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Dabigatran-induced acute liver injury in older patients: case report and literature review

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Objective. Dabigatran, a direct inhibitor of thrombin, represents an effective alternative to warfarin. Despite the good tolerance and predictable pharmacokinetic profile, dabigatran may be associated to adverse reactions, including gastrointestinal disorders. Here we report on a case of hepatotoxicity along with an extensive revision of the available literature on dabigatran induced liver injury

Methods & results. An 84 years old man attended the Emergency Department after experiencing fatigue for a few days. He suffered from atrial fibrillation and had been initiated on dabigatran (110 mg bid) in the last four weeks. Clinical examination revealed tachycardia, scleral icterus in the absence of signs of chronic hepatic disease. Blood chemistry showed altered liver function tests: AST 809 IU/L, ALT 1629 IU/L, total bilirubin 2.42 mg/dL, gGT 381 IU/L, ALP 388 IU/L, LDH 552 IU/L. Screening laboratory investigations for infectious, autoimmune or metabolic hepatotoxic pathology were unremarkable. The abdominal ultrasound examination excluded vascular causes, revealing non-homogeneous echo-structure consistent with mild hepatic steatosis. At admission to our Geriatric ward dabigatran was discontinued and fondaparinux was introduced. Resolution of the hepatitis and normalization of blood chemistry was observed within two weeks. Few cases are described regarding hepatotoxicity likely caused by the recent onset of treatment with dabigatran.

Conclusions. DOACs associated hepatotoxicity is rare but potentially harmful and should be kept in mind, especially in comorbid patients with unexplained liver injury. The mechanism of liver injury during dabigatran therapy is unknown and, not related to cytochrome P450 enzymes since the drug does not affect CYP450 activity.

Key words: dabigatran, hepatotoxicity, drug-induced liver injury (DILI), adverse events

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INTRODUCTION

Long-term anticoagulation is the primary medical therapy for stroke prevention in cardiovascular diseases with high risk for thromboembolism, such as atrial fibrillation (AF) and flutter. Vitamin K antagonists (VKA) have been widely prescribed over the last decades, but several limitations compromise their effectiveness and safety, such as their large inter-individual variability in dose response, narrow therapeutic window and multiple

interactions with food and drugs. Because of variability in drug exposure, anticoagulation therapy with VKA requires routine coagulation monitoring (INR, international normalized ratio), clinical surveillance and patient education about drug and food interactions [1]. Due to the factors mentioned above, patients receiving warfarin have poor compliance to treatment. Dabigatran is a direct inhibitor of thrombin; it binds the active site of thrombin and inactivates both free and fibrin-bound thrombin. This results in the inhibition of fibrinogen-fibrin transition and in the subsequent aggregation of fibrin monomers, platelet activation and inhibition of fibrinolysis [1,2].

In order to prevent embolic events, dabigatran is a valid alternative to warfarin and it is widely used in clinical practice due to its tolerance, good handling, more predictable pharmacokinetic profile and fewer interactions with drugs and food [3]. Compared with Warfarin, dabigatran presents rapid onset of action with no need for bridging, predictable anticoagulant effect which makes routine coagulation monitoring unnecessary, low food and drug interactions [1]. As demonstrated in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, the 110-mg dose of dabigatran had similar incidence of stroke and systemic embolism with lower incidence of major bleeding, compared to warfarin. The 150-mg dose of dabigatran was associated to lower rate of stroke and systemic embolism with similar incidence of major bleeding [2]. Both doses of dabigatran showed similar net clinical benefit outcome, which is a measure of the overall benefit and risk, and were associated with fewer intracranial bleedings than warfarin. However, approximately 80-85% of dabigatran is excreted by the kidneys and, warfarin remains the treatment of choice for patients with severe chronic kidney disease with a creatinine clearance < 15 ml/min [1]. Despite the many advantages of dabigatran, including a lower risk of intracranial bleedings, this direct oral anticoagulant presents adverse effects as increased risk of major gastrointestinal bleedings and gastrointestinal disorders [3]. Among the gastrointestinal disorders, cases of hepatocellular injury (with increase in the levels of aspartate aminotransferase and alanine aminotransferase) are described in literature. Drug-induced liver injury (DILI) is a drug-related adverse reaction that is associated with impaired liver function caused by exposure to a drug. Although drug-related hepatotoxicity is uncommon, its true overall incidence is difficult to determine because of underreporting and issues in detecting the possible causes of hepatic injury from drugs. Diagnosis of drug hepatotoxicity is challenging and requires the exclusion of other reasonable causes of impaired liver function and a compatible temporal relationship between initiation of the drug followed by liver chemistry test elevations [4]. DILI can be classified depending on chemistry test, abnormalities in hepatocellular, cholestatic or mixed injury. According to the mechanism of hepatotoxicity we distinguish predictable hepatotoxicity reactions, which are typically dose-related and occur after threshold for toxicity is reached, and unpredictable or idiosyncratic hepatotoxic reactions, which are unexpected on the basis of the pharmacological action of the drug administered, occurring at therapeutic dose and have variable latency periods from few days to several months. On the basis of different types of hepatocellular damage in histological findings DILI can present with hepatitis, cholestasis, or steatosis [5].

