Management of intracranial bleeding associated with dabigatran use in a neuroscience hospital

Alejandro Perez, MD
*Thomas Jefferson University Hospital, Alejandro.Perez@jefferson.edu*

Lynda Thomson
*Thomas Jefferson University, Lynda.Thomson@jefferson.edu*

Geno J. Merli, MD
*Thomas Jefferson University Hospital, Geno.Merli@jefferson.edu*

Let us know how access to this document benefits you

Follow this and additional works at: https://jdc.jefferson.edu/petfp

Part of the [Medical Specialties Commons](https://jdc.jefferson.edu/petfp)

Recommended Citation

Perez, MD, Alejandro; Thomson, Lynda; and Merli, MD, Geno J., "Management of intracranial bleeding associated with dabigatran use in a neuroscience hospital" (2013). *Department of Pharmacology and Experimental Therapeutics Faculty Papers*. Paper 43. https://jdc.jefferson.edu/petfp/43
Background: Dabigatran, an alternative to warfarin for prevention of stroke with non-valvular atrial fibrillation (AF), offers advantages of a fixed dosage, minimal laboratory monitoring and limited interaction. Dabigatran requires dosing adjustment in renal dysfunction and is contraindicated if severe dysfunction. No identified dabigatran reversal agent exists.

Methods: As part of an ongoing quality initiative, novel anticoagulant associated adverse events (AE) are monitored at a dedicated neuroscience hospital.

Results: 5 cases of intracranial bleeding associated with dabigatran occurred from 12/2011-4/2012. All patients were on anticoagulation for AF, the most common dose of dabigatran was 150 mg BID. Mean admission values were as follows: age 83.2 yrs (range 79-90), serum creatinine 1.48 mg/dL (range 0.9-3.5), creatinine clearance 45.6 mL/min (18-59) and aPTT 49 seconds (range 32-60). Strategies for the management of bleeding included withholding dabigatran, supportive care, administration of blood products and hemodialysis, when required. Dabigatran was initiated on 5 patients. One patient had 3 dialysis sessions in an effort to normalize coagulation assays and had transfusions with 10 units of platelets and 4 units of fresh frozen plasma in an effort to stabilize bleeding. One patient died. Mean time for aPTT to normalize when abnormal on admission was 38.8 hours (range 21-47).

Conclusions: Appropriate patient selection is required to prevent dabigatran associated AE, especially in the setting of advanced age and kidney dysfunction. aPTT values may remain prolonged for extended periods despite efforts to normalize. Hospitals need a defined management plan for major bleeding associated with novel anticoagulants.

Vitamin K antagonists (VKAs), such as warfarin, have been the mainstay of therapy for long-term anticoagulation management of AF for over 60 years. Unfortunately, VKAs have:

- a slow onset of therapeutic effect
- a narrow therapeutic index
- numerous dietary and drug interactions
- a variable anticoagulation response
- a requirement for frequent anticoagulation monitoring

This prompted the development of novel oral anticoagulants which directly target crucial steps in the coagulation cascade, either Factor Xa or thrombin (Factor IIa). Dabigatran exetilate, hereafter referred to as dabigatran, is an oral direct thrombin inhibitor, and the first of the novel oral anticoagulants to gain widespread use in the U.S. for anticoagulation in the setting of non-valvular AF.

There is currently no available reversal agent for dabigatran, although it is dialyzable. Because of the predominant renal elimination, kidney dysfunction can also predispose to potential bleeding complications. As the use of dabigatran began to increase in the community, an initial surveillance of associated bleeding episodes in a neuroscience hospital was characterized.

An emergency management team including the pharmacy, nephrology, hematology and/or vascular medicine consult services were notified when patients were admitted to the hospital for dabigatran - associated intracranial bleeding.

These patients had their hospital course followed for an ongoing quality assessment of how to best manage these occurrences and help prevent them in the future.

REFERENCES (CONTINUED)

RESULTS

5 cases of intracranial bleeding associated with dabigatran occurred from 12/2011-4/12. All patients were on anticoagulation for AF, the most commonly prescribed dose of dabigatran was 150 mg BID.

