REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Apixaban-induced liver injury

Authors:
Salvador Machlab, Mireia Miquel, Mercedes Vergara, María Rosa Escoda, Meritxell Casas

DOI: 10.17235/reed.2018.5877/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
Machlab Salvador, Miquel Mireia, Vergara Mercedes, Escoda María Rosa, Casas Meritxell. Apixaban-induced liver injury. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5877/2018.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

NC 5877 español

Apixaban-induced liver injury

Salvador Machlab[1], Mireia Miquel[1,2], Mercedes Vergara[1,2], María Rosa Escoda[3] and Meritxell Casas[1]

Departments of [1]Digestive Diseases and [3]Pathology. Corporació Sanitària Universitària Parc Taulí. Universitat Autònoma de Barcelona. Sabadell, Barcelona. Spain. [2]CIBERhed Instituto Carlos III. Madrid, Spain

Received: 28/08/2018

Accepted: 22/09/2018

Correspondence: Salvador Machlab. Department of Digestive Diseases. Corporació Sanitària Universitària Parc Taulí. Universitat Autònoma de Barcelona. Parc Taulí, 1. 08208 Sabadell, Barcelona. Spain

e-mail: stmachlab@tauli.cat

ABSTRACT

The use of new oral anticoagulants such as apixaban is increasing. We present the case of an 85-year-old patient who was diagnosed with mixed profile toxic hepatitis due to apixaban use. An etiological study was negative, except for anti-smooth muscle antibodies, and a liver biopsy ruled out autoimmune hepatitis. The patient was assigned a score of 7 on the CIOMS/RUCAM scale, indicating a probable causality. The liver injury improved after the withdrawal of apixaban.

A previous meta-analysis reported that the risk of hepatotoxicity does not increase with the use of apixaban, nor were any cases reported in registry studies. Nonetheless, more than 120 possible cases currently appear in the European pharmacovigilance database (EudraVigilance). We suggest that apixaban should be considered as a possible cause of liver injury.

Key words: Hepatotoxicity. Mixed. Apixaban. DILI. Anticoagulant.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

INTRODUCTION

Apixaban is a selective inhibitor of the factor Xa oral anticoagulant and has been approved in our geographical area since 2011 for the prophylaxis of thromboembolism in patients undergoing patellar or hip surgery. Since 2012, it has also been approved for the treatment of non-valvular atrial fibrillation.

Apixaban has stable pharmacokinetics and therefore does not require monitoring (1). Side effects are rare but include bleeding, headaches, dizziness, fatigue, nausea, arthralgia and a skin rash. The prescription information sheet describes a slight increase in liver enzymes but no hepatotoxicity. Although cases of hepatotoxicity have been recorded in pharmacovigilance registries, they are mostly of the hepatocellular type (2). Only one case of a mixed liver injury profile has been reported and no details are available (2). Here we present a case of toxic hepatitis due to apixaban use with a mixed liver injury profile.

CLINICAL CASE

The case was an 85-year-old female with no toxic habits and a history of diabetes mellitus, arterial hypertension, heart failure, obesity, dyslipidemia and postoperative hypothyroidism due to multinodular goiter. Her usual chronic treatment included eutirox, alprazolam, simvastatin, furosemide, metformin, metamizole, irbesartan, omeprazole and zolpidem. Auricular fibrillation was detected and was treated with bisoprolol at 2.5 mg/24 h and apixaban at 2.5 mg/12 h. Three months later, during a control analysis, alterations of hepatic biology were detected with a mixed pattern of cytolysis and cholestasis (Table 1). An abdominal ultrasound identified only heterogeneous and bright parenchyma without focal lesions compatible with hepatic steatosis; the rest of the exploration was normal. An etiology laboratory study by was normal, except for anti-smooth muscle antibodies of 1/320, with a pattern that was compatible with the presence of anti-F-actin antibodies. The proteinogram was normal, hepatotropic virus (A, B and C) serology was negative, iron metabolism, albumin 41.6 g/l, INR 1,29 ratio, immunoglobulin G 1460 mg/dl were normal and the serology was negative for other autoantibodies (LKM 1, mitochondrial, sp100, Ro-52, M-2, LC1, SLA and gp210 antibodies). Apixaban treatment was withdrawn and replaced with tinzaparin due to the suspicion of liver toxicity.

A liver biopsy was performed to assess the positivity of the anti-smooth muscle antibody. The biopsy, with nine portal spaces, showed necroinflammatory activity and macromicrovacuolar steatosis that was compatible with toxic hepatitis. Eight weeks after apixaban withdrawal, the control analysis showed improved liver biology but persistent mild hypertransaminasemia and increased GGT in the context of hepatic steatosis (Table 1).

DISCUSSION

The use of new oral anticoagulants such as apixaban is increasing in our setting, as they avoid the need for regular coagulation controls. However, our patient had liver injury due to apixaban. The diagnosis was made after ruling out other causes. The patient had a score of 7 and an R factor of 3.47 on the CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method), indicating mixed profile liver damage (3,4). Although bisoprolol treatment was also initiated in our patient, this drug is classified as DILIN (Drug-Induced Liver Injury Network) category E and is not considered as a cause of hepatotoxicity. Furthermore, the hepatotoxicity improved in this case with the withdrawal of apixaban alone. The biopsy showed necroinflammatory lobular activity and macromicrovesical steatosis, which are non-specific findings that rule out other causes and may be compatible with hepatotoxicity (Figs. 1 and 2).

