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CASE REPORT

Effectiveness of apixaban in warfarin hepatotoxicity: A case report

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ABSTRACT

Background: Apixaban is a direct and competitive inhibitor of factor Xa. It has been shown to be effective and safe to Prevent Stroke in Atrial Fibrillation Patients. This study is a case report of warfarin-induced cholestasis that occurred one week after starting warfarin for deep venous thrombosis, in which the cholestasis improved after the offending drug was stopped but worsened after beginning apixaban.

Case Presentation: We presented a case of 79-year-old woman, she was presented to the emergency department with a chief complaint of left lower limb swelling of 3 days duration. On physical examination, her left lower limb was swollen, warm, and tender. Venous Doppler ultrasound showed extensive deep venous thrombosis and anticoagulation with unfractionated heparin and warfarin 7 mg initiated.

Conclusion: Apixaban should be avoided in patients with warfarin-induced cholestasis.

Keywords: Warfarin, apixaban, hepatotoxicity, anticoagulant, thrombosis, case report.

Introduction

Oral anticoagulants such as warfarin and apixaban are commonly used in cardiology for stroke prevention in patients with atrial fibrillation as well as for deep vein thrombosis and pulmonary embolism treatment [1]. Cholestasis is a rare complication of warfarin and is known to resolve after withdrawing the drug [2]. However, an appropriate alternative that might be considered is low molecular weight heparin [2,3]. Apixaban is a direct and competitive inhibitor of factor Xa [4]. It has been shown to be effective and safe to prevent stroke in atrial fibrillation patients [5,6]. This study is a case report of warfarin-induced cholestasis that occurred one week after starting warfarin for deep venous thrombosis, in which the cholestasis improved after the offending drug was stopped but worsened after starting apixaban.

Case Presentation

A 79-year-old woman, known to have systemic hypertension, chronic kidney disease stage 3A (A1), and osteoarthritis was presented to the emergency department with a chief complaint of left lower limb swelling of 3 days duration. On physical examination, her left lower limb was swollen, warm, and tender; other physical tests were unremarkable. Venous Doppler ultrasound showed extensive deep venous thrombosis and anticoagulation with unfractionated heparin and warfarin 7 mg initiated.

The liver function test (LFT) was initially normal (Table 1). However, 6 days after starting warfarin, the case gradually worsened with the mainly cholestatic pattern. The investigations for abnormal LFT including viral hepatitis and autoimmune diseases were requested but did not show any abnormalities (Table 2). Abdomen ultrasound showed non-complicated gallstones with heterogeneous liver parenchyma, and the patient was asymptomatic.

After stopping warfarin and starting enoxaparin, LFT improved. However, before discharging the patient, apixaban 5 mg twice daily was considered the best choice for anticoagulation and was started instead of enoxaparin. After 3 days, the LFT worsened again, and enoxaparin began after stopping apixaban. After one week, the following LFT showed improvement with Gamma-Glutamyl Transpeptidase (GTP) 248 U/L, Alkaline Phosphatase 168 U/L, total bilirubin 6.2 mmol/L, aspartate aminotransferase (AST) 17 U/L, and alanine aminotransferase (ALT) 25 U/L.

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Table 1. *Serial liver function test results.*

Tests	Admission	After Starting Warfarin	After D/C Warfarin	Before Starting Apixaban	After D/C Apixaban	Upon Follow-Up
AST, U/L	21	69	59	21	49	17
ALT, U/L	19	81	119	43	94	25
GTP, U/L	-	360	471	354	531	248
Alk Phos, U/L	110	250	320	212	361	168
Bili T, umol/L	8.9	3.6	8.3	8.6	5.9	6.2

Table 2. *Viral serology and autoimmune screening laboratory results.*

Liver kidney microsome antibody	0.51
Antimitochondrial antibody	<1:20
Anti-smooth muscle antibody	<1:40
Antinuclear antibody	6.6180
Perinuclear anti-neutrophil cytoplasmic antibodies	1.24
Hepatitis B surface antigen QUN	0.00
Hepatitis A virus (HAV) IgG	Positive
HAV IgM	Negative
Hepatitis C antibody	Negative
Cyclic citrullinated peptide IgG	2.44
Rheumatoid Factor	<10.00

The home medications used by the patient were nifedipine 30 mg bid, acetaminophen 1 g BID, and diclofenac transdermal patch.

Discussion

The main findings in this case report were warfarin lead to liver injury within a week of starting treatment which is very rare. Furthermore, apixaban was not the best alternative anticoagulant. Warfarin acts by inhibiting vitamin K epoxide reductase, leading to a reduction of vitamin K-dependent clotting factors production by up to 50% and it is metabolized by the liver and excreted mainly in the urine [7,8]. Warfarin-induced liver injury has been reported yet rare [9].

We reached a diagnosis of warfarin-induced and apixaban induced liver injury by using Hy's law which defines drug-induced hepatic injury by an increase in AST or ALT and direct bilirubin values twofold or more [10], yet direct bilirubin was not performed in our case.

To determine the probability of whether the liver injury happened due to warfarin or not, Naranjo Scale was used and the score was 6 which is a probable adverse drug reaction.

The mechanisms of warfarin and apixaban induced liver damage is unknown but has been suggested to be an idiosyncratic reaction [11,12].

Although all the three anticoagulants (warfarin, enoxaparin, and apixaban) might lead to hepatotoxicity [7,11], enoxaparin was given after warfarin-induced cholestasis [13] and apixaban-induced cholestasis [11]. However, this is a unique case report that combined warfarin, and apixaban-related liver injury occurred in the same patient.

Conclusion

Apixaban should be avoided in patients with warfarin-induced cholestasis, and further studies are needed to determine the appropriate treatment for anticoagulants' induced hepatotoxicity.

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List of Abbreviation

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GTP	Gamma-Glutamyl Transpeptidase
HAV	Hepatitis A Virus

Conflict of Interest
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