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Excess of Dabigatran Associated with Raised INR, PT, APTT in an Elderly Patient with Renal Impairment

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Abstract

Introduction: Dabigatran, a direct thrombin inhibitor, is an oral novel anticoagulant, which is used in stroke prophylaxis in non valvular atrial fibrillation. Despite it's many benefits in use, lack of means to evaluate the anticoagulant effect and reversal agents, raise concerns of its use.

Case report: 74 year old patient admitted with a history of TIA and viral gastroenteritis with chronic bilateral lower limb ischemia, during two medical admissions with three weeks apart, on a complex medical background, including CKD- IIIa, known atrial fibrillation on dabigatran, noted to have raised INR, PT, APTT. No evidence of chronic liver disease and was not on any other anticoagulations.

Conclusion: Lack of ready available reliable means of monitoring dabigatran anticoagulant effect, safer dosing schemes in especially elderly patients with chronic renal impairment, warrants further research and dedicated studies.

Introduction

Dabigatran, a selective inhibitor of thrombin, with an absolute bioavailability of 6.5%, serum half-life 12 to 17 h and 80% of the dose is excreted by the kidneys, where regular monitoring is not required.

Case Presentation

74 year old lady presented to acute medical unit with a history of Transient episode of dysarthria lasted for 1½ h associated with generalised fatigue and lethargy. She had complex medical background with Known atrial fibrillation on Pradaxa 110 mg bd, COPD, CKD-stage IIIa, DM2, Bilateral carotid artery stenosis for medical management, HTN and peripheral vascular disease. Her social history consists of occasional alcohol intake and a current smoker with 10 cigarettes a day [1].

On admission Vitals were stable. On Cardio-vascular and abdominal examination no significant abnormality detected. Neurological examination including cranial nerves examination was unremarkable. GCS was 15/15. Orientation 10/10. ECG: Known atrial fibrillation 94 bpm, CXR: Emphysematous changes, CTB: no acute intracranial abnormality, US Carotid Doppler: Right ICA with PSV measuring 242 cm/s. Left ICA with PAC of 364 cm/s, suggestive of significant bilateral carotid stenosis. Ultrasound abdomen: liver is normal with bilateral atrophied kidneys. ECHO: EF 50-55%, mild MR, TR and mild PAH, Telemetry: Known atrial fibrillation with a rate of 90-100 bpm with pause of 1.74 s [2-4].

Noted raised PT, APTT and INR with no obvious bleeding. PT 28.3 s, APTT 65 s, INR 2.6, fibrinogen 4.2 g/L, FBC and LFT's normal, urea 15.6 umol/L and Creatinine 143 umol/L. Haematology department was contacted and advised to dabigatran and monitor daily INR, PT, APPT, fibrinogen, Dabigatran level. Dabigatran was held for two days and restarted with readjusted dose of 75 mg bd based on Creatinine clearance. Repeat INR 1.3, PT 13.5 s and APTT 35 s. Discharged home to be followed up at outpatient in six to eight weeks, and GP to monitor INR, PT and APTT level while awaiting dabigatran levels.

After three weeks of discharge, was BIBA to ED department with an episode of vomiting clear fluids and loose stools, where viral gastroenteritis was diagnosed. Noted patient was put back on dabigatran 110mg bd on admission. ECG: Known afib 90 bpm, CXR: Emphysematous changes. Urine dipstick: negative. Bloods: WCC 13.4, Hb 13.3, MCV 84 f/L, Plt 143, Neu 10.5, CRP 118 mg/L, INR 4.4, PT 14.3 s, APTT 51 s, urea 20.9 µmol/L, Creatinine 170 µmol/L, calcium, phosphate and magnesium: normal. Stool couture was negative. Treated with IV fluids and repeat bloods with FBC, CRP: normal. Urea 10 and Creatinine 104 µmol/L. She was given vitamin K 5 mg IV. No obvious bleeding noted [5].

