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The Evolution of the Management of Patients with Dabigatran Associated Hemorrhage

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Dabigatran is a competitive direct thrombin inhibitor approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, for the treatment of deep venous thrombosis and pulmonary embolism and to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated. Dabigatran was developed as an alternative to warfarin but, unlike warfarin, dabigatran does not require laboratory monitoring or dose adjustments because of its predictable pharmacokinetics and pharmacodynamics profile. Although three novel oral anticoagulants (NOACs) have subsequently been approved by the FDA, dabigatran remains the only NOAC which is a direct thrombin inhibitor.

In the first major trial involving dabigatran, the RE-LY trial, dabigatran 150 mg twice daily demonstrated superiority for stroke prevention with similar bleeding rates when compared to warfarin [1]. The rate of major bleeding was 3.36% per year in the warfarin group, compared to 3.11% per year in the group receiving 150 mg dabigatran (P=0.31). Although the rate of major bleeding was not significantly different, there were important differences between the two drugs with respect to the types of bleeding. Dabigatran had a lower rate of intracerebral bleeding (0.10% per year vs. 0.38% per year; P<0.001) while the rate of gastrointestinal bleed was increased compared to warfarin (1.51% per year versus 1.02% per year, p<0.001). The mortality rate was 4.13% per year among warfarin treated patients and 3.64% per year among patients receiving dabigatran (P=0.051), suggesting a potential mortality benefit in atrial fibrillation patients taking dabigatran compared to those taking warfarin. Despite these impressive results, concerns remained about how to manage bleeding complications or the need for emergent procedures in patients taking dabigatran without the existence of an antidote.

In spite of this concern, no clear consensus or guidelines had been formed regarding the management of patients that are bleeding on dabigatran. Therefore, in many situations, clinicians were left to manage patients with dabigatran associated hemorrhage without specific guidance or protocols. Furthermore, especially early on, familiarity with the drug itself varied widely between providers and institutions. Gradually, various reversal strategies were suggested including the use of hemodialysis (HD), recombinant human activated factor VII (rhFVIIa), FFP, prothrombin complex concentrates (PCC) and activated charcoal to reverse the effects of dabigatran or delay its absorption [2-4].

Due to a lack of specific guidance for clinicians about how to manage patients with dabigatran associated hemorrhage, we published what was the largest case series to date outlining our experience with dabigatran associated bleeding [5]. Over a 14 months period from 2012-2013, we detailed 8 cases of dabigatran associated hemorrhage that presented to our university medical center. The paucity of cases during that time, despite being a high volume academic referral center, is important to note because it underscores the point that life-threatening dabigatran associated hemorrhage remains a rare clinical event. We observed significant heterogeneity in the management of patients with dabigatran associated hemorrhage which was not surprising given the aforementioned factors. However, despite the wide variance in the management strategies and clinical outcomes for these patients, certain diagnostic and therapeutic modalities began to emerge as beneficial. Based on analysis of our early experiences, we were able to make rational, streamlined recommendations that could be implemented by clinicians who encountered patients with dabigatran associated hemorrhage. From a diagnostic standpoint, we recommended that initial laboratory testing should include a comprehensive metabolic panel, CBC, aPTT, thrombin time (TT) and dabigatran level (if available). Other laboratory tests were not found to be of benefit and caused confusion for clinicians who were not familiar with how to interpret these tests with respect to dabigatran. With respect to treatment we consistently found that hemodialysis (HD) was the best method to reduce dabigatran levels rapidly. If the patient was hemodynamically stable enough for HD, we recommend a 4 hour HD session followed by continuous veno-venous hemodialysis (CVVHD) until the aPTT and TT normalized. Once CVVHD has been stopped, close clinical monitoring for recurrent bleeding along with serial measurements of aPTT and TT were recommended to be done (every 1-2 hours initially) to monitor for dabigatran rebound. If dabigatran rebound was detected, we recommended restarting CVVHD until aPTT and TT return to normal levels. If the patient is not hemodynamically stable enough for HD (usually because of hypotension), CVVHD was recommended.

Although most patients in our case series received recombinant factor VIIa (rFVIIa) and fresh frozen plasma (FFP), there was no clear evidence that either was beneficial in the management of dabigatran associated hemorrhage. There is no theoretical advantage to using rFVIIa or FFP based on the mechanism of action of dabigatran; however, none of our patients were rigorously evaluated with objective coagulation parameters drawn after their administration to accurately assess the extent of the treatment effect. The patients were also concurrently receiving other therapies (dialysis, red blood cell and platelet transfusion, etc.) which complicated understanding the role of FFP and rhFVIIa in promoting hemostasis in dabigatran associated hemorrhage. Others have reported the successful use of prothrombinase complex concentrates (PCCs) in the management of dabigatran associated hemorrhage [6-8] but none of our patients were given PCCs so we were unable to comment on the appropriateness of PCC therapy.

