

A case report of recurrent transient ischaemic attacks on dabigatran for atrial fibrillation: real-world insight into treatment failure

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Background

Non-valvular atrial fibrillation (AF) is an important risk factor for acute ischaemic stroke. There has been an increase in the use of direct-acting oral anticoagulants (DOAC therapy) in stroke prophylaxis due to their convenience and rapid action of onset. However, there is a lack of information in the literature regarding management options and possible mechanisms with the apparent failure of DOAC therapy.

Case summary

We present a clinical case of a 51-year-old man presenting with transient ischaemic attacks on a background of AF on therapeutic doses of dabigatran. His medication box suggested 100% compliance and his admission coagulation studies showed a marginally prolonged activated partial thromboplastin time and thrombin time (TT). While in hospital, our patient had supervised doses of dabigatran (150 mg b.i.d.). Despite this, his peak dabigatran level was undetectable (<40 ng/mL). With the apparent failure of therapy, he was switched to apixaban 5 mg b.i.d., which showed subsequent peak levels in the target range.

Discussion

There are a number of isolated case reports of DOAC failure in stroke prophylaxis and management has simply involved switching to another DOAC or warfarin. This case is unique as we have discovered undetectable levels of dabigatran providing a mechanism for failure.

Keywords

Case report • Stroke • Atrial fibrillation • Direct-acting oral anticoagulation

Learning points

- Patients presenting with stroke on therapeutic doses of direct-acting oral anticoagulants (DOACs) should be reviewed in detail for potential reasons for such failure.
- Subtherapeutic DOAC levels should be considered as a reason for treatment failure.
- If subtherapeutic, considerations into mechanisms should include (though not encompassing) medication compliance, co-administration of medications interacting with the DOAC, gastric surgery, or potential genetic variations to DOAC metabolism.

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Introduction

Non-valvular atrial fibrillation (AF) is associated with a five-fold increased risk of acute ischaemic stroke.¹ For more than 60 years, vitamin K antagonists have been used effectively to prevent stroke.^{1,2} Prescription of direct-acting oral anticoagulants (DOACs) in preference to warfarin for stroke prophylaxis has increased due to a number of attractive features including their rapid onset of action, lack of regular blood tests required for monitoring efficacy, and a much simpler dosing regimen compared with warfarin.^{3,4} However, little has been published about mechanisms of apparent failure of DOAC therapy in thromboembolic prophylaxis in AF. Here, we present a case of a 51-year-old man presenting with neurological symptoms on a background of AF on therapeutic dabigatran.

Timeline

Events	
November 2015	Presented to hospital with symptomatic rapidly conducting atrial flutter. Successful electrical cardioversion to sinus rhythm. Commenced on apixaban 5 mg b.i.d. and sotalol 40 mg b.i.d.
March 2016	Successful ablation of typical atrial flutter. During the electrophysiology study, the patient was noticed to have a tendency to atrial fibrillation (AF). Discharged in sinus rhythm.
May 2016	Remained in sinus rhythm and asymptomatic. Apixaban ceased—CHADsVASC 0 and changed to aspirin 100 mg daily.
October 2016	Presented to hospital with symptomatic AF. Successful electrical cardioversion to sinus rhythm. Recommended on apixaban 5 mg b.i.d. and continued with sotalol 40 mg b.i.d. Blood pressure elevated and commenced antihypertensive therapy (CHADsVASC 1).
September 2018	Elective transoesophageal echocardiogram and direct current cardioversion which was unsuccessful—only remained in sinus rhythm for a few beats then returning to AF. Increased sotalol to 80 mg b.i.d. and introduced digoxin. Patient in and out of sinus rhythm.
October 2018	Catheter ablation for AF discussed with patient. Switched from apixaban to dabigatran 150 mg b.i.d. in preparation.
November 2018	Ablation decided against and for medical therapy. Patient remained on dabigatran 150 mg b.i.d.
March 2019	Presented with several transient neurological symptoms while on dabigatran. Had four doses of observed dabigatran therapy in the hospital. Dabigatran peak level (4 h post-dose) <40 ng/mL. Haematology consulted and therapy switched to apixaban 5 mg b.i.d. resulting in apparently on target levels.

