Clinical Experience of Life-Threatening Dabigatran-Related Bleeding at a Large, Tertiary Care, Academic Medical Center: a Case Series

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Published online: 3 January 2014
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Abstract

Introduction Dabigatran, an oral direct thrombin inhibitor, is FDA approved for the prevention of stroke in patients with nonvalvular atrial fibrillation. No agent exists for the reversal of dabigatran-related major bleeding. Prothrombin complex concentrate (PCC) has been studied in reversal but was not shown to affect the surrogate markers of bleeding such as the thrombin time, ecarin clotting time, or activated partial thromboplastin time (aPTT). Recombinant factor VIIa (rFVIIa) may provide benefit in patients with life-threatening or major bleeding; however, it has not been studied in dabigatran-related bleeding. PCC and rFVIIa are agents utilized at our institution for major bleeding in patients receiving anticoagulant therapy. Due to the high cost and thrombogenic risk of both rFVIIa and PCC and lack of a clear reversal strategy, we reviewed the management of all reported cases of dabigatran-related bleeding.

Methods This was a retrospective chart review of patients admitted to UMass Memorial Medical Center with a bleeding event and also receiving dabigatran therapy.

Results Eleven patients on dabigatran admitted for bleeding were identified. Seven were admitted for an intracranial hem-

orrhage (ICH) and four for a gastrointestinal hemorrhage (GIH). The baseline characteristics are as follows: mean age was 74.55 years (range, 63–89), and seven were male. Admission mean hemoglobin was 11.88 g/dl (range, 6.1–18), mean international normalized ratio (INR) was 2.2 (range, 1.1–7.1), and mean aPTT was 42.21 s (range, 36–81.4). Interventions received included fresh frozen plasma ($n=6$), platelets ($n=3$), packed red blood cells ($n=4$), rFVIIa ($n=2$), intravenous fluids ($n=10$), surgical intervention ($n=3$), and dialysis ($n=2$). No patients received PCC. Four patients survived in the ICH group, and four patients survived in the GIH group.

Conclusion Reversal strategies for dabigatran-related bleeding events at our institution are highly variable. Intracranial hemorrhage in patients on dabigatran was associated with 43 % mortality. Patients with severe dabigatran-related bleeding may benefit from a standardized approach to treatment.

Keywords Dabigatran · Reversal · New oral anticoagulant

Introduction

Atrial fibrillation, the most common arrhythmia, affects approximately 1–2 % of the population in developed countries [1, 2]. The risk of stroke in patients with atrial fibrillation is approximately 5 % per year without anticoagulation [2]. Dabigatran, an oral direct thrombin inhibitor, was FDA approved for the prevention of stroke in patients with nonvalvular atrial fibrillation [3]. Since its approval in October 2010, the American College of Chest Physicians recommends dabigatran as the oral anticoagulant of choice over dose-adjusted warfarin in patients with an intermediate and high risk of stroke [CHADS₂ (congestive heart failure,

Presentations Poster was presented without results at the American Society of Health-Systems Pharmacists (ASHP) midyear clinical meeting, New Orleans, LA, last December 2011.

Data was presented with results in PowerPoint format at the Eastern States Pharmacy conference, Hershey, PA, last May 2012.

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hypertension, age of ≥ 75 years, diabetes mellitus, prior stroke, or transient ischemic attack) score of ≥ 1] [2].

Bleeding is a serious adverse event associated with anticoagulant therapy. The FDA released a statement in December 2011 reporting over 260 fatal bleeding events worldwide between March 2008 and October 2011 in patients receiving dabigatran [4, 5]. Phase III clinical trial data reports a 3.11 % rate of major bleeding in patients receiving dabigatran for nonvalvular atrial fibrillation as compared to 3.36 % who received warfarin [6]. The rate of life-threatening bleeding, however, was higher in the warfarin group compared to the dabigatran groups [6]. Since its approval, multiple case reports have been published citing irreversible bleeding complications, including cardiac tamponade, intracranial hemorrhage, massive gastrointestinal hemorrhage, and death in patients receiving dabigatran [7–12]. Currently, no agent exists for the reversal of dabigatran-related major bleeding. Prothrombin complex concentrate (PCC) has been studied in reversal of dabigatran but was not shown to affect the surrogate markers of bleeding such as the thrombin time (TT), ecarin clotting time (ECT), or the activated partial thromboplastin time (aPTT) in non-bleeding healthy volunteers [13]. Recombinant factor VIIa (rFVIIa) may provide benefit in patients with life-threatening or major bleeding events; however, it has not been prospectively studied in humans for the management of dabigatran-related bleeding [14].