Case 1: 79 year old male with PMH of paroxysmal AF, HTN, CAD, coronary bypass, bioprosthetic aortic valve replacement and COPD presented to an outside hospital (OSH) with acute onset of right sided weakness and facial droop. Outpatient dabigatran dose had been 75 mg po BID. A CT scan of the head showed a left basal ganglia intraparenchymal hemorrhage (3 x 2.1cm) with mild edema and no midline shift. The patient was transferred to our institution and a repeat CT scan of the head confirmed the left temporo-parietal hemorrhage of 3.7 x 2.5 cm with surrounding edema. Admiss 

Case 2: 84 year old woman with a history of AF, HTN, hyperlipidemia, depression, and cutaneous vasculitis presented to an OSH with right sided weakness and facial droop. On admission, aPTT was 60 s, PT was 18.1 s and INR was 1.54. aPTT was elevated for 37 hours.

Days in ICU: Total Length of Stay (Days)

Case 3: 80 year old woman with a history of AF, HTN, hyperlipidemia, depression, and cutaneous vasculitis presented to an OSH with right sided weakness and facial droop. Outpatient dabigatran dose had been 150 mg po BID. Head CT: 1.7 x 2.4 cm hyperdensity in left thalamus. On admission, aPTT was 60 s, PT was 18.1 s and INR was 1.54. aPTT was elevated for 37 hours. No dialysis was initiated.

Case 4: 83 year old man with PMH of AF, cardiomyopathy, hypertension, diabetes, and severe aortic stenosis, with a valve area of 0.6 cm² was admitted with a subdural hemorrhage and cardiogenic shock. He developed progressive multi-organ failure. On admission, aPTT was 59 s, PT was 18.1 s, and INR was 1.4. He had 3 sessions of hemodialysis during days 1 and 2 of hospitalization. Received 4 units of FFP and 10 units of platelets. Repeat imaging showed no interval change in the hemorrhage. The aPTT value after 2 sessions of HD was 36 s; aPTT remained elevated for 28 hours.

Case 5: 90 old female with a history of HTN, CAD, AF, and both a hip and knee replacement was found on the floor after a fall and was transferred from an OSH. Initial laboratory evaluation demonstrated a PT of 22.3 sec, corresponding INR of 2.1, and an aPTT of 65.2 s. CT scan of the head demonstrated a left temporo-parietal acute subdural hemorrhage (SDH) measuring 7 mm, a SAH in the sylvian fissure and suprarenal cistern, as well as trace intraventricular hemorrhage. On transfer, repeat imaging again demonstrated multicompartamental hemorrhage, with evolution. Initial aPTT value was 39 s, PT was 21.5 s, and INR of 1.97. Following a session of high flux hemodialysis for 4 hours the aPTT was 47 s. The patient dislodged her own hemodialysis catheter, however, remained clinically stable with no interval changes on the repeat imaging. Accordingly, no further intervention was required. The aPTT values remained elevated for 27 hours.

DISCUSSION

These data highlight the difficulty with monitoring effect of anticoagulation with traditional anticoagulation monitoring techniques. Although a presumed benefit of the novel anticoagulants is not needing to be monitored, there are instances where effect may need to be quantified. Additionally, the adverse events noted were in the elderly and those with compromised renal function.

We assert the necessity of needing an anticoagulation stewardship program that prepares institutions for the introduction of novel anticoagulants. Essential elements for this type of program include:

- Education of appropriate dosing and indications.
- Plan for management of adverse events including mobilization of dialysis team with involvement of nephrology and vascular/hematology specialists.
- Continuous monitoring for adverse events to target areas of prevention.

CONCLUSIONS

- Appropriate patient selection is required to prevent dabigatran associated AE.
- Advanced age and kidney dysfunction are high risk groups for AE.
- aPTT values may remain prolonged for extended periods.
- Hospitals need a defined management plan for AE and major bleeding associated with novel anticoagulants.

DISCLOSURES

Geno J. Merli:
- Grant/Research Support
  - BMS, Bayer, Sanofi-aventis
- Scientific Consultant
  - BMS, Bayer, Sanofi-aventis

All other Authors: No disclosures