is an issue that could prove life-threatening (ie, should there be a major vascular complication).

A current international multicenter randomized controlled trial in patients undergoing TAVR is ongoing to determine the treatment effect (both safety and efficacy) of using bivalirudin instead of unfractionated heparin (BRAVO) [5]. Further studies are necessary to understand the use of bivalirudin as an anticoagulant in comparison with standard heparin therapy in TAVR.

References

Type A Aortic Dissection in a Patient on Dabigatran: Hemostasis Post Circulatory Arrest

Elena Ashikhmina, MD, PhD, Nicole Tomasello, BA, Jean Marie Connors, MD, Jama Jahanyar, MD, PhD, Michael Davidson, MD, and K. Annette Mizuguchi, MD, PhD

Departments of Anesthesiology, Perioperative and Pain Medicine, and Cardiac Surgery, and Division of Hematology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

We present a successful case of prevention of postoperative hemorrhage in a 70-year-old male on dabigatran, who developed an acute type A aortic dissection and subsequently underwent an emergent ascending aortic replacement.


Dabigatran etexilate is a new oral direct thrombin inhibitor approved for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [1, 2]. The number of patients on dabigatran continues to grow because of its convenience compared with warfarin. However, dabigatran has no antidote and the management of perioperative hemostasis for emergent cardiac surgery is uncertain and challenging.

A 70-year-old, obese (body mass index 51.5 kg/m²) male with a history of atrial fibrillation taking dabigatran 150 mg twice daily, sick sinus syndrome with a permanent pacemaker, hypertension, hyperlipidemia, and obstructive sleep apnea, presented to our hospital with acute sharp chest pain and diaphoresis. Computed tomographic angiogram demonstrated an acute type A aortic dissection requiring an emergent operation despite significant risk of bleeding; the last dose of dabigatran was given 4 hours prior to arrival in the operating room. Initial preoperative coagulation tests showed prothrombin time (PT) of 16 seconds (reference range [RR] 11.9 to 14.1), international normalized ratio (INR) of 1.3 (RR 0.9 to 1.1), partial thromboplastin time (PTT) of 47.5 seconds (RR 23.8 to 36.6). Although serum level of dabigatran test is not available at our institution, documented recent intake of dabigatran, moderately impaired renal function (estimated glomerular filtration rate of 53.3 mL/minute by the Modification of Diet in Renal Disease method), increased INR and PTT with normal liver function all suggested therapeutic level of dabigatran at the time of surgical incision.

Ascending aortic replacement with an allograft was performed with a total of 237 minutes of cardiopulmonary bypass (CPB), 127 minutes of aortic cross-clamp and 28 minutes of circulatory arrest at 18°C. Initial heparin dose was 26,000 units (U) with a total of 50,000 U given during bypass to maintain heparin level of 2 U/mL or greater and activated clotting time greater than 350 seconds. Considering the high probability of excess bleeding, we elected a multimodal approach to ensure adequate hemostasis. We continuously infused aminocaproic acid, and after circulatory arrest while on bypass we initiated zero balanced ultrafiltration (Hemocor HPH hemocoagulator; MEDIVATORS Inc, Minneapolis, MN) with 4L of normal saline and 5 L of renal replacement fluid (PrismaSATE; Gambro, Lakewood, CO) to decrease dabigatran plasma concentration. Additionally, prothrombin complex concentrate (PCC) factor eight inhibitor bypassing activity (FEIBA; Baxter Healthcare, Deerfield, IL), 20 U/kg actual body weight, was given after protamine administration. Post-bypass INR of 1.8 and platelets of 86 K/μL were corrected with a transfusion of 3 units of fresh frozen plasma (FFP) and a unit of platelets. Autologous washed red blood cells (470 mL) were returned to the patient.

On admission to the intensive care unit we noted PT of 16.1 seconds (RR 11.9 to 14.1 seconds), INR of 1.3 (RR 0.9 to 1.1), PTT of 68.2 seconds (RR 23.8 to 36.6), fibrinogen 367 mg/dL (RR 200 to 450 mg/dL). Maximal chest tubes output was 100 ml/hour (0.7 ml/kg/hour) during the first 2 postoperative hours. Chest tubes were removed on postoperative day 3 (total output of 800 cc of serosanguineous exudate). The patient required no blood...
products postoperatively. He was extubated on postoperative day 1 and discharged to home on postoperative day 9.