UMass Memorial Medical Center, a level 1, tertiary care academic medical center, has admitted 11 patients with major bleeding events who were receiving dabigatran. Management of these patients has been variable. Due to the high cost and thrombogenic risk of both PCC and rFVIIa and lack of a clear reversal strategy, the judicious use of these agents should be considered. The objective of this case series was to review the management of all reported cases of dabigatran-related bleeding at UMass Memorial Medical Center.

Methods

Patients were identified retrospectively via verbal communication from the treating physician or clinical pharmacist in the intensive care unit in which the patient was being treated between January 1, 2011 and January 31, 2013. All patients admitted with a dabigatran-related bleed were included. Bleeding was defined as a reduction in hemoglobin of at least 2 g per dl, transfusion of at least 2 units of blood, or evidence of a major bleed such as guaiac-positive stools, head CT with intracranial bleeding, or abdominal CT with retroperitoneal bleeding. During the study period, no defined protocol existed for the management of dabigatran-related bleeding; all

management strategies were at the discretion of individual physicians. This study was approved by the institutional review board at the University of Massachusetts Medical School. The requirement for informed consent was waived.

Baseline characteristics collected for each patient included the following: date of bleed, age, gender, and past medical history including hypertension, coronary artery disease (CAD), end-stage renal disease (ESRD), peptic ulcer disease (PUD), congestive heart failure (CHF), stroke or transient ischemic attack (TIA), cancer, history of bleeding, venous thromboembolism, recent (within the last 2 weeks) major surgery, or trauma. Laboratory values collected at baseline and admission included the following: serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin and hematocrit, and coagulation tests including prothrombin time (PT) and international normalized ratio (INR), activated partial thromboplastin time (aPTT), and if available, thrombin time (TT), and ECT. Interventions including the use of PCC, rFVIIa, packed red blood cells (PRBC), fresh frozen plasma (FFP), and dialysis as well as surgical interventions were also analyzed. Other data collected included the site of the bleed, imaging studies (MRI, CT of the abdomen or head, KUB), concomitant medications, in-hospital and 30-day mortality, length of ICU and hospital stay, and any adverse thromboembolic events. Descriptive statistics were used for all data analyzed.

Results

A total of 11 patients were admitted to UMass Memorial Medical Center with a dabigatran-related bleeding event (Table 1). The average age was 75 years (63–89 years), and seven patients were male (64 %). All patients had a diagnosis of nonvalvular atrial fibrillation, and three (27 %) had a history of stroke or transient ischemic attack. The average serum creatinine and creatinine clearance upon admission was 1.28 mg/dl (0.89–2.19 mg/dl) and 46.5 ml/min (15–86.9 ml/min), respectively. The majority (64 %) of patients were receiving dabigatran 150 mg by mouth twice daily. Baseline coagulation factors including PT and INR were available for all 11 patients, and TT and ECT were available for 2 patients each. The average INR upon admission and at follow-up were 2.1 (1.1–7.1) and 1.1 (0.9–1.6), respectively.

Seven patients (64 %) presented with an intracranial hemorrhage (ICH), and four patients (36 %) presented with a gastrointestinal hemorrhage. Of the patients presenting with

Table 1 Baseline characteristics

Baseline characteristics	Patients, <i>n</i> = 11
Age, years	75 (63–89)
Male sex, no.	7
Scr, mg/dl	1.29 (0.89–2.19)
Crcl, ml/min	46.5 (15–86.9)
Hgb, g/dl	11.9 (6.1–18)
Hct (%)	35.6 (19.1–53.9)
INR ^a	2.2 (1.1–7.1)
aPTT, s	42.2 (36–81.4)
AST ^b , IU/l	27 (8–73)
ALT ^b , IU/l	19 (3–55)
ECT ^c , s	104.8 (84.1–125.5)
SBP, mmHg	120 (70–180)
HR, beats/min	76 (56–99)
Past medical history, no. (%)	
Atrial fibrillation	11 (100)
Hypertension	9 (82)
Diabetes	3 (27)
Heart failure	1 (9)
Stroke/TIA	3 (27)
Renal disease	3 (27)
CAD	4 (36)
PUD/GERD	3 (27)
Cancer	4 (36)
Recent trauma, no. (%)	4 (36)
Transferred from outside hospital ^d , no. (%)	1 (9)
Site of bleed, no. (%)	
Gastrointestinal	4 (36)
Intracranial	7 (64)
Concomitant antiplatelet/antithrombotic agents, no. (%)	
Clopidogrel	1 (9)
Aspirin	4 (36)

