Published in final edited form as:
Thromb Res. 2013 August ; 132(2): e161–e163. doi:10.1016/j.thromres.2013.07.011.

Management of Bleeding Associated with Dabigatran and Rivaroxaban: a Survey of Current Practices

Lisa M. Baumann Kreuziger, MD and
University of Minnesota, Division of Hematology, Oncology, and Transplantation, Mayo Mail Code 480, 420 Delaware St. S.E. Minneapolis, MN, USA 55455 bauma260@umn.edu

Mark T. Reding, M.D.
University of Minnesota, Division of Hematology, Oncology, and Transplantation, Mayo Mail Code 480, 420 Delaware St. S.E. Minneapolis, MN, USA 55455 redin002@umn.edu

Dear Editors,

Dabigatran and rivaroxaban are anticoagulant alternatives to warfarin with advantages including uniform dosing and no required anticoagulation monitoring.[1][2] Assessment and management of dabigatran and rivaroxaban-associated bleeding is challenging because antidotes are not currently available, and the most appropriate assay to measure of the level of anticoagulation is debated.[3–6] Established methods to manage dabigatran and rivaroxaban-associated bleeding do not exist due to lack of comparative clinical trials. Therefore, we surveyed hematologists across the US to gauge how bleeding patients have been evaluated and managed.

Physician members of the Hemostasis and Thrombosis Research Society (HTRS) and US hemophilia center directors were queried electronically regarding the number of patients treated for dabigatran or rivaroxaban-associated bleeding, bleeding management and perceived effectiveness of management, and institutional treatment algorithms. Cases were identified as those experiencing major bleeding[7] or renal failure (creatinine clearance <30 ml/min). Availability and use of laboratory testing to measure the level of anticoagulation were assessed. Lastly, we evaluated physicians' level of concern regarding their ability to manage bleeding patients (scale 1–5). Participants were considered responders if one

Corresponding author: Lisa M. Baumann Kreuziger, MD, University of Minnesota, Mayo Mail Code 480, 420 Delaware St. S.E., Minneapolis, MN, USA 55455, Phone: +1 (612) 624-0123, Fax: +1 (612) 625-6919, bauma260@umn.edu.

Authorship Contributions

LBK designed the survey and completed analysis, manuscript writing and revisions. MTR contributed to survey design, manuscript review, and revisions.

Conflict of Interest Statement

A NIH T32 training grant supported LBK's fellowship. MTR served as consultant, speaker, advisory board member, and has received research funding from Novo Nordisk, Baxter, Bayer, Biogen Idec, Octapharma, and Pfizer.

question was answered. The University of Minnesota Institutional Review Board approved the study.

Overall response rate was 31.5% (48/152 surveyed) and 92% of respondents completed the survey. Our response rate was within previously published ranges of physicians' response to electronic surveys without incentives.[8][9] No significant differences in demographic or practice characteristics were found between survey respondents and non-respondents (Table 1). The lack of difference in baseline characteristics between respondents and non-respondents decreases but does not eliminate the possibility of non-response bias in our survey results.

Detailed management information was provided in 22 of 43 reported cases of dabigatran-associated bleeding (Table 2). Years in practice or participation in clinical trials were not associated with number of cases managed. No fatal bleeds were reported, and bleeding was controlled in all patients. Because dabigatran undergoes 80% renal excretion or metabolism but is only 35% protein bound, dialysis can remove dabigatran.[1] All patients with renal failure received dialysis and required a median of 4–5 sessions (range 1 to >7) to remove dabigatran's anticoagulant effect. Dialysis was reported as the most effective management strategy in 4/5 of dabigatran-associated bleeding episodes managed with dialysis (Table 2). Dabigatran was withheld in all reported cases of dabigatran bleeding and was considered the most effective strategy in 82% of patients. Factor concentrates were used in 9 patients experiencing major bleeding on dabigatran. Reported doses were lower than recommended to treat hemophilia,[10–12] and multiple doses of activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rfVIIa) were used. Factor concentrates were perceived as effective in 50–80% of the patients bleeding with dabigatran. In the 2 cases where both prothrombin complex concentrates (PCC) and rfVIIa were given, both were considered effective by the treating physician. Unfortunately, the limited number of bleeding patients managed with factor concentrates does not allow for recommendations regarding product choice or dosing to be made.

