CASE REPORT

Dabigatran, electrical cardioversion and measuring the aPTT. A safety measure or an unnecessary assessment?

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SUMMARY

We present two case reports of patients treated with dabigatran for stroke prevention. Both have non-valvular atrial fibrillation and both were scheduled for direct current electrical cardioversion (DCCV). Both had their activated partial thromboplastin time (aPTT) measured prior to their DCCV to assess the anticoagulant activity of dabigatran. The decision to measure the aPTT resulted in differing levels to otherwise straightforward cases.

BACKGROUND

These case reports revolve around the activated partial thromboplastin time (aPTT) in relation to dabigatran. When measuring the anticoagulation effect of dabigatran, aPTT is particularly chosen in view of its practicality, and that it is widely available and easily accessible.

CASE PRESENTATION**Case 1**

A 74-year-old man with a history of ischaemic heart disease and recent permanent pacemaker insertion was found to be in atrial fibrillation for 2 months. He was not started on any rate-limiting drugs as his heart rate was within the normal range as stated during the pacemaker check.

He agreed to a direct current electrical cardioversion (DCCV) and was started on dabigatran 110 mg twice daily (D110) based on the European Medicines Agency (EMA) eligibility criteria for stroke prevention. He was also on ramipril, tamsulosin and pravastatin. There were no interacting medications that potentially could interfere with dabigatran concentrations.

Initial blood tests showed normal renal function and normal coagulation assay. His transthoracic echocardiogram showed mild left ventricular impairment with an ejection fraction of 57%, a mildly dilated left atrium, no cardiac thrombus and no significant cardiac valves disease. A transoesophageal echocardiogram was not performed.

His DCCV was scheduled 3 months after taking dabigatran. The day prior to his procedure, routine coagulation assay was performed. This showed a prolonged aPTT of 49 s (normal range: 26–37 s), with international normalised ratio (INR) of 1.2 and fibrinogen 3.68 g/L (normal range 2–4.5 g/L). He went on to have a successful DCCV. Post DCCV he did not develop any complications of bleeding, stroke or systemic embolism.

Case 2

A 67-year-old woman with persistent non-valvular atrial fibrillation (NVAf) presented with debilitating breathlessness due to a poorly controlled heart rate. Her medical history includes hypertension and chronic lymphoedema.

She agreed to a DCCV and was started on dabigatran 150 mg twice daily (D150) in view of the potential difficulties of complying with warfarin and its monitoring. She was also on digoxin, bisoprolol and flecainide. There were no interacting medications that potentially could interfere with dabigatran concentrations.

Initial blood tests showed normal renal function and a normal coagulation profile with an aPTT 30 s, prothrombin time 12 s, INR 1.1 and fibrinogen 4.03 g/L. Her transthoracic echocardiogram showed good left ventricular function with an ejection fraction >50%, mildly dilated left atrium, no cardiac thrombus and no significant cardiac valve disease. Transoesophageal echocardiogram was not performed.

A DCCV was scheduled 2 months after starting dabigatran. On the day of her procedure, as a safety measure, a coagulation assay was performed at peak levels of dabigatran. This, however, showed normal clotting with aPTT 36 s, INR 1.3, prothrombin time 14 s and fibrinogen 4.69 g/L.

In view of the normal aPTT, clinical judgement was made not to conduct DCCV. The issue of adequate anticoagulation was questioned. Plasma concentration of dabigatran was sent to a tertiary institution. This sample was unfortunately lost. Six weeks later, she had a successful DCCV while on warfarin. Post DCCV she did not develop any complications of bleeding, stroke or systemic embolism.

DISCUSSION

The emergence of the novel oral anticoagulants (NOAC) has been a hot topic in the frontier between cardiology and pharmacology. Unlike the well-established warfarin and unfractionated heparin, the NOAC does not need routine coagulation monitoring due to their predictable pharmacology, fixed dosing, wide therapeutic window and rapid onset of action.^{1 2} We present two cases on how the decision to quantify the anticoagulant effect of dabigatran has led to different management options.

Dabigatran etexilate, a direct thrombin inhibitor (DTI),³ is approved for stroke prevention and systemic embolism in patients with NVAf.⁴ Dabigatran

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etexilate, the parent compound, is an active prodrug that is converted to dabigatran by plasma esterases in the plasma and liver.⁵ Dabigatran, mostly excreted by the kidneys, has a half-life of 11–14 h in patients with normal renal function. Its peak anticoagulation effect generally occurs within 0.5–2 h after administration.^{3 6} However, the limitations of dabigatran include gastrointestinal side effects, bleeding complications, route of elimination and lack of antidotes.⁷

Dabigatran has been extensively evaluated clinically and later approved by both the US Food and Drug Administration and the EMA. This was based on the results of the (Randomized Evaluation of Long-term Anticoagulation Therapy)(RE-LY) trial. The RE-LY trial evaluated stroke risk at atrial fibrillation (AF) cardioversion in patients taking dabigatran versus warfarin. Dabigatran at a dose of 150 mg (D150) twice daily was statistically superior to warfarin for prevention of stroke and systemic embolism without increasing bleeding rates. The lower dose of dabigatran 110 mg twice daily (D110) showed similar efficacy but with a lower risk of bleeding.⁸ The peak serum concentrations of dabigatran within two hours range from 64 to 443 ng/mL, usually reaching 184 ng/mL after a 150 mg oral dose.⁵

This discussion focuses on the sequence following the measurement of anticoagulant activity of dabigatran. The first issue addresses the decision to measure the clotting level in what appear like straightforward cases. The levels were measured for two reasons (1) due to concerns around drug compliance and efficacy and (2) routine preprocedure assessment.