^a INR not available for one patient^b AST and ALT only available in nine patients^c ECT only measured in two patients^d Outside hospital management may be different from the management at UMass Memorial Medical Center

an ICH, four were the result of a traumatic event, and three were spontaneous (Fig. 1). Thirty-day mortality, which was determined by follow-up visits at our institution 30 days after discharge, was available for 10 of the 11 patients. Seven patients were alive at 30 days, and one patient was lost to follow-up. Death occurred in two patients with a spontaneous ICH and one patient with a traumatic ICH. The average lengths of hospital and ICU stay were 11 days (2–32 days) and 7 days (0–26 days), respectively.

Fig. 1 Spontaneous vs. traumatic ICH

Individual patient interventions received can be found in Table 2, and the interventions received for the specific site of bleeding can be found in Fig. 2. Six patients (55 %) received FFP, three patients (27 %) received platelets, four patients (36 %) received PRBCs, two patients (18 %) received rFVIIa, three patients (27 %) underwent surgical intervention, two patients received renal replacement therapy, one underwent hemodialysis (HD), and one received continuous veno-venous hemofiltration (CVVH). After consulting the nephrology service on patient number 8, CVVH was initiated, and the patient had TT, ECT, and dabigatran plasma levels drawn approximately every 3 h (Table 3, Fig. 3). After approximately 17 h, the CVVH line clotted, and the patient was switched to HD. The TT, ECT, and dabigatran plasma levels 6 h after CVVH was started were 81.2 s, 55.2 s, and 60 ng/ml (therapeutic range, 42–140 ng/ml), respectively. After 11 h, the TT, ECT, and dabigatran plasma levels dropped to 74.6 s, 41.6 s, and 17 ng/ml, respectively, and steadily fell thereafter.

Discussion

Patients presenting with dabigatran-related bleeding represent a challenge to the treating physician and medical team. Based on very little data regarding the appropriate reversal strategies for dabigatran-related bleeding, our institution has not developed a standard protocol to treating patients presenting with this unique coagulopathy. Although aggressive treatment strategies, including the use of rFVIIa, surgical intervention, and dialysis, were employed in 3 of the 11 patients, those three patients still expired. PCC was not an available option at our institution; therefore, only rFVIIa was used as a reversal agent. Patient number 1 expired on day 8 from massive spontaneous ICH which was not reversed with aggressive treatment

Table 2 Individual patient interventions and outcomes

Patient	Site of bleed	IVF	FFP	Platelets	PRBCs	Vit K	rFVIIa	Surgery	Dialysis	Outcome
1	ICH	+	+	+	–	+	+	+	–	Expired
2	GIH	+	+	–	+	–	–	–	–	Home
3 ^{ab}	GIH	+	+	+	+	+	–	–	–	Home
4 ^b	ICH	+	–	–	–	–	–	–	–	Home
5	ICH	–	–	–	–	–	–	–	–	Home
6	ICH	+	+	+	–	–	–	+	+	Expired
7 ^{bc}	ICH	+	–	–	–	–	–	–	–	Home
8	ICH	+	+	–	–	+	+	+	+	Expired
9	GIH	+	–	–	+	–	–	–	–	Home
10	GIH	+	+	–	+	+	–	–	–	Home
11 ^b	ICH	+	–	–	–	–	–	–	–	Rehab

^a Transferred from OSH on day 8

^b Patients were concomitantly on aspirin

^c Patient was also on clopidogrel

strategies such as surgical intervention and rFVIIa. Patient number 6 expired after only 2 days from a traumatic ICH while receiving dabigatran. Aggressive management strategies for this patient such as surgical intervention and hemodialysis were ineffective. In fact, the patient's ECT only decreased from 125.5 to 83.1 s (reference range, 22.6–29 s) after 3 h of dialysis. Patient number 8 expired after receiving rFVIIa, surgical intervention, and dialysis for the management of the spontaneous ICH that developed secondary to dabigatran anticoagulation. No patients in this observational case series suffered from any thrombotic event. To our knowledge, our study represents the largest case series of patients who presented with dabigatran-related bleeding to a large academic medical center. The high mortality rate (43 %) seen in the ICH group reflects a disparity in the lack of an effective reversal strategy for major, life-threatening hemorrhages in patients receiving dabigatran.

