Factor Xa Induced Hepatobiliary Dysfunction in an Eastern Asian Male

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Abstract

Factor Xa inhibitors are approved for the prevention of clot formation in non-valvular atrial fibrillation and for treating deep venous thromboembolism and pulmonary embolism. This class of medications are known CYP3A4 and CYP2J2 inhibitors vulnerable to drug-drug interactions and are known to be risk factors for GI bleeding. Although not a common finding, these medications are possible risk factors for acute liver injury, as seen in our patient. We present an uncommon case of persistent Factor Xa inhibitor induced liver injury in an Eastern Asian male.

Keywords: Factor Xa; Kidney; Atrial fibrillation; Stroke; Bleeding

Introduction

Factor Xa inhibitors, such as Rivaroxaban and Apixaban, are approved for the prevention of clot formation in non-valvular atrial fibrillation and for treating deep venous thromboembolism and pulmonary embolism [1-3]. These drugs selectively inhibit the active site of factor Xa and are eliminated by both the liver and the kidney (one-third by the liver and two-thirds by the kidney). An impairment of either of these organs can alter pharmacokinetics and pharmacodynamics of these drugs. Hepatic metabolism of Factor Xa Inhibitors is through the Cytochrome P450 3A4 and 2J2 system, making them subject to drug-drug interactions [1]. Common and known side effects of rivaroxaban include bleeding, bowel and bladder dysfunction, non-specific neurosensory symptoms, dizziness, headache, and leg weakness. Except for known increased risk of GI bleeding, gastrointestinal side effects are quite uncommon, and their incidence is not widely recognized.

Although the risk of GI bleeding is widely recognized as a risk in Factor Xa Inhibitors, drug induced liver injury (DILI) on the other hand, is not widely recognized. Cases of DILI have been reported with rivaroxaban and other Factor Xa inhibitors in a few circumstances [4-6]. Studies have shown that Rivaroxaban has been associated with serum aminotransferase elevations greater than three times the upper limit of normal in approximately 1-2% of treated patients [7]. Despite this, premarket studies did not show clinically significant events of acute liver injury associated with Rivaroxaban or any other Factor Xa inhibitors. The severity of liver injury associated with Factor Xa inhibitors has ranged from mild, asymptomatic elevations in liver aminotransferases to symptomatic hepatitis with jaundice. There have not been any reports of fulminant liver failure associated with Factor Xa inhibitors to date. Patients with acute liver injury from Factor Xa inhibitors have generally tolerated substituted Factor Xa inhibitors without recurrence of liver abnormalities [6]. Here we present a highly probable occurrence of Factor Xa induced hepatobiliary dysfunction in an Eastern Asian Male following a serial course of Factor Xa Inhibitors.

Case Presentation

A 72-year-old Eastern Asian male with a past medical history of diabetes and hyperlipidemia presented to our hospital with jaundice and pruritis approximately six weeks after initiating Apixaban following a cerebrovascular incident. In addition to starting a DOAC (Direct Oral Anti-Coagulation), a LINQ device was placed for suspected atrial fibrillation. Despite not having any rhythm abnormalities during the course of his LINQ placement, the patient continued to have jaundice, nausea, and pruritis and was found to have profound increases in his liver enzymes. Patient had no past history of liver or biliary disease except for remote history of Hepatitis A in his early twenties. He had no record of gallstones. Due to suspected drug induced liver injury, Apixaban was switched to Rivaroxaban, an alternative Factor Xa inhibitor.

Due to persistent symptoms of jaundice and pruritis despite being switched to Rivaroxaban, the patient was admitted to our hospital for further testing. Rivaroxaban was held during his course, along with Atorvastatin and Metformin which the patient took for Hyperlipidemia and Diabetes Mellitus, respectively. The patient denied any history of alcohol or drug abuse and all hepatitis testing (including Hep A Ab IgM, Hep Bc Ab, Hep Bs Ag, Hep C Ab) was negative. Patient did not display any overt signs of infection including fever, chills, tachycardia, tachypnea, or leukocytosis. Laboratory analysis showed an elevated Alk phos of 759, AST 204, ALT 475 and a Total Bilirubin of 18.7 (Direct Bilirubin of 13.4). CT abdomen showed a nondilated gallbladder with multiple gallstones, without any hepatobiliary process identified (Figure 1). Subsequent MRCP done during same admission found gallstones without pericholecystic fluid or wall edema. No indication of cholecystitis, choledocholithiasis or obstructive and/or inflammatory cholangitis was found. Following the discontinuation of Rivaroxaban there was a marked decrease in the patient’s jaundice and liver enzymes. After one week of holding Rivaroxaban, Alkaline phosphatase levels came down to 479, AST down to 97 and ALT down to 219, and T. bilirubin down to 8.4 (D. Bili 6.5).

