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

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ABSTRACT SUMMARY

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 medication interactions. Dabigatran requires dosage 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. Dialysis was initiated on 3 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 30.8 hours (range 21-37).

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.

BACKGROUND

- 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 etexilate, hereafter referred to as dabigatran, is an oral direct thrombin inhibitor, and the first of the novel anticoagulants to gain widespread use in the U.S. for anticoagulation in the setting of non-valvular AF.
- There is no currently 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.

METHODS

- 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.

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 showed an irregular left lentiform nucleus hemorrhage of 3.7 x 2.5 cm with surrounding edema. Admission laboratory values revealed an aPTT of 54 seconds (reference range: 20-38 s), PT 17.5 s (reference range: 11.2-14.8 s) and an INR of 1.48. Hemodialysis (HD) was initiated for 4 hrs (Day 1). Following HD, the aPTT declined to 41 s with a repeat assay showing 55 s six hrs later. A second HD session for 3.5 hrs was initiated on Day 2 for worsening mental status in the setting of an elevated aPTT. After the second dialysis session the aPTT decreased to 40 s. In an attempt to normalize the aPTT, the pt also received rFVIIa (Novoseven^{R}) 1560 mcg IV x 1 on Day 2. Repeat CT head showed no interval change in the hemorrhage and combined MRI/MRA was negative for aneurysm. The aPTT values remained elevated for 37 hours.

Case 2: 84 year old woman with a history of AF, HTN, hypothyroidism, depression, and cutaneous vasculitis presented to an OSH with right sided weakness, 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.

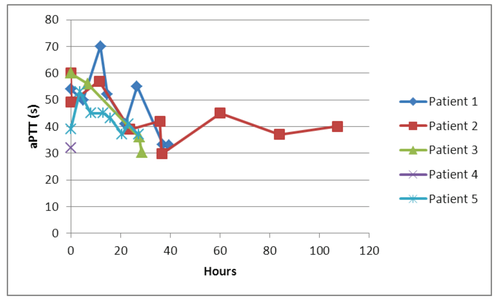
Case 3: 80 year old woman with a PMH of HTN, AF, and CAD presented following a fall at home to an outside emergency department. On arrival a CT scan of the head showed a subarachnoid hemorrhage (SAH). Dabigatran dose had been 150 mg po BID. On transfer to our facility, a repeat CT scan of the head showed interval development of a large SAH within the suprasellar cistern, right perimesencepahlic cistern, and the left prepontine cistern. On admission, aPTT was 60 s, PT was 16.8 s, and INR = 1.4. She had 3 sessions of hemodialysis during days 1 and 2 of hospitalization. Received 4 units FFP and 10 units 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.

RESULTS (CONTINUED)

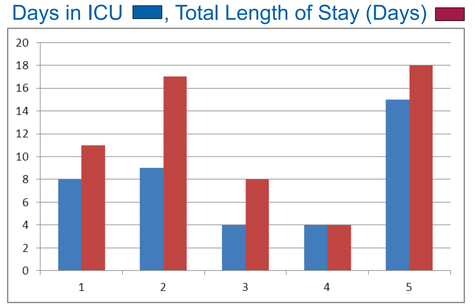
Table
Characteristics of patients presenting to neuroscience hospital with intracranial bleeding associated with dabigatran.

Patient	Age, Gender (M/F)	Dabigatran dose	Creatinine(mg/dL)/ Creatinine Clearance (mL/min)	Admission PT (seconds)/INR	Admission aPTT (seconds)	Elevated aPTT duration (hours)	Admission Hemoglobin/ Hematocrit/ Platelets	Dialysis During Admission (Yes/No)
1	79, M	75 mg BID	3.5/ 18	17.5/1.48	54	37	9.8/28.9/174	Yes
2	84, F	150 mg BID	0.7/ 49	18.1/1.54	60	37	11.5/34.5/253	No
3	80, F	150 mg BID	0.9/54	16.8/1.4	60	28	14.8/43.3/240	Yes
4	83, M (expired)	Unknown	1.4/48	15.9/1.3	32	0	12.8/39.5/192	No
5	90, F	150 mg BID	0.9/59	21.8/1.97	39	21	12.6/39.5/267	Yes

aPTT values for 5 patients according to time collection



Days in ICU, Total Length of Stay (Days)



Case 4: 83 year old man with PMH of AF, cardiomyopathy, (ejection fraction 15%), AICD with pacemaker, COPD and severe aortic stenosis ,with a valve area of 0.8 cm^2 was admitted with a subdural hemorrhage and cardiogenic shock. He developed progressive multi-organ failure. On admission, aPTT 32 s, PT 15.9 s, and INR 1.3. The patient expired during the hospitalization. Dabigatran dose was unknown. No dialysis was initiated.

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-pariatal acute subdural hemorrhage (SDH) measuring 7 mm, a SAH in the sylvian fissure and supracellar cistern, as well as trace intraventricular hemorrhage. On transfer, repeat imaging again demonstrated multicompartmental hemorrhage, with evolution. Initial aPTT value was 39 s, PT was 21.8 s, with INR of 1.97. Following a session of high flux hemodialysis for 4 hours the aPTT was 41 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

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