Activated prothrombin complex in the management of direct thrombin inhibitor-associated intracerebral haemorrhage.

N.R. Evans[1], M.W. Besser[2], K. Khadjooi[3]

[1] Department of Clinical Neurosciences, University of Cambridge, R3 Clinical Neurosciences (Box 83), Cambridge Biomedical Campus, Hills Road, Cambridge. CB2 0QQ
[2] Department of Haematology, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge. CB2 0QQ
[3] Department of Stroke Medicine, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge. CB2 0QQ

Address correspondence to:
Dr N.R. Evans, Department of Clinical Neurosciences, University of Cambridge, R3 Clinical Neurosciences (Box 83), Cambridge Biomedical Campus, Hills Road, Cambridge. CB2 0QQ

Learning point for clinicians:

Intracerebral haematoma expansion independently predicts poor functional outcome and mortality. Therefore, it is important to act quickly to arrest this expansion. Whilst a direct antidote to dabigatran remains in development, the use of FEIBA may offer a practical strategy for arresting haemorrhage in individuals taking direct thrombin inhibitors.

Case:

A 78 year-old man developed sudden-onset aphasia and right hemiparesis 14 days after hospitalisation for severe cellulitis, for which he was receiving meropenem and clindamycin. His medical history included a porcine aortic valve replacement and atrial fibrillation treated with dabigatran (a direct thrombin inhibitor, DTI) 150mg twice daily. His weight was 79kg, body mass index 25mg/m^2, and estimated glomerular filtration rate 97ml/min/1.73m^2.

Computed tomography revealed a four by two centimetre left frontoparietal haemorrhage with associated vasogenic oedema and mass effect. Acutely he was given factor VIII inhibitor bypassing activity (FEIBA) 50 units/kg, an activated prothrombin complex concentrate (aPCC) containing predominantly activated factor VII and non-activated factors II, IX, and X, after which his neurological symptoms stabilised. Repeat imaging after 24-hours showed no expansion in haematoma volume (figure 1).

12 hours after FEIBA administration, thrombin time (TT) reduced from 53.6 seconds (pre-dose) to 36.7 seconds. Activated partial thromboplastin time (aPTT) remained unchanged (41.8 seconds to 41.5 seconds).

The patient improved clinically with rehabilitation. He was discharged home one month later, mobilising with one stick and experiencing improving mixed (predominantly expressive) dysphasia. No intracranial aneurysm or arteriovenous malformations were seen on subsequent neuroimaging. Anticoagulation was not restarted as its risks were deemed to outweigh benefits.

Discussion:

Haematoma expansion occurs in 72.9% of intracerebral haemorrhages, independently predicting poor functional outcome and mortality.[1] Haematoma expansion may be accelerated in anticoagulated patients and urgent reversal is of paramount importance.

Until the monoclonal antibody idarucizumab becomes clinically available as a specific antidote for dabigatran, reversing DTI-associated bleeding remains a challenge. This challenge is compounded by difficulty quantifying dabigatran's anticoagulative effects. Prothrombin time (PT), aPTT, and TT are affected by DTIs but do not correlate to dabigatran levels sufficiently to allow dosing or level estimation. However, a significant concentration of dabigatran is unlikely if TT and aPTT are normal. Currently the best estimation of dabigatran level is the dilute TT.

No systematic studies using FEIBA to treat DTI-associated haemorrhage exist. Instead information comes from spiking experiments and animal models. Using thrombin generation, viscoelastic tests, and routine coagulation tests, FEIBA was shown to counter-act dabigatran's thrombin inhibition by enhancing peak thrombin generation to a greater extent than either activated factor VII or prothrombin complex (PCC) alone.[2] In an ex vivo porcine model PCC over-corrected these parameters whilst idarucizumab reversed these parameters to baseline.[3] Whilst FEIBA has been shown to reverse these coagulative parameters, this must be balanced against potential side-effects, particularly thrombotic complications. A review by Aledort et al found thrombotic complications in individuals with haemophilia receiving FEIBA were rare (below 0.01%), with low rates of anaemia, no reported pathogen transmission, and good clinical tolerance.[4] Interim results from the phase III study of dabigatran reversal with idarucizumab in human subjects showed normalisation of dilute TT within minutes,[5] though study completion is not expected until mid-2017. In September 2015 the European Medicines Agency adopted a positive opinion recommending the granting of marketing authorisation for idarucizumab.

The use of FEIBA to overcome inhibitors to treat haemorrhage in haemophilias A and B makes it a logical candidate treatment for DTI-associated bleeding. Its mechanism as a non-specific reversal agent is poorly understood, though its efficacy is likely due to a combination of activated factor VII and PCC. There are

few reports of the use of aPCCs for DTI-associated haemorrhage in clinical settings, though haemorrhage was arrested successfully.[6]

Whilst specific reversal agents are developed, the use of non-specific reversal agents, such as FEIBA, may provide a feasible strategy for managing DTI-associated haemorrhage. It is important to discuss their use with a haematologist urgently in order to prevent haematoma expansion and clinical deterioration.

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