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Editorial

Management of Dabigatran Associated Hemorrhage

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Dabigatran, an oral direct thrombin inhibitor (DTI), is approved by the Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation with at least one risk factor for stroke [1]. In the RE-LY trial, dabigatran 150 mg twice daily demonstrated superiority in preventing stroke and systemic embolism (RR 0.66 95%CI 0.53-0.82, $p<0.001$) with similar major bleeding rates (RR 0.93 95%CI 0.81-1.07, p=0.31) when compared to warfarin [2]. Due to its predictable pharmacokinetics and pharmacodynamics, dabigatran does not require routine monitoring [3]. However, there are certain clinical settings such as the need for an emergent invasive procedure, overdose or hemorrhage, where knowing the patient's degree of anticoagulation is necessary.

Despite the excitement generated by evidence of a decrease in stroke without an increased risk of bleeding and apparent mortality benefit, the bleeding risk on dabigatran is not zero and some patients will inevitably experience clinically significant or life-threatening bleeding. Many physicians feel comfortable managing bleeding complications on older anticoagulants like warfarin and heparin, due to extensive experience with the medications along with antidotes to reverse their effects as well ad established protocols for treating anticoagulant associated hemorrhage. However, most physicians have no physicians, they have no such experience with dabigatran; there is neither a method to assess dabigatran activity nor specific antidote for its reversal. There is a paucity of protocols, guidelines and recommendations for how to manage dabigatran associated hemorrhage bleeding.

Peak plasma concentration of dabigatran is reached 0.5-2 hours after oral administration [3]. The timing of dabigatran administration relative to the blood sampling should be taken into consideration when interpreting the coagulation tests. Although the increase in activated partial thromboplastin time (aPTT) is initially linear, as the dose of dabigatran increases, it has a curvilinear dose response curve at higher levels of dabigatran (>200ng/ml) [4]. Therefore, aPTT correlates better to dabigatran at lower plasma concentrations. Even with the above limitations, aPTT is widely available and can be rapidly reported, and is recommended for qualitative assessment of dabigatran activity. Therefore thrombin time (TT) cannot be used to monitor dabigatran activity because it is highly sensitive and exceeds its maximum measurable value even for sub-therapeutic dabigatran levels [4]. Nevertheless, high sensitivity makes TT an excellent screening test to rule out any anticoagulant activity. The prothrombin time (PT) is relatively insensitive to plasma dabigatran level and is not recommended to measure its anticoagulation activity [4]. Ecarin clotting time (ECT) is a meizothrombin generation test which measures the activity of direct thrombin inhibitors and is insensitive to the presence of heparinoids. Although ECT is highly sensitive to dabigatran concentration, it is neither widely available nor standardized for routine laboratory monitoring of dabigatran [4,5]. Plasma dabigatran levels can be semi-quantitated using dilute thrombin time (DTI) methods. The minimum detectable dabigatran level using this method is 40ng/ml but the turnaround time of up to 24 hours limits its use in emergency settings.

Dabigatran is a low molecular weight molecule (630 Daltons) with a low plasma protein binding of ~35% and its primary route of excretion is via the kidneys (~80%) [6]. These properties suggest that dabigatran can be removed by hemodialysis (HD). The manufacturer suggests that a high flux dialyzer with a dialysate flow rate of 700 mL/min is capable of removing ~49% to 57% of dabigatran from plasma over a 4 hour period when the blood flow rate is between 200 to 300 ml/min. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen [6]. In settings of dabigatran toxicity, rebound increase in plasma level up to 87%, post-dialysis, have been reported [7]. It has been proposed that this issue of dabigatran rebound should be addressed by using CVVHD after intermittent HD [7]. Recombinant activated human factor VII (rhFVIIa) is non-plasma derived potent procoagulant. It is an activated form of coagulation factor VII which bypasses the need for active factor VIII and IX. Beneficial effect of rhFVIIa in dabigatran associated hemorrhage has been reported but there is no clear evidence of its effectiveness in the literature [8]. The use of rhFVIIa in non-hemophilic patients may increase the risk of thromboembolism and should be used with caution [9]. Prothrombin complex concentrates (PCCs) contains vitamin K dependent coagulation factors II, VII, IX and X and the antithrombotic factors, protein C and S. The PCCs are available in two categories: nonactivated (3- and 4-factor PCC) and activated (FEIBA- factor eight inhibitor bypassing activity). In a study of 12 healthy volunteers receiving dabigatran 150 mg twice daily for 2.5 days, 4-factor PCC had no effect on dabigatran activity [10]. In a case report of a 67 year

Table 1: Recommended laboratory studies and therapeutic interventions for managing dabigatran associated hemorrhage.

	Recommended	Consider if clinically indicated
Coagulation and laboratory Studies	➢ aPTT ➢ TT ➢ Dabigatran level ➢ ECT ➢ CBC	➢ Fibrinogen
Therapeutic Interventions	➢ Hemodialysis followed by CVVHD ➢ CVVHD (if too hypotensive for HD)	➢ Activated Charcoal ➢ Volume resuscitation ➢ PRBC transfusion ➢ Platelet Transfusion ➢ Insufficient data: ➢ PCC ➢ rhFVIIa

old with symptomatic atrial fibrillation who developed a life threatening hemorrhage bleeding during cardiac ablation, FEIBA (26U/kg) administration effectively controlled the bleeding within 15 minutes [11]. The use of PCCs can also increase the risk of thromboembolism. Lack of sufficient clinical data supporting its effectiveness, limits its role in reversal of dabigatran. Unlike the reversal of warfarin, fresh frozen plasma (FFP) and vitamin K have no role in reversal of dabigatran activity. Dabigatran as a DTI does not reduce circulating clotting factors, so the effect of administering FFP to supplement clotting factors will not reverse dabigatran's effect [4]. Vitamin K, even in large doses, has no ability to affect the binding of dabigatran to the active site of thrombin. Platelet transfusion should be considered in patients on antiplatelet therapy. Clinical judgment should be used to make the decision regarding platelet transfusion in actively bleeding patients as platelet count is less informative in patients taking antiplatelet agents because their bleeding diathesis is secondary to an acquired platelet dysfunction, not thrombocytopenia.

Based on current knowledge, the following recommendations are made the management of dabigatran associated hemorrhage (Table 1). These recommendations may change significantly in the future as new data becomes available.

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