The prescription information of apixaban does not mention hepatotoxicity but includes an increase in transaminases and/or cholestasis enzymes with a frequency between 0.1 and 1% (1). Its use is not recommended in patients with severe hepatic insufficiency and caution is advised in patients with Child A and B cirrhosis, as these patients have been excluded from clinical trials. However, a subsequent retrospective study compared patients with Child A and B cirrhosis treated with rivaroxaban or apixaban *vs* warfarin and did not find statistically significant differences in the bleeding rate (5). According to a meta-analysis, treatment with apixaban does not imply an increased risk of hepatotoxicity (6).

Nevertheless, cases of hepatotoxicity due to apixaban have been reported, mainly of the hepatocellular type (7). The update of the European pharmacovigilance database (EudraVigilance) in August 2018 reported 50 cases of hepatotoxicity due to apixaban since its approval by the European Medicines Agency (EMA). These were mainly the hepatocellular type but there were also two cases of hepatotoxicity with a cholestatic

profile and one with a mixed profile that may be similar to our case (2). At least 166 cases of liver injury due to apixaban and 60 due to dabigatran have been reported. An observational and prospective study found that apixaban had a lower risk of hospitalization due to hepatotoxicity compared to other oral anticoagulants such as rivaroxaban and warfarin (although higher than dabigatran). However, this study had certain limitations, including the fact that the criteria for admission or the diagnostic criteria for hepatotoxicity were not specified (8).

In conclusion, treatment with apixaban may cause hepatotoxicity, even though this eventuality is not included in the prescription information. The mixed type that was recorded in our patient is very infrequent.

REFERENCES

1. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol 2013;76:776-86. DOI: 10.1111/bcp.12106

2. EudraVigilance. European database of suspected adverse drug reaction reports. Accessed in August 2018. Available from: http://www.adrreports.eu/

3. DeLeve LD, Kaplowitz N. Mechanisms of drug-induced liver disease. Gastroenterol Clin North Am 1995;24:787-810.

4. Danan G, Benichou C. Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323-30. DOI: 10.1016/0895-4356(93)90101-6

5. Intagliata NM, Henry ZH, Maitland H, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci 2016;61:1721-7. DOI: 10.1007/s10620-015-4012-2

6. Caldeira D, Barra M, Santos AT, et al. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart 2014;100:550-6. DOI: 10.1136/heartjnl-2013-305288

7. Cordeanu M, Lambert A, Gaertner S, et al. Apixaban-induced hepatotoxicity. Int J Cardiol 2016;204:4-5. DOI: 10.1016/j.ijcard.2015.11.147

8. Alonso A, MacLehose RF, Chen LY, et al. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. Heart 2017;103:834-9. DOI: 10.1136/heartjnl-2016-310586

Table 1. Biochemical evolution

	Basal 12 months previous	*Initial*	*2 weeks after apixaban withdrawal*	*4 weeks*	*8 weeks*	*9 weeks*	*20 weeks*
ALT (U/l)	34	327	325	101	57	31	55
AST (U/l)	11	243	207	67	35	19	43
Alkaline phosphatase (U/l)	93	323	295	122	80	66	85
GGT (U/l)	103	2,378	2,398	1,144	525	362	409
Total bilirubin (mg/dl)	0.33	0.64	0.6	0.5	0.6	0.5	0.3

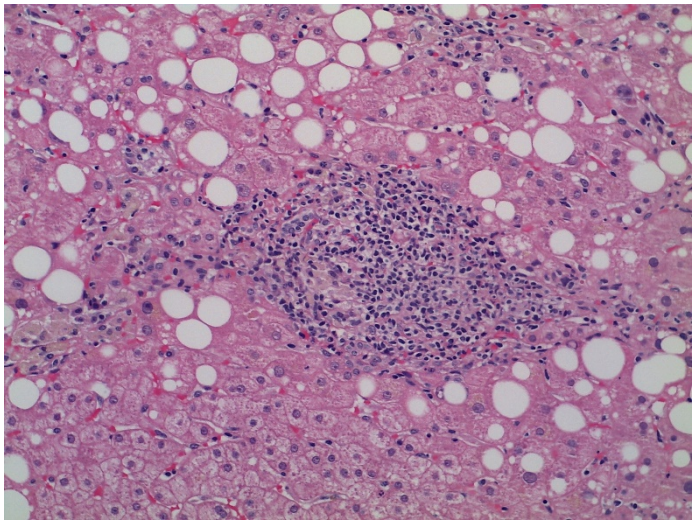

Fig. 1. Liver biopsy. Hematoxylin-eosin 20x. Moderate lobular necroinflammatory activity, accumulation of macrophages with ceroid pigment and macromicrovacuolar steatosis.

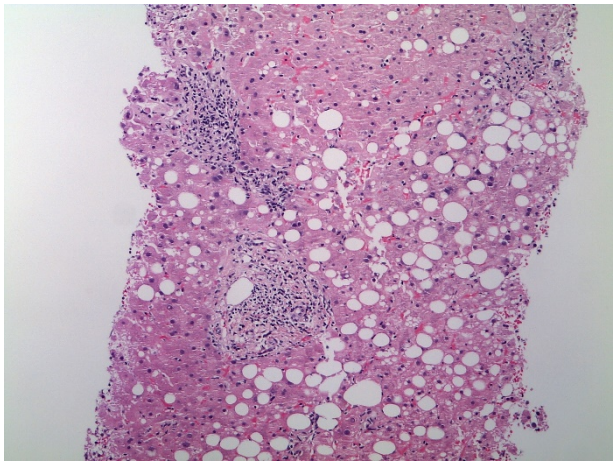

Fig. 2. Liver biopsy. Hematoxylin-eosin 10x. Portal spaces with discrete chronic lymphoplasmacytic inflammatory infiltrate, no damage to the bile ducts and mild periportal erosive necrosis.