Case presentation

A 51-year-old man on dabigatran for known AF (CHADsVASC 1 for hypertension) presented to emergency describing intermittent dysgraphia and short-lived episodes of receptive dysphasia in the prior week. He awoke at 6.30 am on the morning of his presentation with a diffuse headache. At 10.30 am, he developed a right superior visual field disturbance marked by colourful pixilation, lasting 2 min. These exact symptoms recurred at 4.30 pm with complete resolution.

Our patient had a background of rapid atrial flutter requiring direct current cardioversion (DCCV) in 2015, with maintenance sotalol 40 mg b.i.d. and apixaban 5 mg b.i.d. He underwent atrial flutter ablation in 2016 but required repeat DCCV for recurrent AF. In September 2018, he was in asymptomatic rapid AF with unsuccessful DCCV. While being considered for AF ablation his apixaban was changed to dabigatran 150 mg b.i.d. given the availability of a reversal agent and lower bleeding risk⁵ as recommended by the cardiac electrophysiologist. Medical management was preferred but he remained on dabigatran. Other medications included digoxin 125 µg daily, fenofibrate 145 mg mane, atorvastatin 80 mg nocte, allopurinol 300 mg daily, fluvoxamine 50 mg mane, and metoprolol 100 mg b.i.d. The patient used a pharmacy packed medication box.

On presentation, his heart rate was 81 b.p.m. (irregular pulse), blood pressure was 127/98 mmHg, respiratory rate was 18 breaths/minute, oxygen saturation was 98% on room air, and he was afebrile. His cardiovascular examination was unremarkable. Initial blood work was normal except an eGFR of 36 mL/min/1.73 m² (≥ 60 mL/min/1.73 m²) and creatinine 182 µmol/L (60–110 µmol/L). The renal function was normal previously. His electrocardiogram demonstrated AF. A computed tomography brain, carotid and circle of Willis angiogram, and brain magnetic resonance imaging did not show evidence of acute or recent infarct. The provisional diagnosis was a transient ischaemic attack (TIA) occurring despite therapeutic dabigatran administration.

The patient's medication box indicated 100% medication compliance. Admission coagulation studies showed a marginally prolonged activated partial thromboplastin time (APTT) of 38 s (range 25–37 s) and thrombin time (TT) of 83.7 s (range 14–20 s). The TT suggested possible presence of dabigatran but only at subtherapeutic levels. After four further supervised doses of dabigatran 150 mg b.i.d., levels were undetectable by Hemoclot assay (Hyphen Biomed) on STA-R analyser (Stago) (<40 ng/mL). Anticoagulation was changed to apixaban 5 mg b.i.d. with subsequent peak levels of 299 ng/mL (on target range: 91–321 ng/mL). He has had no further neurological events at his most recent follow-up.

Discussion

When a patient with AF prescribed therapeutic anticoagulation presents with a thromboembolic event, several issues need to be considered. First, the thromboembolic nature of the event must be confirmed. While our patient did not show conclusive evidence of a stroke on investigation, his symptoms were consistent with TIAs. Once established, the reasons for anticoagulation 'failure' should be considered. These are broadly categorized as due to subtherapeutic drug levels or an underlying pro-thrombotic disease state.⁶

Table 1 Reasons for failing to achieve dabigatran levels

1. Poor medication compliance.
2. Drug degradation
 - a. The drug monograph states that the drug should be stored protected from moisture and suggests relative instability when removed from original packaging, for example, when stored in pharmacy blister packs.
3. Poor absorption in the lower oesophagus and duodenum, e.g. after bariatric surgery.
4. P-glycoprotein efflux pump activity can be altered due to drug interactions (see Wessler *et al.*¹² for full list).
 - a. Drugs that inhibit P-gp activity (e.g. amiodarone, carvedilol and atorvastatin) may increase DOAC bioavailability and subsequent bleeding risk.
 - b. Rifampicin, an inducer of P-gp activity, St. John's wort and carbamazepine have the potential to increase thromboembolic complications by reducing dabigatran levels.
5. Single nucleotide polymorphism leading to loss of function mutation in carboxylesterase 1 and 2, enzymes crucial for dabigatran prodrug conversion.