Fewer cases of rivaroxaban-associated bleeding were reported (Table 2). Similar to dabigatran, management of bleeding involved withholding the drug and local measures. aPCC was administered in 1 case. All interventions used to treat rivaroxaban-associated bleeding were perceived as effective. These patients are the first reported cases of managing rivaroxaban-associated bleeding in the literature.

Algorithms to manage bleeding patients have been proposed by several authors based on animal data and expert opinion.[2][3] Management algorithms were available at 12 (25%) of the respondents' institutions. Only 25% of the algorithms recommended antifibrinolytic medication, whereas all but one algorithm contained the use of factor concentrate (50% aPCC, 66% PCC, and 83% rfVIIa). Nine of the 12 institutional algorithms contained more than one factor concentrate. Factor concentrates were widely available; 62% of institutions had PCC, 87% had aPCC, and 98% had rfVIIa on-site. Only three bleeding patients were managed at hospitals with treatment algorithms; thus, inferences as to the influence of the treatment algorithm on the management strategy cannot be made.

Due to predictable pharmacokinetics, dabigatran and rivaroxaban do not require monitoring during treatment, but understanding the degree of anticoagulation is essential in a bleeding patient.[13] Dabigatran increases the prothrombin time (PT/INR) variably and the activated partial thromboplastin time (aPTT) in a non-linear fashion.[1] In the reported dabigatran bleeding cases, the PT/INR and aPTT were used to assess level of anticoagulation in 59% and 100% of cases, respectively. The thrombin time (TT) is the most sensitive assay to measure dabigatran's effects[1] and was used in 91% of dabigatran-associated bleeding. At high dabigatran concentrations, the TT may be unmeasureable. A dilute TT can be used reliably to measure dabigatran even at high concentrations;[14] however, this assay was only available in 4 institutions and was not used in any of the bleeding cases. The ecarin clotting time (ECT) may more effectively assess dabigatran concentrations in overdose settings because of decreased sensitivity compared to the TT.[1] ECT was used in only 23% of dabigatran bleeding episodes, and these cases were managed in 2 of the 10 hospitals that had ECT available on-site. Laboratory assessment of bleeding patients on dabigatran is challenging because the assays most efficacious in overdose settings, ECT and dilute TT, are not widely available even at academic US centers.

Similar to the dabigatran bleeding cases, 60% of the rivaroxaban bleeding patients were evaluated with PT/INR and 100% with aPTT. Chromogenic anti-Xa assays can be standardized to measure rivaroxaban[15] and rivaroxaban anticoagulation was assessed using an anti-Xa assay in all reported bleeding cases. Anti-Xa assays were available on-site in 91% of the respondents' hospitals including academic, academic affiliated and community practices. Therefore, the ability to measure rivaroxaban anticoagulation via anti-Xa is more accessible than assays for dabigatran.

A majority of physicians remain concerned about their ability to manage bleeding patients on the new oral anticoagulants; 27% of physicians reported moderate concern, 30% noted moderately high and 25% reported high concern. Only 9% of physicians reported mild and no concern. Physicians with moderate to high levels of concern attributed their apprehension to lack of established effective management, antidote, or experience with managing bleeding patients. Whereas physicians with only mild concern referenced infrequent major bleeding rates as the reason for their minimal concern. Average level of concern was lower in physicians who participated in clinical trials than in physicians who had not participated in trials, but this was not statistically significant (Mean 2.6 vs 3.6, p=0.07). Level of concern was not associated with years in practice, number of cases managed, or availability of treatment algorithm. Respondents' high level of concern regarding their ability to manage hemorrhage illustrates the unease associated with widespread use of the new anticoagulants.

Our survey results show management of dabigatran and rivaroxaban-associated bleeding varies. Effective management included withholding the drug or local measures in most cases. Factor concentrates were prescribed in 41% of dabigatran-associated bleeding, but a specific product cannot be recommended because of similar frequency of concentrate use and perceived effectiveness. Surprisingly, most US academic institutions do not have dilute TT or ECT to measure elevated concentrations of dabigatran; whereas anti-Xa assays are widely available. Non-malignant hematologists remain concerned about their ability to

manage patients, which reiterates the need for registries or multicenter trials to determine the best management strategy for dabigatran and rivaroxaban-associated bleeding.

Acknowledgments

Thank you to Eileen Harwood, Ph.D. for survey design assistance, Ryan Shanley for biostatistical review, Michael Franklin for manuscript editing, and the HTRS leadership, membership and staff for supporting the survey.

