CASE REPORT

Novel oral anticoagulants and HIV: dabigatran use with antiretrovirals

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Accepted 26 October 2015

SUMMARY

Compatibility of novel oral anticoagulants in patients with HIV taking combined antiretroviral therapy has not been established, with no published reports of successful concurrent use. We present a case where chronic anticoagulation was indicated in a patient with treated HIV and non-valvular atrial fibrillation who refused warfarin therapy. The patient tolerated the combination, with dabigatran blood levels within the expected range at a standard dosing regimen, without evidence of bleeding or other adverse outcomes. While further research is needed to establish the role of novel oral anticoagulants in patients taking antiretrovirals, this case suggests that dabigatran may be a viable option for selected patients.

BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia, estimated to affect 1–2% of the population.[1] An increasing incidence has translated into increased length of hospital admissions for initiation of therapy, including initiation of appropriate anticoagulation, with significant associated cost.[2] Until recently, warfarin was the sole agent approved for use in the prevention of stroke and systemic embolism in patients with non-valvular AF. Between 2010 and 2012, three new oral anti-coagulants (NOACs), two factor Xa inhibitors (apixaban and rivaroxaban) and one direct thrombin inhibitor (dabigatran), were approved for this indication.[3] Current guidelines for the management of AF recommend warfarin or NOACs as equivalent options,[1 4] though there is concern regarding the interaction of combined antiretroviral therapy (cART) and NOACs in patients with HIV.

A recent large US study (n=30 533) of patients with newly diagnosed HIV found a 2.1% incidence rate for AF over an average 6.8-year follow-up,[5] suggesting similar rates of AF in the wider population. Of concern, HIV infection is an independent risk factor for stroke, with an unadjusted HR of 1.40 for ischaemic stroke in HIV positive patients,[6] highlighting the need for appropriate use of anticoagulants in patients with HIV at risk of thromboembolic disease.

Prior to the licencing of NOACs, warfarin was the mainstay of thromboembolism prophylaxis in patients with AF, including those concurrently using antiretrovirals (ARVs). Warfarin is metabolised by hepatic CYP2C9, and a recent literature review of interactions between warfarin and ARVs reported a high likelihood of interaction between warfarin and protease inhibitors (PIs) as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs), some of which act as inducers and others as inhibitors of CYP2C9.[7] This concern over interactions is largely mitigated by the close monitoring of INRs in warfarinised patients, allowing adjustment for any potential interaction. The use of warfarin is also fraught with concerns surrounding interactions with other medications, foods and alcohol, in addition to the need for regular monitoring, underpinning the widespread use of NOACs in the general population.

A review article by Egan *et al* provides a concise evaluation of theoretically expected interactions between NOACs and ARVs, however, clinical evaluation has not been performed. Unlike rivaroxaban and apixaban, which are substrates of CYP3A4, dabigatran does not rely on metabolism by CYP450 and is renally excreted, avoiding most of the anticipated interactions with PIs and NNRTIs. Dabigatran, therefore, has theoretical advantages over other NOACs in patients with treated HIV. Dabigatran's prodrug is a P-glycoprotein substrate and P-glycoprotein is inhibited by some PIs, thus a dosing interval of >2 h between ARVs and dabigatran is recommended to avoid increased serum levels of dabigatran.[8]

Interaction of NOACs with NRTIs, integrase inhibitors or CCR5 receptor antagonists, is not expected. There is the potential for interaction of rivaroxaban and apixaban with cobicistat.[8]

Hemoclot is the most accurate commercially available predictor of anticoagulant effect of dabigatran, as presented at the International Society on Thrombosis and Haemostasis conference in 2011.[9] It is the manufacturer-recommended test for assessment of anticoagulation status in patients with high-risk bleeding on dabigatran.

We sought to prescribe a NOAC in a patient with treated HIV who refused warfarin therapy.

CASE PRESENTATION

A 60-year old man with HIV was found to have asymptomatic AF with a rapid ventricular response on routine cardiology review.