Direct-acting oral anticoagulants have been marketed as anticoagulants that do not require monitoring. This case illustrates a circumstance in which testing a drug level is important: a thrombotic event during therapeutic DOAC dosing. In this case, documentation of the inability to achieve therapeutic dosing with dabigatran explained the 'event on anticoagulation' allowing a switch to a different anticoagulant. This case also demonstrates the importance of understanding surrogate laboratory markers, such as the APTT and TT. Thrombin time is very sensitive to dabigatran and within our laboratory, a plasma level of dabigatran within the on-target range for therapy would be expected to return a result above the limit of the assay (>150 s). In a compliant patient with renal impairment, dabigatran would be expected to accumulate leading to a markedly prolonged APTT and TT. It is useful to systematically examine causes when subtherapeutic dabigatran levels are discovered (Table 1). Poor medication compliance was not the reason in our patient as his dabigatran plasma levels were <40 ng/mL (on target range for peak levels: 100–400 ng/mL) after directly observed therapy.

Several points in the absorption and metabolism process may interfere with achieving adequate dabigatran levels. Dabigatran is a highly selective direct thrombin inhibitor taken as a prodrug. Dabigatran etexilate is rapidly converted to its active form by carboxylesterase 1 and 2, in the intestine and liver, respectively.⁷ The prodrug capsules are composed of a tartaric acid core surrounded by dabigatran etexilate. This ensures an acidic microenvironment promoting drug dissolution and absorption independent of gastric pH but requires airtight storage to ensure stability (Table 1). A recent study reassuringly shows that drug levels in pharmacy blister packed tablets were stable out to 120 days.⁸

Reduced long-term cardiovascular event rates have been shown following bariatric surgery.⁹ Drug levels can be affected by the anatomical and biochemical changes seen following metabolic surgery.¹⁰ Our patient was obese with a weight of 102.4 kg and a body mass index (BMI) of 31.6 kg/m² with no history of upper gastrointestinal

surgery. ISTH guidelines indicate caution with DOAC use in patients >120 kg or BMI >40 kg/m² until further data emerges.

Intestinal absorption of both anti-FXa- and direct thrombin inhibitors is dependent on the P-gp efflux pump system. Many cardiovascular drugs affect the activity of the P-gp system^{11,12}; our patient was not taking drugs or herbal medications likely to interact with dabigatran. Furthermore, an abnormality in the P-gp system should not be responsible for our patient's dabigatran failure as apixaban absorption would also be affected given the common absorption pathway. Shi *et al.* identified a single nucleotide polymorphism, rs71647871, which confers a loss of function mutation in carboxylesterase 1.⁷ When hepatocytes expressing rs71647871 were incubated with dabigatran etexilate there was nil dabigatran detected. We suspect that our patient harbours a non-functioning variant of carboxylesterase 1 or 2 which renders him unable to metabolize the pro-drug. Further identification with genetic sequencing is in progress to validate our hypothesis and characterize the underlying mutation.

Our patient had a TIA consequent to failure to achieve adequate anticoagulation. Best management is unclear if stroke occurs despite adequate anticoagulation; however, it is reasonable to consider an underlying procoagulant state. While underlying malignancy is the most common condition attributed to breakthrough venous thromboembolism,^{6,13} Elbadawi *et al.*¹⁴ argue that cancer does not increase stroke risk in AF patients. Other clinical conditions associated with venous thrombosis despite adequate anticoagulation include myeloproliferative disorders, anti-phospholipid syndrome, paroxysmal nocturnal haemoglobinuria, and Behcet's disease. It may be reasonable to consider these as part of the differential diagnosis in stroke occurring with adequate anticoagulation.

Conclusion

In summary, we present a patient who suffered symptoms consistent with a TIA on a background of AF while on full-dose dabigatran. There have been isolated case reports of apparent DOAC treatment failure, where management had simply involved switching to another DOAC or warfarin. Our case is unique as we discovered undetectable levels of dabigatran providing a mechanism for treatment failure. Additionally, we found therapeutic anticoagulant levels with a different DOAC, apixaban. Understanding the mechanisms of this anomaly will assist in understanding treatment failures with DOACs in the setting of stroke prophylaxis and AF.

Lead author biography



Ronald Huynh completed his medical studies at the University of Notre Dame in Sydney Australia in 2013. He completed his Basic Physician's Training in 2017 and is currently a cardiology advanced trainee at Concord Repatriation General Hospital in Sydney, Australia.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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