Overnight patient developed fast atrial fibrillation 140-160 bpm, cold, clammy and sweaty bilateral lower limbs with cramps and absence of peripheral pulse. Also increased dyspnoea and audible wheeze. ABG: pH 7.148 pO_2 21.5, pCO_2 2.62, HCO_3^- 10, Lac 9.7. IV hydrocortisone 100 mg, IV cyclomrph 5 mg, IV

Digoxin 500 mcg, bisoprolol 2.5 mg, IV $NaHOC_3$ 100 ml were given and was transferred to ICU for close monitoring. CT Brian: nil acute intracranial abnormality. CT abdominal aorta: Extensive athermanous ossifications with probable complete occlusion of distal part of the abdominal aorta and both common iliac arteries and collaterals in the anterior abdominal wall. No evidence of aneurysm or dissection seen. CT abdomen and pelvis: Bilateral pleural effusion with atrophied right kidney. CTPA: No PE. Commenced on innohep therapeutic dose and held dabigatran.

Vascular team was contacted and was accepted for further management at a tietary centre. Initially was treated with innohep infusion, acute ischemia excluded and was transferred back our care with the diagnosis of chronic ischemia on a back ground of PVD. Repeat bloods, Urea 24.6, Creatinine 182, Total Protein 43 g/L, Albumin 20 g/L, ALT 756U/L, AST 690 U/L, GGT 44 U, ALP and Bilirubin: normal. Deranged LFTS's were secondary to probable shock liver. FBC normal, PT 13.9, INR 1.2, APTT 39.8. ECG: known Afib 80 bpm. Treated with slow IV fluids. PT and OT assessment done. Respite of 1week then discharge home afterwards was arranged.

Discussion

Dabigatran's anticoagulant effect on INR, PT, APTT

Table 1: Dabigatran's anticoagulant effect on INR, PT, APTT

Coagulation assay:	
Plasma peak level	2 h after ingestion
Plasma trough level	12 h after ingestion
Prothrombin time (PT)	Cannot be used
International normalized ratio (INR)	Cannot be used
Activated partial thromboplastin time (APTT)	May provide qualitative assessment of drug level and activity. Level at trough (12 to 24 h after ingestion) >2 ULN, may associate with higher risk of bleeding.
Diluted thrombin time (dTT)	Both dTT and ECT have best correlation throughout the therapeutic range, but not readily available. ECT at trough greater than three-fold of baseline, associated with higher risk of bleeding, while closer to baseline indicating no significant anticoagulant effect clinically. dTT at trough (>12 h after the previous dose) higher or equal of 65s indicates a higher risk of bleeding.
Ecarin clotting time (ECT)	
AntiFXa (chromogenic)	Insensitive
Activated clotting time (ACT)	Limited use. Not being assessed for it's use.
Thrombin time (TT)	Very sensitive and normal level excludes even low levels of dabigatran. Not suitable in clinical setting.
Coagulation assay should be cautiously interpreted in clinical use.	

FDA and the European Commission has approved the use of Praxbind (Idarucizumab) as a rapid and specific reversal agent of pradaxa anticoagulant effect, in cases of emergency surgical intervention or in life threatening/uncontrolled bleeding (Table 1).

Use of Dabigatran in elderly patients with renal impairment

Chronic kidney disease is a risk factor for stroke in atrial fibrillation, which may also increase the risk of bleeding while on all oral anticoagulants, especially in end stage kidney disease.

It is recommended to assess renal function with CrCL (creatinine clearance) prior to initiation of treatment with pradaxa and to monitor renal function at least once a year. In elderly (>75-80 years) patients renal function should be evaluated every six months. Pradaxa is contraindicated in severe renal impairment (CrCL<30 ml/min) [6].

Approved dabigatran dose based on creatinine clearance as given below.

CrC: >50 mL/min: no adjustment dose required (150 mg bd)

CrCl 30-49 mL/min: 150 mg bd possible, but 110 mg bd should be considered (as per ESC guidelines). CrCl <30 mL/min: not recommended.

RE-LY in 2009 on Dabigatran *vs.* Warfarin in Patients with Atrial Fibrillation, a randomized trial, administrating, two doses of dabigatran, 100 mg bd and 150 mg bd in a blinded manner, compared with open-label use warfarin. Despite 80% of dabigatran dose being renally excreted, no significant divergence on it's effect noted across the levels based on creatinine clearance [7].

It is recommended to avoid NOAC's and consider vitamin K antagonists as a more suitable alternate in CKD stage V (CrCL <15 mL/min) on patients on haemodialysis.

Conclusion

Readily available efficient means of monitoring anticoagulant effect of dabigatran are still lacking.

Further studies on safer reduce dosing schemes in chronic renal impairment and in elderly patients considering risk versus benefit are required. Vitamin K antagonists would be a safer alternative to NOAC's in end stage renal disease.

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