Here we describe the case of an 84 years old man admitted to our Geriatric ward with dabigatran-associated acute liver injury, along with an extensive literature review about DILI and DOACs. For the aim of this review we selected original papers on PubMed searching for “atrial fibrillation”, “dabigatran”, “drug induced liver injury”, “DILI”, “hepatotoxicity”, “acute hepatitis” and “DOACs”. We considered original papers, case reports, reviews and meta-analysis published within the last 15 years.

CASE REPORT

On May 2020 an 84 years old Caucasian man with a history of heart failure with preserved ejection fraction, atrial fibrillation, aortic stenosis and diabetes mellitus presented to the Emergency Department after experiencing fatigue for a few days; he denied fever, cough or dyspnea. He had been initiated on dabigatran for stroke prevention one month prior during a hospitalization for acute heart failure, in which he was firstly diagnosed with atrial fibrillation. He was prescribed with Proton Pump Inhibitor, Metformin, Vitamin D. Bisoprolol, Furosemide, Ramipril, Ezetimibe for more than 6 months. There had been no other recent change to medications or exposure to other potential hepatotoxic substances or Over-the-Counter (OTC) or herbal substances. He had no premorbid history of hepatic disease. On admission, the patient was afebrile, alert, oriented, with mild tachypnea under resting conditions. Clinical examination revealed tachycardia, scleral icterus in the absence of signs of chronic hepatic disease (hepatomegaly, ascites, edema, itching, spider like blood vessels, gynecomastia, confusion, drowsiness). The abdominal examination was unremarkable. Blood investigation revealed a total leucocyte count of 8180/μL (normal 4.000-11.000/μL), Haemoglobin (Hb) 10.5 g/dL (normal 13-18 g/dL), platelets (PLT) 88.000/μL (normal 140.000-450.000/μL), glucose 411 mg/dL

(normal 74-109 mg/dL), creatinine 1.62 mg/dL (normal 0.7-1.20 mg/dL), electrolytes were normal, C-reactive protein (CRP) 3.82 mg/dL (normal < 0.50 mg/dL), ferritin 35 mg/dL (normal 30-400 mg/dL), brain natriuretic peptide (BNP) 1029 pg/dL (normal < 100 pg/dL), high sensitivity (HS) – troponin 34 ng/L (normal < 14 ng/L), aspartate aminotransferase (AST) 809 IU/L (normal < 45 IU/L), alanine aminostransferase (ALT) 1629 IU/L (normal < 40 IU/L), total bilirubin 2.42 mg/dL (normal < 1.2 mg/dL), g-glutamyl transferase (gGT) 381 IU/L (normal < 60 IU/L), alkaline phosphatase (ALP) 388 IU/L (normal 30-130 IU/L), lactate dehydrogenase (LDH) 552 IU/L (normal 135-225 IU/L), INR 1.89 (normal 0.82-1.19). Even though the BNP levels were above the normal rages, the patient did not show any clinical sign or symptom of acute cardiac failure, such as dyspnea or orthopnea, peripheral edema, crackles or pathological thoracic murmur, hepato-jugular reflux, jugular venous distention. Moreover, the chest CT did not show signs of interstitial lung edema or vascular congestion. The blood gas analysis demonstrated mixed metabolic and respiratory alkalosis with mild respiratory failure (pH 7.47, pO2 74, pCO2 46, HCO3- 33.5, SO2 94.8%, FiO_2 24%). The patient was admitted to our Geriatric ward, dabigatran was discontinued at the time of admission and fondaparinux was introduced. Screening laboratory investigations for infectious, autoimmune and metabolic hepatotoxic pathology were performed and resulted unremarkable (Tab. I). The abdominal ultrasound excluded vascular causes, did not show congestive hepatopathy and dilatation of inferior vena cava, revealed non-homogeneous echo-structure consistent with mild hepatic steatosis, but was unremarkable for hepatobiliary pathology. The patient received supportive treatment with adequate hydration and nutrition in addition to the drug withdrawal, obtaining a gradual resolution of the hepatitis and improvement of the blood investigations within two weeks from hospital admission (AST 69 U/L, ALT 93 U/L, GGT 161 U/L, ALP 492 U/L, total bilirubin 0.92 mg/dL). He was also treated with furosemide and bisoprolol was titrated in order to control heart rate. Adequate glycemic control was achieved with insulin therapy. The patient attended the Outpatient Clinic two months after discharge, showing good clinical condition and normal hepatic function tests (AST 34 U/L, ALT 29 U/L, GGT 112 U/L, ALP 212 U/L, total bilirubin 1.36 mg/dL).

