CASE REPORT

Apixaban-induced liver injury

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SUMMARY

An 81-year-old woman with well-controlled hypertension presented to the emergency department with new-onset atrial fibrillation with rapid ventricular response. Treatment for atrial fibrillation was initiated, including rate control and anticoagulation with 5 mg of apixaban two times per day for primary stroke prophylaxis. Three days after initiation of apixaban, the patient noted new-onset abdominal pain, worsening shortness of breath and weakness. Laboratory results showed elevated liver enzymes. Workup for elevated transaminase did not reveal any underlying infectious or autoimmune process. Apixaban, a probable cause for the hepatocellular injury, was discontinued and replaced with intravenous unfractionated heparin to bridge anticoagulation with warfarin. The patient's symptoms resolved as her transaminases improved by discontinuation of apixaban. We illustrate this case of drug-induced hepatotoxicity secondary to treatment with apixaban. It is important for physicians to be aware of this rare adverse effect caused by a widely used novel oral anticoagulant.

BACKGROUND

Apixaban is a direct, selective, reversible, factor Xa inhibitor that inhibits the coagulation cascade at the intersection of the intrinsic and extrinsic pathways.¹ The pharmacokinetic and pharmacodynamics of apixaban are predictable; thus, no blood level monitoring is generally required when treatment is initiated or maintained with this novel oral anticoagulant.¹ Apixaban has been approved by the United States Food and Drugs Administration (FDA) since October 2012 and is used to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation.² Between 2.7 and 6.1 million people in the USA are diagnosed with atrial fibrillation each year, many of whom will be prescribed apixaban.³ Interestingly, apixaban has rarely been shown to cause hepatotoxicity.

CASE PRESENTATION

An 81-year-old woman with a history of hypertension that had been managed with 25 mg of atenolol daily for the past 5 years presented to the emergency department with palpitations and shortness of breath that had increased during the past 24 hours. She had experienced similar symptoms intermittently for the past 3 years but never sought medical attention. ECG demonstrated new-onset atrial fibrillation with rapid ventricular rate of 141 bpm (figure 1). The patient was not noted to have any history of atrial fibrillation, and her last ECG from 2 years prior to presentation showed normal sinus rhythm.

The patient was admitted to the hospital and treated with two 5 mg doses of intravenous metoprolol tartrate. Calculated CHA2DS2VASC score at time of admission was 4 (2 points for age, 1 point for female sex and 1 point for hypertension). Thus, anticoagulation with 5 mg of apixaban administered two times per day was initiated. After achieving rate control for the atrial fibrillation (heart rate of 90–110 bpm), the dose of atenolol was increased to 50 mg daily (from 25 mg daily), and the patient was discharged home with a scheduled follow-up in the cardiology clinic. Total hospitalisation time (time since apixaban was initiated) was 24 hours.

Two days after discharge from the hospital, the patient returned to the emergency department with new-onset abdominal pain, shortness of breath and generalised weakness. She also described bloating, nausea and vomiting, with no diarrhoea and no change in appetite. She reported no changes in her diet over the past few days. The patient was a former smoker (15 packs per year). She denied any alcohol intake, recreational drug use and injectable drugs use.

Physical examination showed mild scleral icterus and moderate right upper quadrant tenderness, with no other abdominal findings or signs of acute abdomen. Examination of the precordium, lungs, lower extremities and nervous system revealed no abnormalities.

INVESTIGATIONS

In the emergency department, laboratory testing revealed elevated liver enzymes: alanine aminotransferase (ALT) of 199 U/L (reference value, 7–45 U/L); aspartate aminotransferase (AST) of 110 U/L (reference value, 8–43 U/L), alkaline phosphatase (ALP) of 72 U/L (reference value, 55–142 U/L) and total bilirubin of 2.5 mg/dL (reference value, ≤1.2 mg/dL), with direct bilirubin of 1.0 mg/dL (reference value, ≤0.3 mg/dL). Those values were significantly elevated from her last admission 2 days prior to this presentation when she had a normal liver function

Figure 1 ECG at the time of the first admission showing atrial fibrillation with rapid ventricular response (ventricular rate 141 bpm). No previous history of atrial fibrillation was known for the patient.