Fig. 2 Interventions vs. site of bleed

The American College of Chest Physician's Antithrombotic Therapy and Prevention of Thrombosis 2012 evidence-based clinical practice guidelines offer weak suggestions for containing major or life-threatening bleeding associated with dabigatran [15]. In the absence of urgent or emergent surgery in a patient receiving dabigatran, the guidelines recommend holding therapy for 24–48 h prior to a planned procedure [15]. In cases where immediate reversal is required, volume repletion; PRBC administration; local containment via surgery, suture, or cautery; and hemodialysis appear to be reasonable options [15]. Multiple case reports and animal studies have been published describing the use of rFVIIa or PCC to reverse dabigatran-related bleeding with mixed results on survival as well as reversal of laboratory parameters used to monitor dabigatran (i.e., TT, ECT, aPTT) [7–12, 16, 17]. Overall, based on the available published cases, current reversal strategies convey uncertain benefit, and patients presenting with massive hemorrhages have had dismal outcomes.

Due to the lack of an effective antidote and clearly defined reversal strategies, a systematic approach to evaluating patients who present with a dabigatran-related bleeding event should be employed by institutions who manage such patients. Treatment should be approached on an individual case-by-case basis, starting with identifying a few key factors. Obtaining information on when the last dose was taken can be extremely helpful in deciding how long the drug is expected to be active in the patient's body. Also, renal function is another important factor to consider, as any renal insult will prolong the half-life of dabigatran and, therefore, the patient's exposure to the drug. In our study, for example, 10 (91 %) patients were treated appropriately for their baseline renal

Table 3 TT, ECT, and dabigatran plasma levels of patient 8

Date	Time	Renal replacement	TT (s), (normal, 14–21)	ECT (s), (normal, 22–29)	Dabigatran plasma level (ng/ml) (normal, 42–140)
4/5	02:45			84.1	60
4/5	03:30	CVVH		79.5	37
4/5	06:30	CVVH		66.8	29
4/5	09:30	CVVH	81.2 (09:42)	55.2	31
4/5	12:30	CVVH	62.6	49.5	22
4/5	16:30	CVVH	61.9	45.9	63
4/5	20:30	CVVH	74.6	41.6	17
4/5	23:30	HD	52.3		
4/6	00:30	HD		33.9	15
4/6	04:30	HD	31.8	30.8	12
4/6	07:00	CVVH	27 (06:30)	31.3	None detected
4/6	12:00	CVVH	22 (11:00)	34.5	10
4/6	16:00	CVVH (off at 15:00)	23.4		
4/6	17:00		28.8		

function as well as their creatinine clearance on admission. One patient received inappropriate dosing with 150 mg of dabigatran twice daily with a baseline creatinine clearance of 24 ml/min, which may have contributed to the patient presenting with a GI bleed. In addition, laboratory tests such as aPTT, TT, and ECT may help in determining if dabigatran is still present. Although the aPTT is more a qualitative laboratory parameter that may help determine the presence of dabigatran in the serum, the TT and ECT may allow for a more quantitative measurement of dabigatran exposure, although not always readily available [18].

Current research is examining the effects of various reversal strategies including rFVIIa, PCC, as well as a neutralizing antibody selective for dabigatran both in vitro and in vivo [19–21]. Based on preliminary results, the neutralizing antibody demonstrated effective and specific binding and rapid

reversal of dabigatran [21]. Several other studies looking specifically at rFVIIa and PCC are currently ongoing [19, 20]. These studies will hopefully shed some light on an appropriate and effective reversal strategy for this potentially life-threatening bleeding condition.

The limitations of the present study should be considered. The retrospective design is inherently biased, and the data represents the experiences of only one large, academic medical center. Our identification of patients relied solely on the treating physician to contact a member of the pharmacy department; therefore, patients may have been missed if they were not reported to a pharmacist or cared for by a pharmacist on a critical care team. Another limitation to consider when evaluating the patients treated for dabigatran-related bleeding is the fact that 4 out of the 11 patients were concomitantly receiving antiplatelet therapy. All four of those patients did survive their bleeding event, so the impact of concomitant antiplatelet therapy is of questionable significance. Finally, our institution currently does not have a standard protocol for managing patients with dabigatran-related bleeding, and management varied depending on the treating physician.

Conclusions

Management and reversal of dabigatran-related bleeding present a challenge to any treating clinician as a patient presentation can be highly variable. Each case should be evaluated on a case-by-case basis, and management should be individualized for patients presenting with major and life-threatening dabigatran-related bleeding.

Fig. 3 TT, ECT, and dabigatran plasma levels of patient 8

Conflict of Interest The authors of this paper have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this study.

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