DISCUSSION AND LITERATURE REVISION

Liver injury is a frequent drug-related adverse reaction (annual estimated incidence of 13.9 ± 2.4 cases per 100.000 inhabitants) [6] and a common cause of acute liver failure. Almost any pharmaceutical or xenobiotic substance can cause hepatotoxicity, making the diagnosis of DILI complex and challenging. According to clinical studies and pharmacovigilance reports, hepatotoxicity related to direct oral anticoagulants (DOACs) is uncommon. The mechanism of toxicity is idiosyncratic, it appears at therapeutic doses and it is unexpected on the basis of the pharmacological action of the drug. However, the mechanism of hepatotoxicity of DOACs still remains unknown [7]. A possible explanation for liver dysfunction caused by dabigatran may be that first-pass elimination occurs in the liver [8]. The RE-LY trial showed that impairment of liver function caused by dabigatran did not occur more frequently than with warfarin [2,8].
In a systematic review and meta-analysis of phase III randomized controlled trials, Caldeira et al. concluded

Table I. Patient's blood chemistry.

CBC		Chemistry		LFTs		Other labs	
WBC /mmc	8180	**Sodium mEq/L**	137	**T. Bili mg/dl**	2.42	**Ammonium**	73
Hgb g/dl	10.5	**Kalium mEq/L**	3.93	**ALP U/L**	388	**AntiANA**	1:80
Hct%	30.9	**BUN mg/dl**	48	**AST U/L**	809	**AntiLKM**	Negative
PTL /mmc	88000	**Creatinine mg/dl**	1.62	**ALT U/L**	1629	**AntiASMA**	Negative
MCV fl	89.3	**Glucose mg/dl**	411	**GGT U/L**	381	**HBsAg**	Negative
				T. Protein g/dl	5.7	**AntiHBc IgM**	Negative
				Albumin g/dl	3.3	**AntiHCV**	Negative
				INR	1.89	**AntiHAV IgM**	Negative
				aPTT sec	30.7	**AntiHEV IgM**	Negative
						AntiCMV IgM	Negative
						AntiEBV VCA IgM	Negative

WBC: white blood cells; Hgb: Hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase; INR: international normalized ratio; aPTT: activated partial thromboplastin time; ANA: antinuclear antibody; LKM: liver/kidney microsomal; ASMA: anti-smooth muscle antibody; HBsAg: Hepatitis B surface antigen; HCV: hepatitis C virus; HAV: hepatitis A virus; HEV: hepatitis E virus; CMV: Cytomegalovirus; EBV VCA: Epstein-Barr viral capsid antigen; Ig: Immunoglobulin

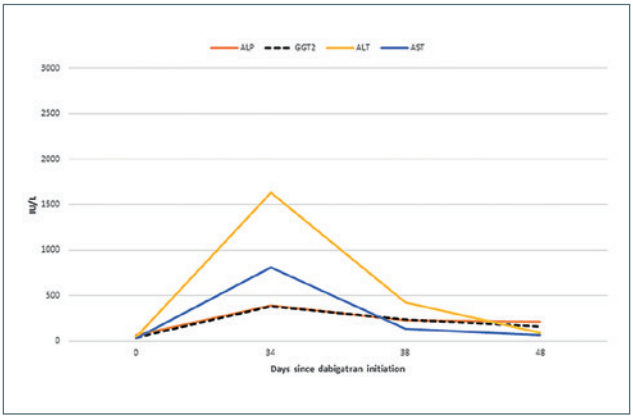

Figure 1. Liver enzymes trend since starting dabigatran.