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Figure 2 A graphic representation of the values of bilirubin and liver enzyme levels. The top graph shows a rise in bilirubin from baseline 0.4 mg/dL on the first day when anticoagulation with apixaban was initiated to 2.5 mg/dL on day 3. The bottom graph shows the rise and drop in the values of the liver enzymes: ALT, AST and ALP. Apixaban was initiated on day 0 and discontinued on day 3. (Bilirubin values represented by mg/dL and liver enzyme values represented by U/L measurement units.) ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D1, discharge from the first hospitalisation; D2, discharge from the second hospitalisation; H1, first hospitalisation for atrial fibrillation when apixaban was initiated; H2, second hospitalisation for elevated liver enzymes when apixaban was discontinued; M, inpatient monitoring.

test (figure 2). Haemoglobin, white cell count, platelets count, electrolytes, thyroid-stimulating hormone, blood-urea nitrogen and creatinine were all within normal ranges. Lipase and γ -glutamyltransferase were within normal range. The prothrombin time was 15.8 s (reference value, 11.6–14.7 s), international normalised ratio (INR) was 1.3 and activated partial thromboplastin time (aPTT) was 200 s (reference value, 22.7–36.1 s). This was a significant change from her previous admission, which showed a prothrombin time of 11.9 s, INR of 0.9 and aPTT of 118 s. The patient was admitted to the hospital for further management of her condition.

In the hospital, further diagnostic workup revealed negative infectious causes of acutely elevated liver enzymes, including anti-hepatitis A virus IgM, hepatitis B panel, hepatitis C virus by PCR, Epstein-Barr virus PCR and cytomegalovirus PCR. Similarly, autoimmune diagnostic workup revealed negative antinuclear antibody, rheumatoid factor, antismooth muscle antibody and antimitochondrial antibody. Liver and biliary ultrasound was non-contributory. No liver biopsy was performed due to risk of bleeding because the patient was on anticoagulation with apixaban.

DIFFERENTIAL DIAGNOSIS

Acute to subacute mild to moderately elevated transaminase levels have many causes such as drug-induced liver injury, viral hepatitis, alcoholic liver disease and autoimmune hepatitis. Haemochromatosis, Wilson disease and non-alcoholic fatty liver disease tend to have more chronic course with certain clinical and diagnostic features.

TREATMENT

Owing to the lack of contributory results from the diagnostic workup and threefold or more rise in the ALT combined with

elevated total bilirubin, the patient's condition raised the suspicion for drug-induced hepatotoxicity.^{4 5} Apixaban was suspected to be the culprit for the elevated transaminase because it was the only newly started medication. Three days since the treatment initiation, apixaban was immediately discontinued. The patient was bridged with intravenous unfractionated heparin and underwent an elective transoesophageal echocardiography cardioversion to normal sinus rhythm. Warfarin was initiated with an INR goal of 2.0–3.0 and atenolol (50 mg daily) was continued. Since the initiation of therapy, the patient had received a total of seven doses (5 mg each) of apixaban.

OUTCOME AND FOLLOW-UP

After 24 hours of discontinuation of apixaban therapy, the liver enzyme levels (ALT, AST and ALP) started to decline as well as the bilirubin level (figure 2). The abdominal pain, shortness of breath and generalised weakness improved gradually after apixaban was discontinued. The patient was discharged from the hospital after 5 days with a primary care physician follow-up.

Follow-up on the patient's condition after 2 weeks, 1 month and 3 months revealed stable clinical state, and normalisation of her liver function test was achieved by discontinuation of apixaban.

DISCUSSION

We illustrate a potential adverse effect of a very commonly used direct oral anticoagulant (DOAC), apixaban. Our patient received apixaban as a newly introduced anticoagulant agent for thromboembolic stroke prevention due to atrial fibrillation and developed apixaban-induced hepatocellular toxicity. We established the diagnosis based on Hy's law and causality assessment using the Roussel-Uclaf Causality Assessment Method (RUCAM) score.⁶

Hy's law states that an increase in the AST or ALT value twofold or more than the upper normal limit (UNL) along with rise in direct bilirubin twofold or more from the UNL is suggestive of a drug-induced hepatocellular toxicity.^{4 5} Therefore, our patient's laboratory findings are suggestive of apixaban-induced hepatocellular injury.