Coagulation monitoring is not required for dabigatran. However, it has been stated in several publications that testing is useful in certain situations. These include suspected drug failure, overdose, treatment adherence, bleeding complication, thrombosis recurrence, urgent/emergency surgery or invasive procedures.⁶

There is no gold standard for measuring the anticoagulant effect of dabigatran. However, aPTT has been suggested as one of the potential laboratory measurements. aPTT is not adequately sensitive to dabigatran, but it is a practical selection as this test is widely available and easily accessible.^{1 9} Others include the ecarin clotting time or thrombin time for DTIs, which are currently the more sensitive laboratory tests; however, they are not readily available in many clinical settings.^{1 6}

The aPTT values in patients with NVAF on dabigatran seem to show a wide distribution.¹⁰ According to the University of Utah Thrombosis Service's website, a normal aPTT means little anticoagulant activity is present.⁶ However, a normal aPTT also does not provide clear reassurance to indicate the absence of dabigatran activity.⁵ Fifteen per cent of patients on D150 had no or minimal aPTT prolongation (<40 s).¹¹ A mildly elevated aPTT may also be associated with clinically important levels of dabigatran.⁶ The expected median peak aPTT level (for D150) is two-fold that of control while the median trough aPTT is approximately 1.5× control values.^{6 11} However, aPTT also becomes increasingly insensitive at higher dabigatran levels (ie, plasma dabigatran concentrations above 200 ng/mL) as seen in an overdose.^{6 12} Studies have also shown that aPTT is most useful in the initial assessment to determine if dabigatran contributes to a haemorrhagic event.^{6 9 10} Box 1 summarises this test.

Following the normal aPTT in the second case report, further issues were raised. (1) If anticoagulant activity is present, is it producing the desired anticoagulant effect? (2) If anticoagulant activity is absent, could this also be a case of drug inefficacy or resistance? The most obvious reason for the normal drug levels was due to potential non-adherence. Measurement of plasma

Box 1 Summary of aPTT as a qualitative assessment for dabigatran

- ▶ aPTT is most useful in the initial assessment to determine if dabigatran contributes to a haemorrhagic event⁹
 - ▶ Although normal aPTT suggests little anticoagulant activity,⁶ this does not indicate absence of drug⁵
 - ▶ Mildly elevated aPTT may also be associated with clinically important levels of dabigatran⁶
 - ▶ The expected median peak aPTT level (for D150) is two-fold that of control while the median trough aPTT is 1.5× control values^{6 11}
 - ▶ 15% of patients on D150 had no or minimal aPTT prolongation (<40 s).¹¹
- aPTT, activated partial thromboplastin time.

dabigatran concentrations would be useful here; however, not many institutions possess this assay.

Anticoagulant resistance is influenced by many factors. It is characterised by the high doses required to achieve therapeutic anticoagulation or its inability to reach the desired range. The drug may be ineffective the first time it is being used, or may occur over time.¹³ Warfarin resistance should be considered when more than 15 mg/day is needed to prolong the INR into the therapeutic range.¹⁴ Heparin resistance has been proposed as patients requiring unusually high doses of heparin, usually greater than 35 000 ug/day, to maintain the aPTT in the target therapeutic range.¹⁵ To our knowledge, the phenomenon of dabigatran resistance or inefficacy has never been reported in medical literature. We will never be absolutely sure of this phenomenon until accurate monitoring assays are developed.

These case reports have shown that measuring an aPTT prior to an elective DCCV could leave clinicians in dilemma if the aPTT was normal. Would it be ethical to cardiovert this patient? Thromboembolism is highest during the first week postcardioversion (5.6%) thus adequate anticoagulation is compulsory.^{3 16} In principle, it is important to first understand that the potential benefits of a procedure must outweigh the risks. By balancing the two pillars of ethics, non-maleficence and beneficence, the

Learning points/take home messages

- ▶ Information on the anticoagulant activity may be required in certain circumstances and thus the need to measure the therapeutic levels of dabigatran will arise. This requirement should be assessed individually.
- ▶ Activated partial thromboplastin time (aPTT) is more useful for a rapid assessment to detect the presence of dabigatran in haemorrhaging patient.⁹
- ▶ Owing to concerns in the ability to interpret results accurately, aPTT measurement prior to an elective direct current electrical cardioversion is meaningless.¹¹
- ▶ There is an understandable reluctance on the part of the clinician performing an electrical cardioversion in patients on dabigatran with normal aPTT.
- ▶ No clinician should perform such procedure in such cases if he or she conscientiously objects.

clinician has obliged to 'first, do no harm' and act in the best interest of the patient. Her dabigatran was stopped, warfarin was started and the DCCV rescheduled.

These case reports have shown examples where resources can be limited but decisions still have to be made. It reflects that clinicians vary in their practice of ethical issues, and that the responsibility of good practice remains up to the clinicians involved. Information on the anticoagulant activity will be required in certain circumstances and this should be individually assessed. However, experts recommend that due to concerns in the ability to interpret results accurately, aPTT measurement prior to an elective DCCV is meaningless.¹¹

Competing interests None.

Patient consent Obtained.

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