In lieu of a specific antidote or reversal agent, the goal of our work was to help inform medical decision makers and enhance their ability to treat patients with dabigatran associated hemorrhage. Fortunately, a specific antidote for dabigatran, idarucizumab, has recently been approved for clinical use. Idarucizumab is a monoclonal antibody fragment that binds dabigatran with 350 times greater affinity than thrombin [9]. Consequently, idarucizumab binds dabigatran and neutralizes its activity [9]. The first clinical trial to describe the safety and efficacy of idarucizumab was the recently published REVERSE-AD trial [10]. REVERSE-AD is an ongoing prospective cohort study designed to determine the safety of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran [10,11]. The trial consists of 2 groups, patients who have serious bleeding while taking dabigatran (group A) or patients taking dabigatran who require an urgent procedure (group B) [10,11]. The primary end point is the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after administration of idarucizumab, based on dilute thrombin time (dTT) or ecarin clotting time (ECT). An interim analysis recently published in the New England Journal of Medicine, included 90 patients who received idarucizumab (51 patients in group A and 39 in group B) [10]. There were 68 patients with an elevated dTT and 81 with an elevated ECT and after administration of 5 g idarucizumab, the median maximum percentage reversal was 100%. Within minutes after the administration of idarucizumab, 88-98% of patients had normalization of their dTT and/or ECT. Furthermore, the duration of the complete reversal effect was still present 24 hours after administration in 79% of patients. As a secondary endpoint, restoration of hemostasis was also reported in REVERSE-AD. Among 35 group A patients, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 group B patients who underwent a procedure, normal intraoperative hemostasis was reported in 33 patients, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated [10].

Since the approval of dabigatran in 2010, the management of dabigatran associated hemorrhage has rapidly evolved. In a relatively short period of time, management of these patients has gone from theoretical and intuitive to a more rational and streamlined approach to potent and highly effective and specific antidote. NOACs continue to grow in popularity and there safety has been shown to be similar or superior to warfarin with respect to bleeding and mortality despite the lack of established antidotes or reversal agents [12-14]. Fortunately, life threatening NOAC associated bleeding remains uncommon but with the development of idarucizumab it will be interesting to see how the safety profile of dabigatran changes. Given the unprecedented outcomes with respect to complete reversal of anticoagulation within minutes of administration, one would presume that idarucizumab will add a significant level of safety which has never previously existed for any anticoagulant. As the availability of idarucizumab becomes more widespread, this could become a game changer with respect to how we as clinicians council our patients about their anticoagulation options, especially those at the highest risk for bleeding complications.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 361: 1139-1151
2. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, et al. (2010) Dabigatranetexilate--a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 103: 1116-1127.
3. Peacock WF, Gearhart MM, Mills RM (2012) Emergency management of bleeding associated with old and new oral anticoagulants. Clin Cardiol 35: 730-737.
4. Singh T, Maw TT, Henry BL, Pastor-Soler NM, Unruh ML, et al. (2013) Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: A single center experience. Clin J Am Soc Nephrol 8: 1533-1539.
5. Kumar R, Smith RE, Henry BL (2015) A review of and recommendations for the management of patients with life-threatening dabigatran-associated hemorrhage: A single-center university hospital experience. J Intensive Care Med 30: 462-472.
6. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, et al. (2011) Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. Circulation 124: 1573-1579.
7. Weitz JI, Quinlan DJ, Eikelboom JW (2012) Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation 126: 2428-2432.
8. Dager WE, Gosselin RC, Roberts AJ (2013) Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. Crit Care Med 41: e42-e46.
9. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, et al. (2013) A specific antidote for dabigatran: Functional and structural characterization. Blood. 121: 3554-3562.
10. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, et al. (2015) Idarucizumab for dabigatran reversal. N Engl J Med 373: 511-520.
11. Pollack CV Jr, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, et al. (2015) Design and rationale for re-verse ad: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost 114: 198-205
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365: 883-889.
13. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365: 981-992.
14. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, et al. (2011) Apixaban in patients with atrial fibrillation. N Engl J Med 364: 806-817.