CASE REPORT

Novel oral anticoagulant and kidney injury: apixaban-related acute interstitial nephritis

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SUMMARY

Non-vitamin K oral anticoagulants (NOACs) are being increasingly prescribed. These drugs act rapidly, have predictable dose-related anticoagulation effect and require no routine laboratory monitoring, making them attractive for both patients and healthcare providers. All NOACs are at least partially excreted through the kidneys. Renal injury related to NOAC use is being increasingly reported. NOAC-related acute interstitial nephritis (AIN) has only been reported once and that was in context of dabigatran use. We describe the first case of apixaban-related AIN. This case adds an important differential diagnoses that should be considered for any patient presenting with renal injury while being treated with NOACs.

BACKGROUND

Non-vitamin K oral anticoagulants (NOACs) have emerged as important alternatives to warfarin in patients requiring chronic anticoagulation. These drugs act rapidly, have a predictable dose-related anticoagulant effect, less drug-drug interactions and require no routine laboratory monitoring. This makes them appealing to both patients and healthcare providers. All NOACs are at least partially excreted through the kidneys and are generally considered safe for the kidneys. Renal injury is being increasingly recognised as a complication of novel oral anticoagulants (NOAC) use, including anticoagulation-related nephropathy (ARN).^{1–4} However, there is limited data on the spectrum of nephrotoxicity with NOAC use. Acute interstitial nephritis (AIN) related to NOAC use has only been reported once in the medical literature. This was a case of dabigatran-related AIN.⁴ In this report, we describe the second case of NOAC-related AIN but the first case of AIN related to Apixaban use.

CASE PRESENTATION

A 76-year-old woman with stage 4 chronic kidney disease (CKD) (baseline creatinine of 247.52 $\mu\text{mol/L}$), hypertension, pulmonary hypertension, type 2 diabetes mellitus and paroxysmal atrial fibrillation was admitted for acute kidney injury. Her home medications included nifedipine, amiodarone, glipizide, hydralazine, metoprolol, atorvastatin, aspirin and sildenafil. She had been started on apixaban 2.5 mg twice daily 6 months prior to this admission, for atrial fibrillation. No ingestion of non-prescription supplements,

non-steroidal anti-inflammatory drugs (NSAIDs) or herbal medications was reported.

INVESTIGATIONS

Physical examination was unremarkable including cardiopulmonary examination. Laboratory testing revealed creatinine of 1281.80 $\mu\text{mol/L}$, blood urea nitrogen of 72.83 mmol/L, bicarbonate 17 mmol/L and an anion gap of 26. Her creatinine was 247.52 $\mu\text{mol/L}$ 2 months prior to this presentation. Liver function was also within normal limits. A renal ultrasound showed diffuse echogenicity in both kidneys but no obstructive uropathy. Differential cell count was unremarkable. Urine studies revealed a urinary sodium of 44 mmol/L and a creatinine of 115.4 $\mu\text{mol/L}$ with a fractional sodium excretion of 3.98%. Urine microscopy was only notable for sterile pyuria without red blood cell cast or overt proteinuria. However, eosinophiluria was identified on Hansel's staining.

A clinical diagnosis of AIN was made, and the patient was switched to warfarin from apixaban. Apixaban was presumed to be the likely culprit since it was the most recently introduced medication. The patient responded well to a short course of high-dose steroids (1 mg/kg tapered over 14 days). A kidney biopsy was not pursued due to her history of significant CKD and the high bleeding risk of the procedure with therapeutic anticoagulation. Her serum creatinine improved significantly from 1281.80 $\mu\text{mol/L}$ to 804.44 $\mu\text{mol/L}$ within 1 week of withdrawal of apixaban. No renal replacement therapy was required. Her serum creatinine continued to improve after discharge from the hospital and was noted to be 433.04 $\mu\text{mol/L}$ after 16 days of withdrawing apixaban.

DISCUSSION

Apixaban is an oral factor Xa inhibitor that was approved for use by the Food and Drug Administration in 2012. It is rapidly absorbed after oral administration, reaches peak plasma concentration within 1–3.5 hours and has a half-life of around 12 hours.¹ An analysis of outpatient office visits for anticoagulation in 2014 showed that NOAC use has dramatically increased.⁵ It accounted for around 4.21 million visits for anticoagulation (around 38.2% of total anticoagulation visits).⁵ Another study showed that NOACs accounted for 62% of all new anticoagulant prescriptions by mid-2013.⁶ Rapid onset of action, predictable dose-related effects and no requirement for frequent laboratory

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monitoring are some of the key factors responsible for growing popularity of NOACs.

Renal complications of NOACs are being increasingly recognised as a significant cause of morbidity in these patients. ARN has been recently reported as one of the renal complications of NOAC use.^{4 7 8} AIN has been described in one report associated with the use of dabigatran.⁴ An uncommon side effect such as AIN may be more frequently encountered as NOAC use increases. This necessitates a high index of suspicion by clinicians to facilitate early detection of AIN, and timely discontinuation of the NOAC. The gold standard to establish a diagnosis of AIN is a kidney biopsy. However, patients on NOACs tend to be older, with higher likelihood of underlying CKD and other cardiovascular comorbidities. These factors in combination with a higher bleeding risk due to anticoagulation may pose unique challenges for a kidney biopsy. In addition, the risks of discontinuing anticoagulation must be weighed into the decision of pursuing a kidney biopsy.

The classic clinical phenotype for AIN includes fever, rash, eosinophilia/eosinophiluria and renal dysfunction.^{9 10} However, certain classes of drugs such as NSAIDs can present with a paucity of supporting clinical findings as well as significantly delayed onset of renal injury after exposure to the drug.^{9 10} The previously described case of AIN from dabigatran and our case are similar in the lack of overt clinical findings for AIN, and a relatively late onset of kidney injury after initiation of the NOAC.

NOAC-related AIN is a newly recognised clinical entity that should be suspected in patients with new-onset kidney injury

after initiation of these drugs. If the patient is suspected to have an intrinsic cause of acute kidney injury, the differential diagnosis should include AIN as a possible aetiology, as prompt recognition is crucial to limit progression of kidney damage.

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Learning points

- This is the second case of NOAC-related AIN and the first one related to apixaban use. It highlights the importance of considering AIN in the differential diagnosis for patients presenting with deterioration of renal function after starting NOACs.

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