Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 2 (2015) 54–56

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

journal homepage: www.inat-journal.com

Case Reports & Case Series (CRP)

Spontaneous cerebellar hemorrhage in a patient taking apixaban ☆

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ARTICLE INFO

Article history:
Received 10 November 2014
Accepted 20 December 2014

Keywords:
Apixaban
Anti-coagulation
Intracerebral hemorrhage
Atrial fibrillation

ABSTRACT

Objectives: Atrial fibrillation is closely associated with cardioembolic stroke. Until recently, warfarin has been the gold standard for the treatment of atrial fibrillation. Since 2010 the United States Food and Drug Administration has approved three new agents for anticoagulation in patients with atrial fibrillation. The purpose of this case report is to discuss some of the practical implications for using these agents.

Methods: A patient taking apixaban presented with a spontaneous cerebellar hemorrhage. While the patient was initially considered a candidate for surgical intervention, the lack of literature addressing surgical intervention in patients on novel anticoagulation clouded the clinical decision-making. The patient was ultimately managed with administration of activated prothrombin complex concentrate, blood pressure control, frequent clinical assessments and airway protection. The patient did not undergo craniotomy for hematoma evacuation.

Conclusions: Recent FDA approval of several novel oral anticoagulants for use in patients with atrial fibrillation has resulted in a significant number of patients formerly treated with warfarin being switched to these newer agents. There remains a lack of clear guidelines for the management of hemorrhagic complications. This case report describes one management strategy and highlights the paucity of current evidence to support critical clinical decisions.

Introduction

In 2010, dabigatran (Pradaxa) became the first novel oral anti-coagulant (NOAC) approved in the United States followed by rivaroxaban (Xarelto) in 2011 and apixaban (Eliquis) in 2012. The introduction of each of these agents was supported by a randomized clinical trial: RE-LY for dabigatran, ROCKET-AF for rivaroxaban, and ARISTOTLE for apixaban [1–3]. With respect to efficacy in preventing ischemic stroke and rate of systemic hemorrhagic complications, each trial reported their respective NOAC as non-inferior to the current gold standard, warfarin.

Since their approval, many governing bodies in organized medicine, e.g. the American Academy of Neurology, now encourage the use of the novel agents over warfarin [4] and many physicians began prescribing these NOACs. Since their introduction into the American pharmacological armamentarium there have been an increasing number of publications reporting hemorrhagic complications and urging caution when using NOACs [4–6]. We present one such hemorrhagic complication and discuss several salient aspects of NOACs.

Summary of case

A patient presented to the emergency department after developing acute onset dizziness, nausea and somnolence. Blood pressure was 190/93 mm Hg and physical exam revealed a somnolent, yet arousable individual. The Glasgow coma score (GCS) was 14. The initial NIHSS was 4 (2 — nystagmus on right lateral gaze, 2 — ataxia on left finger–nose–finger). Initial non-contrast head computerized tomography (CT) (Fig. 1) revealed a left cerebellar intra-parenchymal hemorrhage measuring 3.3 cm × 3.6 cm extending into the fourth ventricle without acute hydrocephalus.

Past medical history was significant for coronary artery disease, hypertension, sick sinus syndrome status post implanted pacemaker and atrial fibrillation. After several years of compliant anticoagulation with warfarin, the patient had been switched to apixaban 5 mg approximately 10 months prior to presentation. Initial laboratory values included platelets 152,000 per microliter (reference range (RR) 150,000–400,000 per microliter), partial thromboplastin time (PTT) 34 seconds (RR 25–35 seconds), anti-Xa abnormal, consistent with drug in the plasma, and prothrombin time of 15 seconds (RR: 12–14 seconds).

At the recommendation of Hematology and Transfusion Medicine, a single weight-based dose of Factor Eight Inhibitor Bypass Activity (FEIBA or Anti-Inhibitor Coagulant Complex) was administered on arrival to the NICU. Blood pressure was controlled using a nicardipine infusion titrated for a goal systolic blood pressure less than 160 mm Hg.

☆ Disclosures: None.

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http://dx.doi.org/10.1016/j.inat.2014.12.002

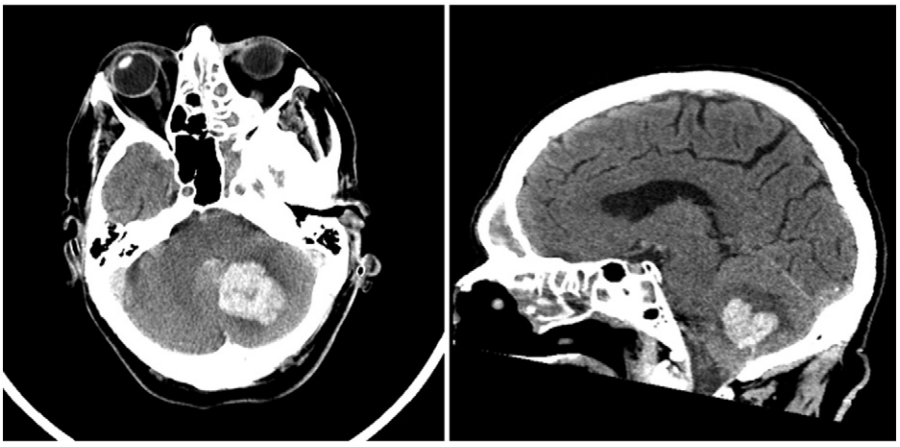

Fig. 1. Initial head CT.