Comment

Dabigatran (Pradaxa; Boehringer Ingelheim, Ridgefield, CT) is an oral direct thrombin inhibitor approved in 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [1]. It is a specific competitive inhibitor of free and fibrin-bound thrombin, affecting thrombin-mediated conversion of fibrinogen to fibrin. Peak plasma levels are achieved within 2 hours of administration and the half-life is 12 to 14 hours. It is mainly eliminated by the kidneys with greater than 80% excreted unchanged in the urine. At present it does not have a reversal agent.

Dabigatran can be removed by hemodialysis [2] and ultrafiltration as its molecule is small (627.75 g/mol), and only 35% of the drug is protein bound. Two to 4 hours of dialysis has been shown to reduce dabigatran plasma concentration by approximately 60% [1, 3]. Hemodialysis for dabigatran reversal has been described in case reports pre- and post-bypass [4, 5]. However, in our case, pre-bypass hemodialysis was not feasible because of the need for emergent surgical intervention. Instead, we added a hemoconcentrator into the CPB circuit, and performed hemo-ultrafiltration while on bypass.

Other strategies to reverse dabigatran include the use of recombinant activated factor VII and PCCs. Both activated and nonactivated PCCs have been shown to normalize coagulation tests in vitro [6, 7]. In our case we chose FEIBA, containing nonactivated II, IX, X, and activated VII factors. We used FEIBA, as in vitro nonactivated 4-factor PCC has shown limited efficacy in correcting dabigatran associated coagulopathy, whereas FEIBA has an in vitro effect against dabigatran [7] and is less expensive than rVIIa. Administration of activated clotting factors comes with a higher potential for thrombus. Thus we used a lower dose of FEIBA (20 U/kg), compared with its optimal dose (20 to 50 U/kg) for off-label (non-hemophiliac bleed) use.

Protamine, vitamin K, and FFP do not reverse the anticoagulant effect of dabigatran. Although FFP can be useful in treating coagulation factor depletion, it is not effective in reversing inhibition of coagulating factors. Activated charcoal with sorbitol can decrease dabigatran concentration if given within 2 to 3 hours of drug ingestion but because of the need of emergent aortic surgery, this was not considered.

We were unable to monitor the effectiveness of dabigatran elimination in our patient due to lack of appropriate tests (dabigatran plasma concentration, dilute thrombin clotting time, thrombin activity) in our clinical laboratory, as conventional tests of coagulation do not accurately reflect dabigatran concentration. Activated partial thromboplastin time is unsuitable for precise quantification of the anticoagulant effect of dabigatran [8]. Similarly, PT/INR changes very little despite larger changes in dabigatran concentration. Activated clotting time is unreliable as it changes nonlinearly at higher dabigatran concentrations. Hemoclot Thrombin Inhibitor assay (Aniara, West Chester, OH) could be of help, but it is not yet commercially available.

Our patient was at a high risk for bleeding after aortic dissection repair due to recent dabigatran administration, impaired renal function, extensive surgical intervention, and multifactorial bleeding after deep hypothermic circulatory arrest. Thus, we elected a multimodal approach to prevent and control the bleeding. We infused amino-caproic acid to prevent hyperfibrinolysis from CPB and performed a hemo-ultrafiltration during CPB. Once off bypass, the surgeons noted good clot formation but because of the uncertainty of the effectiveness of dabigatran elimination by ultrafiltration, FEIBA was administered. We administered FFP and platelets based on the results of post-bypass coagulation tests demonstrating thrombocytopenia and likely deficit of clotting factors in the presence of normal fibrinogen. Despite the magnitude of the operation and the tendency toward coagulopathy, this patient received no transfusions of packed red blood cells.

In conclusion, a multimodal approach for prevention of postoperative hemorrhage, consisting of a continuous infusion of an antifibrinolytic, intraoperative ultrafiltration, anti-inhibitor coagulant complex administration, and a transfusion of FFP and platelets was successful in a patient with moderate renal impairment on dabigatran presenting for an emergent type A aortic dissection repair with circulatory arrest.

References