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Follow up Fibroscan was done at the clinic, two weeks after discharge, which showed a CAP score of 169 out of 400, which is negative for clinically significant hepatosteatosis. The METAVIR Fibrosis score was F0-F1, implying no clinically significant portal fibrosis was found. After a total of four weeks of holding Rivaroxaban, liver enzyme values came down significantly, to near baseline (Figure 2). The patient had been taking for years prior to starting Apixaban, making it possibly a confounding factor and much less likely a direct culprit of acute liver injury in this clinical scenario.

We are increasingly recognizing Factor Xa induced liver injury as a possible but rare complication of this medication class, due to a mechanism that is not fully understood. The literature has shown that with some patients with liver injury due to one Factor Xa inhibitor have tolerated an alternate Factor Xa inhibitor without recurrence of liver injury. However, our patient continued to have elevated liver enzymes despite being switched to an alternative Factor Xa Inhibitor. This finding raises the concern of a possible increased susceptibility of acute liver injury in Eastern Asian Males on Factor Xa Inhibitors.

While the epidemiology and causes of DILI are often difficult to ascertain in any given clinical scenario, the literature shows some key differences between Eastern populations and Western populations in their manifestations of acute liver injury. Some studies have shown that the cause of liver injury among Eastern populations compared to Western populations differ, in that, drug induced liver injury is more common among Eastern nations compared to Western nations (US, UK and Sweden) [8]. This phenomenon is mainly attributed to the use of anti-tubercular medications used in India along with traditional Chinese medications used in Mainland Asia and Southeast Asia. DILI in the West, however, is predominantly caused by NSAIDs and antimicrobial medications such as Diclofenac and Amoxicillin-Clavulinate respectively [9]. Despite these interesting findings there have not been any studies on an overall increase in DILI in Eastern populations from certain medication classes, including DOACs such as Factor Xa Inhibitors [10-12]. This case overview highlights a possible increased propensity of DILI with the use of this medication class in Eastern Asian people and further studies are recommended to further investigate this possible phenomenon.

**Discussion**

Rivaroxaban and other Factor Xa inhibitors are approved for the treatment of VTE and for the prevention of stroke in patients with nonvalvular atrial fibrillation. Salient side effects include major and minor bleeding, including well documented GI bleeding. Several case studies have shown an association between initiation of Rivaroxaban and/or Apixaban and subsequent elevated liver enzymes. The temporal relationship between initiating Rivaroxaban and derangements in liver enzymes have been shown to occur one to eight weeks after initiation of this medication [4]. Given our patient’s history of present illness, we believe that the most likely cause for his acute liver injury was the initiation of Apixaban, with a subsequent failure in improvement after switching to Rivaroxaban.

There was a direct correlation between the initiation of Apixaban and this patient’s elevated liver enzymes. Moreover, the patient’s liver enzymes subsequently decreased to near normal levels after permanently discontinuing any Factor Xa Inhibitors. Seeing that DILI is often a diagnosis of exclusion we may highlight the negative diagnostic tests done for viral hepatitis and hepatobiliary pathology as seen on CT abdomen and MRCP during his course and the negative workup in the clinic two weeks after discharge. Other relevant factors include the concomitant use of Atorvastatin which the patient had been taking for years prior to starting Apixaban, making it possibly a confounding factor and much less likely a direct culprit of acute liver injury in this clinical scenario.

We are increasingly recognizing Factor Xa induced liver injury as a possible but rare complication of this medication class, due to a mechanism that is not fully understood. The literature has shown that with some patients with liver injury due to one Factor Xa inhibitor have tolerated an alternate Factor Xa inhibitor without recurrence of liver injury. However, our patient continued to have elevated liver enzymes despite being switched to an alternative Factor Xa Inhibitor. This finding raises the concern of a possible increased susceptibility of acute liver injury in Eastern Asian Males on Factor Xa Inhibitors.

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**Conclusion**

Factor Xa inhibitors are approved for the prevention of clot formation in non-valvular atrial fibrillation and for treating deep venous thromboembolism and pulmonary embolism. This class of medications are known CYP3A4 and CYP2J2 inhibitors vulnerable to drug-drug interactions and are known to be risk factors for GI bleeding. Although not a common finding, these medications are possible risk factors for acute liver injury, as seen in our patient. Our case serves to raise awareness of the potential risk of acute liver injury in Factor Xa Inhibitors and to open the door for further studies on whether there is an increased risk of liver injury in Eastern Asian people.

**Conflicts of Interest**

Authors have no conflict of interest to declare.

**References**


