5.4 ± 3.1 days, and the mean time for the platelet counts to recover after the start date of dabigatran administration was 7.4 ± 4.3 days. The platelet counts did not recover in 2 patients.

One of our study patients, who had a prior history of lower-extremity DVT, suffered another episode of DVT in the opposite lower extremity during the study follow-up period. Two patients had minor bleeding episodes in the form of skin ecchymosis, which resolved spontaneously without any complications.

The mortality rate during our 12-month follow-up period was 20%. None of these deaths were related to thromboembolic events, hemorrhagic complications or dabigatran adverse reactions. Four patients died because of sepsis between 6 and 50 days after initiation of dabigatran, 2 within 1 month after discharge (because of advanced esophageal cancer and heart failure) and 2 within 3 and 4 months after discharge (because of severe chronic obstructive pulmonary disease exacerbations and renal failure).

Discussion

To our knowledge, the presented study is the largest case series examining the safety and efficacy of dabigatran in patients with suspected HIT based on 4Ts scores. Our results support the potential use of dabigatran in the management of HIT, for which other approved agents might not be readily available.

Dabigatran binds to both free and clot-bound thrombin.[10,11] The interaction between dabigatran and the PF4/heparin complex and its effect on platelet activation via anti-PF4/heparin antibodies have been evaluated in in vitro studies.[10,11] Dabigatran does not react with PF4 or PF4/heparin complex binding to platelets, nor does it influence antibody binding to the PF4/heparin complex. Hence, dabigatran does not affect platelet activation via anti-PF4/heparin antibodies, which is the fundamental process in the development of HIT.

The evaluation of efficacy and safety of direct oral anticoagulants (DOACs), including dabigatran, as well as the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), in the treatment of clinical-pathological HIT has been rapidly increasing in recent years, although most studies have focused on direct factor Xa inhibitors.[19] Warkentin et al performed a study and literature review on the use of DOACs in the management of HIT.[19] Their study consisted of 89 patients, of whom 16 belonged to their own investigation and 73 were from 25 other reports in the literature. Sixty-four patients were included in their study, and 9 patients had to be excluded because of the uncertainty of the diagnosis of HIT. These authors classified patients into 3 groups. Group A consisted of patients for whom DOACs were used as primary therapy for HIT (ie, the DOACs were the first nonheparin anticoagulant used for the treatment of acute HIT). Patients in group A were subclassified into subgroup A1 if the DOACs were started while the patient was still thrombocytopenic (platelet count, 150×10^9 L^{-1}) and subgroup A2 if the DOACs were started as the primary anticoagulant, but the platelet count never fell below 150×10^9 L^{-1}. The patients in subgroup A2 included those in whom HIT was suspected because of the potential HIT-associated hypercoagulability state, despite the absence of thrombocytopenia, conventionally defined by a threshold platelet count of 150×10^9 L^{-1}.

Patients were classified as group B if they received at least 1 dose of 1 or more of the nonheparin anticoagulants, other than a DOACs, such as fondaparinux, danaparoid, argatroban, or bivalirudin, for acute HIT management. In this group, conversion to the secondary treatment with a DOAC had to have occurred before the platelet count increased to greater than 150×10^9 L^{-1}.

Patients were classified as group C if they received 1 or more of the nonheparin anticoagulants (other than a DOAC) and in whom conversion to the secondary treatment with a DOAC occurred only after the platelet count had recovered to 150×10^9 L^{-1}.

Eighty patients received a DOAC for the treatment of probable HIT, of whom 69 were classified as either group A1 (n = 25), group A2 (n = 5), or group B (n = 39) and suitable for the final analysis. Forty-six patients (66.6%) were treated with rivaroxaban, 12 (17.4%) with apixaban, none with edoxaban, and 11 (15.9%) with dabigatran. A total of 11 patients received a DOAC classified as group C (rivaroxaban, n = 7; apixaban, n = 3; edoxaban, n = 0; and dabigatran, n = 1). Among the 12 patients who received dabigatran for HIT management, only 1 patient had a possible thrombotic event while receiving a DOAC (multiple strokes, which might have been present before starting dabigatran). None of the patients experienced major hemorrhagic events.[12–19]

The profile of our patients matched those in group A of the study mentioned above. Our results also indicated dabigatran to be effective in preventing recurrent or new thrombosis, in all but 1 patient, who experienced DVT on the opposite leg, which was not found to be

a result of dabigatran failure. None of the patients in our study experienced any major bleeding while being treated with dabigatran. Platelet counts increased in all but 2 patients, which could have been a result of the underlying conditions. Both patients died of sepsis, on the 6th and 10th days after the initiation of dabigatran.

In a study by Sharifi et al, at 19 months of follow-up, a total mortality rate of 27% was reported in patients with HIT who received a short course of low-dose parenteral argatroban followed by the administration of a DOAC.[12] In another study, by Lewis et al, a mortality rate of 17.5% was reported in the argatroban group versus 23% in the control group on a 37-day follow-up.[20] Thrombosis-related mortality in the argatroban group occurred in only 1 patient (0.3%) in their study.[20] In our study, 8 of the 40 patients who received dabigatran (20%) died within 12 months of therapy. None of these deaths could be directly attributed to the dabigatran administration or fatal thrombotic events.

To our knowledge, our case series is the largest of its kind demonstrating the efficacy and safety of dabigatran as an alternative oral agent for the management of HIT. Our findings could provide grounds for furthering the investigations for the use of dabigatran in this patient population. Larger, prospectively designed clinical trials to compare the efficacy and safety of dabigatran with other US Food and Drug Administration-approved parenteral agents for the management of HIT are required to validate our findings.

The limitations of our study were; a retrospective collection of patients who were already on dabigatran at enrollment, drug use in an open-label fashion, single study arm, the lack of an immunoassay for heparin PF4 antibody detection, small sample size, and the heterogeneity of our patients.

Conclusions

In this study, consisting of retrospective patient collection and prospective follow-up for 12 months, we evaluated the efficacy and safety of dabigatran administration in the management of HIT. We found dabigatran to be safe and effective in preventing thrombosis and helping the recovery of platelet counts in patients with a suspected diagnosis of HIT.

Cost constraints and difficulties in obtaining parenteral agents, particularly in the resource-poor countries, could make dabigatran a safe and effective alternative agent for the management of HIT. Future clinical trials with better study design might be warranted to evaluate the role of dabigatran and other DOACs in the management of HIT.

Declaration of Conflicting Interests

None of the authors declare any potential conflicts of interest with respect to this research and its publication.

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