CASE REPORT

Apixaban-induced subdural bleeding: case presentation and literature review

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Accepted 19 February 2018

SUMMARY

Apixaban is a factor Xa inhibitor which is a non-vitamin K dependent oral anticoagulant known to cause the lowest rate of intracranial bleeding among the same kind of inhibitors. In this paper, we report a rare case in a 60-year-old man with a history of hypertension and oligodendroglioma on apixaban for deep venous thrombosis who presented to our hospital with decreased level of consciousness and slurred speech with rapid deterioration. We highlight the risk of subdural bleeding requiring immediate neurosurgical intervention due to apixaban, with literature review.

BACKGROUND

Anticoagulants have been used for several years for a variety of conditions. Owing to the growing number of these medications over the past few years, managing complications are limited. The global motivation towards the prevention of ischaemic stroke and deep venous thrombosis to reduce their burden and morbidity has increased the number of people using blood-thinning agents including the non-vitamin K dependent oral anticoagulants (NOACs) like factor Xa inhibitors.¹

These new oral anticoagulants with direct Xa inhibiting activity and currently used are apixaban, rivaroxaban and edoxaban. These medications ensure a safe and effective treatment for many conditions such as deep venous thrombosis, pulmonary embolism and stroke prevention in non-valvular atrial fibrillation.

Since the Food and Drug Administration approved apixaban in 2014, it is considered to be a safe alternative to warfarin in treating many cases such as deep venous thrombosis.² Like other anticoagulants, apixaban carries a risk of intracranial bleeding but this risk is lesser than warfarin and even less than other medications in the same group. With these advantages, this medication unfortunately has no direct reversal agent.³

We report and challenge the case of acute subdural haematoma in a patient on apixaban. Also, we highlight some learning points from a neurosurgeon's point of view.

CASE PRESENTATION

This is a case of a 60-year-old man with a history of hypertension and oligodendroglioma. Postcraniotomy and tumour debulking, he completed chemotherapy and radiotherapy sessions 3 months ago. He developed a deep venous thrombosis

during his chemotherapy, and he was discharged on apixaban.

He presented to our hospital with a 3-hour history of decreased level of consciousness and slurred speech. There was no history of trauma, seizure or vomiting. He was conscious, disoriented, aphasic and barely obeying commands. He was able to open his eyes to verbal stimuli and reacting only to the pain. Pupils were equal, symmetrical and reactive bilaterally, without facial asymmetry or cranial nerve involvement. His platelets were $198 \times 10^9/L$. Coagulation profile and other laboratory tests were within normal limits. CT scan was performed in the emergency department and showed bilateral subdural haematoma, more on the right side (figure 1).

As the last dose of his apixaban was 5 hours before arrival to our hospital, the patient's surgery was postponed for 24 hours from the last apixaban dose. Unfortunately, the patient deteriorated after 5 hours from admission with a drop in his level of consciousness. We transfused him with 4 units of fresh frozen plasma (FFP), and he received injection of prothrombin complex concentrate 25–30 units/kg. Evacuation of his subdural haematoma was done immediately with right-sided craniotomy and left frontal bur hole to evacuate the chronic and acute on top of chronic subdural haematomas (figure 2).

OUTCOME AND FOLLOW-UP

Postoperatively, he improved gradually. His speech improved, and his level of consciousness

Figure 1 CT brain showing bilateral subdural haematomas, larger on the right side with acute component and mass effect.

To cite: Alayad E, Khairy S, Aloraidi A. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224495

Figure 2 Postoperative CT brain showing evacuation of subdural haematoma and pneumocephalus.

also improved. He was discharged 10 days after the surgery in his baseline condition.

DISCUSSION

Apixaban-induced intracranial haemorrhages had a variety of clinical presentations. In 2015, the first reported case of apixaban-induced intracranial bleeding required neurosurgical intervention in a 76-year-old man with subdural haematoma.² However, phase II apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intra-Cerebral HaEmorrhage in patients with Atrial Fibrillation trial showed that the best and safest stroke and venous thromboembolism prevention drug is apixaban. The results of this trial are not published and deferred awaiting the results of phase III trial.³ Although meta-analysis of randomised controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists showed that apixaban had a lower risk of intracranial bleeding (RR 0.42, 95% CI 0.31 to 0.58).¹ A case reported an alcoholic patient on apixaban developed multiple fatal traumatic intracranial bleeds and died without neurosurgical intervention due to the failure of anticoagulation reversal.⁴

Another case reported a patient from Japan with a rare presentation of non-traumatic convexal subarachnoid haemorrhage due to apixaban.⁵ However, factor VIII inhibitor bypassing activity used in the management of apixaban-associated subdural bleeding and gave a non-invasive option of reversal for apixaban-induced subdural bleeding^{6,7} two cases with non-operable intracranial bleeding due to apixaban, managed effectively by 25 U/kg prothrombin complex concentrate.⁸ Emergent neurosurgical intervention due to apixaban intracranial bleeding was required in other cases.⁹ Globally and specially in Saudi Arabia, the growing market of these NOACS without having an available antidote, clear lines of management or neurosurgical approach required immediate action and attention.

According to the published literature, yet there are no clear guidelines for the reversal of factor Xa inhibitor-induced intracranial bleeding guiding neurosurgical approach in such life-threatening conditions. However, there is some limited role of FFP and 4-factor prothrombin complex concentrate and charcoal administration in the reversal of factor Xa inhibitor-induced intracranial bleeding.¹⁰ Andexanet alfa is the only antidote which is in phase III trial for the reversal of factor Xa inhibitors.¹¹

Apixaban-induced subdural bleeding is rare but life-threatening condition. Close monitoring and rapid reversal of the medication with timely surgical intervention are always advisable to reduce mortality and morbidity.

Learning points

- Serious types of bleeding can result from novel oral anticoagulants.
- Neurosurgeons need to have clear guidelines in the management of intracranial bleeding side effect.
- Without having available an effective antidote, clinicians should use these non-vitamin K dependent oral anticoagulants cautiously.

Contributors AA: conception and design, helped in editing the final manuscript. SK: acquisition of data and images, helped in editing the final manuscript. EA: writing the case report.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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