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Apixaban-induced fatal liver injury with a cholestatic pattern

A case report and brief review of the Literature

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The hepatobiliary effects of direct oral anticoagulants (DOACs) have been under close surveillance since hepatotoxicity was demonstrated with ximelagatran during the post marketing phase, necessitating its withdrawal in 2006 [1]. All currently available DOACs are associated with a small risk of idiosyncratic hepatotoxicity [2]. The 2013 European guidance for the use of DOACs recommends yearly monitoring of liver function. With the exception of dabigatran, all DOACs are metabolized in the liver, and therefore associated with liver function alteration. The risk of hepatotoxicity with apixaban appears lower than with other DOACs [2,3]. Drug induced liver injury (DILI) covers a broad spectrum of manifestations, ranging from asymptomatic liver enzyme elevation to severe hepatic failure and death. We described herein a case of fatal liver injury with both hepatocellular and cholestatic pattern attributable to apixaban. A 87-yeras-old woman with non valvular atrial fibrillation was treated with apixaban (2,5 mg bid) to prevent systemic embolism. Five weeks after starting apixaban treatment, she devoloped fatigue, jaundice, and itching and required hospitalization. The patient's features are reported in Table 1. On admission, blood test revealed elevated serum liver enzyme levels compatible with liver hepatocellular and cholestatic acute injury: aspartate aminotransferase (AST) was 50 times above upper normal limit (UNL; alanine aminotransferase (ALT) was 36 x UNL; total bilirubin was 36 mg/dl, alkaline phosphatase was 2 x UNL and gamma glutamiyl transpeptidase (GGT) was 8 x UNL. The patient had no history of alchool or drug abuse or metabolic disease. Viral hepatitis was escluded by serological laboratory tests (IgM anti HAV, HbsAg and IgG anti HCV, EBV, CMV and HSV). Non organ specific autoantibodies, antinuclear antibody, antimitochondrial, liver-kidney, microsomal antibody were also negative. Abdominal ultrasound and contrast enhanced computed tomography scan did not show liver steatosis, biliary obstruction, or pancreatic or liver mass. Biliary tract RMN resulted negative. Apixaban was discontinued on the first day on admission, and low molecolar weight heparin was started . Other drugs such as bisoprolol, furosemide, ramipril were continued because the patient had been following this therapy for a long time. The causality assessment on this case was assigned using the Roussel Uclaf Causality Assessment Method (RUCAM) [4]. The Naranjo algorithm for causality assessment was also applied although it is not liver specific and possibly lacking in specificity and reproducibility for evaluating drug associated hepatotixicities. RUCAM score was calculated as 9 (apixaban-induced DILI highly probable). The Naranjo probability scale for causality assessment score was 7 (probable). Relevant criteria for this case assessment were a close and plausible temporal relationship, a known and labeled adverse drug reaction, and negative differential diagnosis for any alternative diagnosis. Despite the immediate discontinuing of apixaban and the therapetic measures taken, the patient died after 21 days due to liver failure. Recently, analysis of large international farmacovigilance databases showed that DOACs are likely associated with a rare but clinically relevant risk of hepatotoxicity [5,6]. Regarding the risk of hepatotoxicity, when DOACs and warfarin are compared, the latter shows lower liver injury hospitalization rates during a follow-up of 12 months. However, among DOACs, rivaroxaban shows the highest risk compared with dabigatran and apixaban. Predictors of liver injury hospitalization are the type of anticoagulant given, previous liver and kidney disease, cancer, anemia, heart failure and alchool abuse. The occurence of hepatotoxicity and the majority of fatal reports were significantly higher in patients older than 65 years [6]. Both hepatocellular and cholestatic patterns of liver injury have been reported with rivaroxaban and dabigatran. In the cases reviewed, the liver injury pattern was predominantly hepatocellular (42,3%); cholestatic and mixed categories were also well distribuited (26,9% and 15,4%). Recovery was generally observed. Two cases resulted in death from acute liver failure. Among cholestatic cases in rivaroxaban therapy, only one resulted in death [6]. All suspected cases of DOACs associated hepatotoxicity should be reported to national pharmacovigilance services to improve our understating of this potentially life-threatening adverse drug reaction. A complete and thorough assessment, fully analyzing the pertinent data of postauthorization safety studies, should be undertaken, and an active post marketing surveillance of this DOAC should be continued.

Declaration of Competing Interest

None,

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Table 1
Demographic, clinical and laboratory features of case with drug induced live injury.

Age (years/sex)	87/F
Latency (weeks)	5
Symptoms	Fatigue jaundice Itching
Liver enzyme x ULN	
ALT	>36
AST	>50
BIL T mg/dl	36 mg/dl
Viral causes	Negative
HAV, HBV, HCV, EBV, CMV, HSV	
Non organ specific autoantibodies	Negative
ANA, AMA, ASMA, LKM	
Liver US, CT and RNM	Normal
Causality assessment RUCAM score	9
Recovery after discontinuation	death

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