On repeat exam, the patient was more somnolent, GCS 13, and NIHSS 6 (1 LOC, 1 orientation, 2 nystagmus, 2 ataxia) with a diminished gag reflex. The patient was intubated for anticipated need for airway protection.

Although the clinical situation would often dictate neurosurgical intervention, the patient was felt to be at high risk for intracranial surgery due to limited data on reversal of apixaban and an expectant management approach was elected, with plans to re-consider surgical intervention if evidence of hematoma expansion, development of hydrocephalus, or further neurologic decline occurred.

Over the next several days, the patient's neurologic exam improved. Head CT on post-hemorrhage day 5 (Fig. 2) demonstrated decreased mass effect in the posterior fossa, with stable to decreased hematoma size.

The patient was extubated on hospital day 11 and discharged to an inpatient rehabilitation facility on hospital day 15, without requiring operative intervention during his hospital course. NIHSS at discharge was 1 (ataxia) and Modified Rankin Scale was 1, which were both stable at six-month clinic follow-up.

Conclusion

Several concerns exist regarding the initial trials conducted on NOACs. One is that patients with any history of intracranial hemorrhage (ICH), renal failure, active liver disease, or severe hypertension were excluded [6,7]. Another concern is that there are no head-to-head studies directly comparing NOACs. To date, there are only indirect comparisons of the newer agents [8].

Perhaps the most worrisome evidentiary deficit involves their potential for hemorrhagic complications. While there are several studies comparing the rates of warfarin- and NOAC-related ICH, [9,10] there is no evidence comparing the respective clinical outcome or case fatality in these two groups [11]. Furthermore, while several studies claim superior cost-effectiveness of NOACs over warfarin, and apixaban over other novel agents, these studies failed to include the costs associated with ICH in the analyses [12,13].

Perhaps the most widely-toted advantage of the NOACs is their predictable pharmacokinetics, obviating the need for routine laboratory monitoring [14]. In the outpatient setting, this is an advantage to the patient and provider. However, in the bleeding trauma or neurosurgery patient, the lack of a reliable assay is a potentially fatal disadvantage.

The final issue is the most germane to the current case discussion: How can the effects of NOACs in the actively bleeding patient be reversed? Currently we have, at best, Class III and IV evidence supporting the use of various reversal strategies depending on the anticoagulant on board. Historical reversal strategies (e.g. vitamin K and fresh frozen plasma) are slow and have little impact on the effect of NOACs [15]. Several authors have demonstrated the successful use of emergent hemodialysis in patients on dabigatran. Unfortunately,

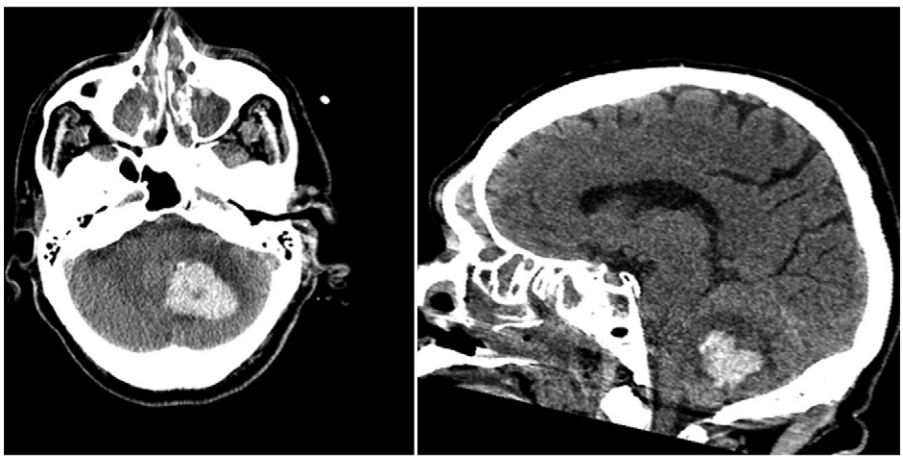

Fig. 2. Head CT on post-hemorrhage day 5.

this strategy does not translate to rivaroxaban or apixaban, as the latter two are highly protein bound [5]. Available alternative strategies are those used in the current case: administration of prothrombin complex concentrate (PCC) or their activated counterparts (aPCCs such as FEIBA). While this strategy appeared to work in the current case, and while the plurality of the currently available evidence supports the use of PCCs or aPCCs in this setting [4], there are, to date, no guidelines or prospective studies to guide the decision-making process regarding surgical intervention.

Despite positive evidence on their efficacy, these concerns and the lack of evidence on managing complications associated with NOACs have led many authors to advise caution when prescribing these agents.

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