Role of the Funding Source

We acknowledge NIH T32 Training grant 5T32HL00706 for funding LBK's time to complete this project. The funding source had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication

References

1. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010; 103:1116–1127. [PubMed: 20352166]
2. Schulman S, Crowther M. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012; 119:3016–3023. [PubMed: 22302737]
3. Kaatz S, Kouides P, Garcia D, Spyropolous AC, Crowther M, Douketis JD, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol. 2012; 87(Suppl 1):S141–S145. [PubMed: 22473649]
4. Samama MM. Which test to use to measure the anticoagulant effect of rivaroxaban: The antifactor Xa assay. J Thromb Haemost. 2013; 11:579–580. [PubMed: 23398670]
5. Tripodi A. Which test to use to measure the anticoagulant effect of rivaroxaban: The prothrombin time test. J Thromb Haemost. 2013; 11:576–578. [PubMed: 23398681]
6. Baumann Kreuziger L, Morton C, Dries D. New anticoagulants: A concise review. J Trauma Acute Care Surg. 2012; 73:983–992. [PubMed: 22976421]
7. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3:692–694. [PubMed: 15842354]
8. Braithwaite D, Emery J, De Lusignan S, Sutton S. Using the Internet to conduct surveys of health professionals: a valid alternative? Fam Pract. 2003; 20:545–551. [PubMed: 14507796]
9. Viera A, Edwards T. Does an offer for a free on-line continuing medical education (CME) activity increase physician survey response rate? A randomized trial. BMC Res notes. 2012; 5:129. [PubMed: 22397624]
10. Grifols Biologicals Inc. Profilnine® SD prescribing information. 2010 Aug.
11. Baxter. FEIBA® prescribing information. 2010 Oct. 3/11/2013.
12. Novo Nordisk Inc. NovoSeven RT® Coagulation Factor VIIa prescribing information. 2010 Jan. 3/11/2013.
13. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. Clin pharmacokinet. 2009; 48:1–22. [PubMed: 19071881]
14. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. Blood Coagul Fibrinolysis. 2012; 23:138–143. [PubMed: 22227958]
15. Lindhoff-Last E, Samama MM, Ortel TL, Weitz JI, Spiro TE. Assays for measuring rivaroxaban: their suitability and limitations. Ther Drug Monitoring. 2010; 32:673–679.

Table 1

Baseline characteristics of survey respondents and non-respondents. Chi-square testing compared respondents to non-respondents.

	Respondent (n=48)	Non-Respondent (n=104)	p-value
Male n (%)	24 (50%)	56 (54%)	0.66
Academic Practice n (%)	37 (77%)	88 (85%)	0.26
Hemophilia Treatment Center n (%)	42 (88%)	88 (85%)	0.64
Level 1 Trauma Center n (%)	30 (63%)	71 (69%)	0.43
Duration in Practice median (range) years	15.5 (1–40)		
Clinical Trial Participants n (%)	6 (13%)		

Table 2

Reported dabigatran and rivaroxaban-associated bleeding episodes and perceived effectiveness of management strategies used in bleeding.

	Dabigatran	Rivaroxaban
Reported Cases n	43	5
Available Management Information n	22	5
Bleeding stopped n (%)	22 (100%)	5 (100%)
Major Bleeding[4] n (%)	11/21 (52%)	3/5 (60%)
Renal failure n (%)	5/21 (24%)	2/5 (40%)
Effectiveness of Management Strategies		
Withholding Medication	18/22 (82%)	4/4 (100%)
Local Measures	7/10 (70%)	2/2 (100%)
Invasive Procedure	0/1 (0%)	
Dialysis	4/5 (80%)	
Antifibrinolytic	1/2 (50%)	
PCC	3/4 (75%)	
Reported Dose	20–50 Units/kg	
Mean Number of Doses	1	
aPCC	1/2 (50%)	1/1(100%)
Reported Dose	NR	
Mean Number of Doses	2	
rfVIIa	4/5 (80%)	
Reported Dose	10–40 mcg/kg	
Mean Number of Doses	2 (range 1–3)	

Effectiveness of Management Strategies: Fractions represent cases when perceived effective/cases when intervention used.

PCC=prothrombin complex concentrate, aPCC= activated prothrombin complex concentrate, NR=Not Reported, rfVIIa=recombinant activated Factor VII.