His medical history included 15 years of ART for HIV; smoking, with a 40 pack year history; hypercholesterolaemia and moderate obstructive sleep apnoea. Owing to systemic thromboembolic disease to one leg on a background of established peripheral vascular disease, he required a femoral-popliteal bypass the year prior, however, he subsequently underwent a below knee amputation due to severe leg ischaemia.

To cite: Perram J, Joseph J, Holloway C. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-211651

Table 1 Dabigatran dose levels and coagulation markers

	Dabigatran level (ng/mL)		PT (NR: 11–15)		APTT (NR: 25–35)	
Dose	Trough	Peak	Trough	Peak	Trough	Peak
110 mg daily	<30	Not done	14	15	39	44
110 mg BD	<32	120	15	Not done	46	Not done
150 mg BD	<32	229	14	19	36	69

APTT, activated partial thromboplastin time; BD, twice daily; PT, prothrombin time; RE-LY, Randomized Evaluation of Long-Term Anti- coagulation Therapy; NR, normal range.

A transthoracic echocardiogram excluded a valvular cause for his AF. He was started on rate control therapy. His risk for thromboembolic complications was calculated (CHA2DS2-VASc score) at 1/9. Given the previous embolic disease, anticoagulation was recommended.

The patient refused warfarin, given that his reduced mobility prevented regular monitoring. The option of using a NOAC was explored given his risk profile. His cART regimen was abacavir, lamivudine, ritonavir boosted atazanair and tenofovir. Given the patient's high thromboembolic risk, and the lower theoretical interaction of dabigatran and ART, this was thought the safest alternative.

High dabigatran levels correlate with bleeding risk and, on this basis, the Hemoclot test was used to direct dosing to minimise bleeding risk. Trough levels averaged 116 ng/mL in patients who bled on dabigatran, versus 75 ng/mL in those with no major bleeding, in the RE-LY study.[10] Given this association, and our primary concern being for high levels with concurrent use of cART, we monitored dabigatran concentration and titrated up to the marketed dose while ensuring a trough ≤75 ng/mL.

A dose of 110 mg daily was started and drug level testing was undertaken using the Hemoclot assay, with a trough level of <30 ng/mL. Dabigatran dosing was subsequently increased to 110 mg twice daily, then 150 mg twice daily with serum levels as shown in table 1.

OUTCOME AND FOLLOW-UP

After 12 months follow-up, the patient remained well, without recurrence of thromboembolic disease and with no bleeding complications.

DISCUSSION

There are no cases reported of successful coadministration of NOAC with cART. We found that ritonavir-boosted ART did not significantly increase dabigatran levels in this patient, and it may be a suitable anticoagulant in selected patients on ART.

The role of dabigatran-level monitoring remains unclear. Recent findings indicating efficacy of idarucizumab in neutralisation of dabigatran may lead to a role for dabigatran levels in cases of bleeding,[11] however, use of routine dabigatran concentration monitoring is not currently recommended by the marketing company or by regulatory bodies. Given the established association between high dabigatran trough level and bleeding, we suggest that our approach of monitoring trough levels while titrating towards the marketed dose is of value when initiating dabigatran in settings with potential drug interactions, or in unstudied populations.

This is the first reported case of concurrent antiretroviral use with dabigatran for non-valvular AF, and suggests that dabigatran may be an option for patients requiring oral anticoagulation for AF. Further research is warranted to assess the safety and efficacy of NOACs in patients receiving various ARTs, and to answer important questions such as how to manage missed ARV or NOAC doses, before NOACs and warfarin can be considered interchangeable in this population.

Learning points

- New oral anti-coagulants (NOACs) are alternative agents for anticoagulation in non-valvular atrial fibrillation.
- The concurrent use of NOACs and antiretroviral medications has not been studied.
- Dabigatran may be an alternative anticoagulant in some patients using antiretrovirals.

Contributors JP carried out the literature review and prepared the manuscript for publication. JJ and CH were involved in clinical care of the patient and editing the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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