that DOACs were not associated with an increased risk of DILI. The DOACs evaluated were apixaban, dabigatran, darexaban, edoxaban and rivaroxaban, while the control groups included vitamin K antagonists, low molecular weight heparin (LMWH) and placebo. Patients on DOACs had low rate of transaminases elevation > 3 × upper limit of normal (ULN), particularly in comparison to LMWH-treated patients [9]. In a cohort study on the MarketScan Commercial and Medicare database to assess the risk of liver injury hospitalization, Alonso et al. demonstrated that patients receiving DOACs do not have an increased risk of liver injury, compared to patients prescribed with warfarin. Their study was the first to evaluate risk of liver injury across different oral anticoagulants. They also found that dabigatran was associated with the lowest risk of liver injury among the different oral anticoagulants (dabigatran, apixaban, rivaroxaban); risk of hospitalization for liver disease was higher in patients receiving rivaroxaban compared to those receiving dabigatran and apixaban. Moreover, they found that patients with prior history of hepatobiliary disease, alcoholism, kidney disease, cancer, anemia and heart failure had increased risk of DILI [10]. To our knowledge, three patients who developed liver injury while being treated with dabigatran have been reported so far.

A 71-years old man with a history of atrial fibrillation presented to the Emergency Department with jaundice, fatigue and anorexia. He had been prescribed dabigatran one month prior to hospital admission and there had been no recent exposure to other medications or hepatotoxin. Blood investigations demonstrated increase of serum liver enzymes and biochemical markers of cholestasis (AST was 19 x ULN, ALT 14 x ULN, ALP 5 x ULN and serum bilirubin 21 x ULN). Screening laboratory investigations and abdominal ultrasonography were unremarkable for any infectious, autoimmune, metabolic or hepatobiliary pathology. Dabigatran was discontinued, the patient was treated supportively and completely recovered within 2 weeks of presentation to hospital [11].

The second patient was an 86-years old woman on dabigatran therapy for six weeks for atrial fibrillation; she was hospitalized for pyelonephritis and acute kidney injury. Blood investigations revealed AST 50 x ULN and ALT x 100 N with modest elevation of serum bilirubin. Dabigatran was stopped and she recovered within few days [12].

The third patient was a 74-years old caucasian female with atrial fibrillation treated with dabigatran for six weeks; she presented to the Emergency Department with acute lower gastro-intestinal bleeding, acute metabolic encephalopathy and acute kidney failure. She had a known history of hypertension, gout, congestive heart failure, type II diabetes mellitus and atrial fibrillation. Clinical examination revealed altered mental status, hypotension (blood pressure 89/47 mmHg) and bright red blood at the digital rectal examination. Blood investigation revealed increase in the levels of aspartate aminotransferase and alanine aminotransferase (AST 7 x ULN, ALT 40 x ULN), elevation of INR 15.4, slight elevation of serum bilirubin and severe elevation of creatinine 4.22 mg/dL. The patient was found to have acute liver injury with severe hepatic dysfunction and acute renal failure induced by the recent introduction of anticoagulation therapy. Dabigatran was discontinued and her conditions improved after hemodialysis and administration of fresh frozen plasma [13].

The mechanism of liver injury during dabigatran therapy remains unknown. The hepatotoxicity associated with DOACs is idiosyncratic, not related to their pharmacological action. The prodrug dabigatran etexilate is hydrolyzed to the active form dabigatran after oral administration and hepatic processing, but it is not a substrate of cytochrome P450 enzymes [7]. The first clinically used direct thrombin inhibitor, ximelagatran, showed hepatotoxicity in the 5-10% of the patients treated for longer than 1 month, with transient elevated levels of serum alanine aminotransferase > 3 ULN [14,15]. No immunological features were described in the three case reports we cited nor in our literature review. Although this fact does not support an immune mechanism, we are not able to exclude it.

CONCLUSIONS

The direct oral anticoagulant dabigatran is used widely due to its good tolerance, rapid onset of action with no need for bridging, predictable pharmacokinetics and anticoagulant effect which makes routine coagulation monitoring unnecessary, low food and drug interactions.

Despite the many advantages of this direct inhibitor of thrombin, an increasing prevalence of adverse events has emerged in recent years. Our case report and literature review emphasize the need of monitoring patients starting dabigatran therapy to early identify adverse events such as cases of drug-induced liver injury, especially in older patients on other potentially hepatotoxic medications or with prior history of hepatobiliary disease, alcoholism, kidney disease, cancer, anemia and heart failure. It is important to bear in mind that hepatotoxicity is rare but possible with DOACs and that it should be always reported to the national pharmacovigilance centers in order to improve patients' safety and our knowledge about this adverse drug reaction. Further studies will be crucial to better understand the mechanisms underlying dabigatran induced liver injury in order to define strategies and assessment procedure to minimize the chance of hepatotoxicity occurring.

Ethical consideration
None.

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Conflict of interest
The authors have no conflict of interest to declare.

Author contributions
All the authors contributed in the development of this manuscript.

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