Our patient had an R ratio of 8.84 (calculated by $R = (ALT/ALT\ UNL)/(ALP/ALP\ UNL)$), which is suggestive of hepatocellular injury (not a cholestatic or mixed injury).⁶ The calculated RUCAM score was +6 (+1 point for time of onset within 3 days since treatment with apixaban initiated; +3 points for fall in ALT $\geq 50\%$ within 2 days of the apixaban discontinuation; +1 point for age of 81 years; +1 point for ruling out all other causes of elevated transaminases; –1 point because apixaban is not known to cause hepatocellular injury; and +1 point for the few published case reports describing apixaban-induced liver injury).⁶ A RUCAM score of +6 is suggestive that apixaban is a probable cause for hepatocellular injury.⁷

Although the mechanism of apixaban-induced hepatotoxicity is unclear, in most cases, it is thought to be an idiosyncratic reaction at therapeutic doses and not related to the pharmacological action of the drug. It is suggested that patients with prior liver injury may be at a higher risk of apixaban-induced hepatotoxicity.⁸ Also, concomitant administration of CYP3A4 inhibitors (like certain antimicrobials) may precipitate apixaban-induced liver injury.⁹

Few case reports have described drug-induced hepatotoxicity in patients receiving DOACs such as apixaban and rivaroxaban.^{2 8} A meta-analysis of 152 116 patients in 29 stage III clinical trials concluded that there was no increased risk of hepatotoxicity with DOACs.¹⁰ However, case reports,

pharmacovigilance data and patient series reveal hepatotoxicity associated with DOACs in patients with normal and impaired liver function.^{2 8 10 11} Of all available DOACs, apixaban is less frequently associated with hepatotoxicity.^{12 13} However, other DOACs such as rivaroxaban and dabigatran have been available on the market longer than apixaban, making this statement vulnerable to bias.¹² Apixaban-induced hepatotoxicity resulting in permanent severe liver injury is rare, but it has been reported.⁸ Also, a complete resolution of the liver injury can be achieved by discontinuing apixaban.¹⁰

Our case is unique from the other published cases for several reasons. First, the apixaban-induced toxicity profile, represented by elevation in liver enzymes (particularly ALT), occurred within 2–3 days of initiation of apixaban, which is a significantly shorter time than the other published cases.^{2 8} Second, a rapid and remarkable clinical and laboratory improvement was encountered in a relatively short time (1–2 days) after discontinuation of apixaban. Third, our patient had no previous exposure to apixaban, making the possibility of an idiosyncratic reaction a plausible explanation.

The causality of the liver enzyme elevation is more likely consistent with apixaban intake than the other two concomitantly taken medications, metoprolol and atenolol. Only two doses of metoprolol tartrate were administered intravenously during the first hospitalisation for atrial fibrillation rate control. Importantly, a third dose was administered during the second hospitalisation (prior to the elective transoesophageal echocardiography cardioversion) and was not associated with elevation in the liver enzymes (figure 2). Atenolol is a medication that was well tolerated by the patient for 5 years prior to her presentation, making the imputability of atenolol-induced liver injury unlikely.

Our patient had elevated values of PT, INR and aPTT, which are attributed to the effect of apixaban therapy. Apixaban has a pharmacological property to increase the values of PT, INR and aPTT; however, it is not recommended for assessing treatment effectiveness or guiding clinical decisions.

Although no liver biopsy was performed due to anticoagulation with apixaban and increased risk of bleeding, criteria for liver injury (Hy's law) and the causality assessment using R ratio and RUCAM score were suggestive of the diagnosis of hepatocellular injury and probable drug-induced liver injury. We did not perform a liver biopsy afterwards due to the rapid and remarkable improvement in the transaminases.

Patient's perspective

I was worried that I might have a serious liver disease. But my doctor reassured me that the blood thinner I was taking is the cause for my symptoms. My symptoms improved after I stopped taking apixaban and my strength was back to normal after 2 weeks.

Learning points

- ▶ Apixaban is a commonly prescribed novel oral anticoagulant that may be associated with a risk for drug-induced hepatotoxicity.
- ▶ A high-index of suspicion is required when an elevated liver function test is encountered in a patient recently treated with apixaban.
- ▶ Apixaban-induced liver injury can be managed by discontinuation of apixaban, and level monitoring of liver enzymes and bilirubin.

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