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Unpredictable Course of an Escitalopram-Induced Liver Injury: A Case Report

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Abstract **Case Report**

Escitalopram is a selective serotonin reuptake inhibitor and one of the most widely prescribed antidepressants in the world. Very few cases of drug induced liver injury (DILI) have been reported in patients on escitalopram. We describe here an unusual case of hepatocellular injury in a 32-year-old Moroccan woman on birth control by second-generation combined oral contraceptives (COCs) treated for depression by escitalopram. Despite initial improvement upon escitalopram discontinuation, liver enzyme levels fluctuated, necessitating further management adjustments. This case highlights the complexity and unpredictable course of DILI and suggests a possible synergetic drug-interaction as a contributing factor.

Keywords: Drug induced liver injury; Escitalopram; Depression.

INTRODUCTION

Drug-Induced Liver Injury (DILI) is the fourth leading cause of liver damage in Western countries, increasingly becoming a matter of concern for drug prescription (Björnsson *et al*., 2013). Depression is a common mental disorder affecting more than 280 million of individuals worldwide and is a leading cause of non-fatal health loss (« Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019 », 2022). Among the first line treatment of this disease, we find escitalopram, which is a selective serotonin reuptake inhibitor that is widely prescribed for its relatively high tolerability and lower toxicity profile (Dodd *et al*., 2011). The safety of this drug is well-established, with only a few reported cases of DILI in any clinical setting (Voican *et al*., 2014). We present a rare case of hepatocellular injury in a 32-year-old Moroccan patient, presumably due to an escitalopram intake.

CASE PRESENTATION

A 32-year-old female patient was on birth control for 10 years by a second-generation COC combining 0,15mg of Levonorgestrel and 0,03mg of ethinylestradiol, with no clinically or biologically detected side-effects. She was treated by her psychiatrist for a minor depressive disorder since the covid outburst in 2020 by escitalopram. The dose was initially 15mg per day then was progressively decreased to 5mg per day which she has been taking for a year before her consultation. The patient had also a history of repeated urinary infections for which her doctor prescribed a complete blood checkup revealing a disturbed liver test result. The patient had no known allergies, did not consume any herbal supplements or alcohol, and had no notable family history. At presentation, the patient didn't report any symptoms, and the clinical examination was without abnormalities particularly no jaundice or hyperthermia.

Laboratory examinations showed a normal hemogram and serum electrolytes, urea, creatinine, and thyroid function test within normal limits**.** Her liver panel revealed a persistent elevation of alanine aminotransferase (ALAT, 251 U/L), aspartate aminotransferase (ASAT, 74 U/L) and normal alkaline phosphatase (ALP, 83 U/L), GGT (18 U/L) and total bilirubin levels (TBIL, 9.7µmol/L).

A hepatitis screening (HVB, HVC) was done along with HIV serology, which were negative. Serum immunoglobulin levels and autoantibodies were negative and included antinuclear antibody anti-smooth muscle antibody, and antimitochondrial M2 antibody. Ceruloplasmin, serum copper value, transferrin saturation and ferritin levels were all within normal limits. We also evaluated hepatic fibrosis by a fibrotest

(F0) and fibroscan (4.3 Kpa) which were not in favor of liver fibrosis. The patient refused a liver biopsy.

Final diagnosis

The Roussel Uclaf Causality Assessment Method (RUCAM) is a score used in assessing causality of drug induced liver injury (Danan & Benichou, 1993). The RUCAM considers multiple factors: the time to onset of reaction after drug initiation, the clinical course, risk factors, concomitant drugs with hepatotoxic potential, non-drug causes of liver injury, previous information on the drug's hepatotoxicity and the response to rechallenge. The RUCAM score ranges from -8 to +14. Its interpretation follows a five-category scale: Highly probable (> 8), probable (6-8), possible (3-5), unlikely (1-2), and excluded (≤ 0).

In our case, the RUCAM score of escitalopram was of 6, meaning the drug was a "probable" cause of hepatocellular DILI.

After good consideration of the history, examination and investigation findings, a drug-induced liver injury (DILI) due to escitalopram was retained as the final diagnosis for our patient.

Treatment

Following a consultation with an experienced psychiatrist in our hospital, escitalopram was withdrawn and replaced with alprazolam which is a medication prescribed for anxiety disorder.

Outcome and follow-up

Liver function tests were repeated after the treatment discontinuation and showed a decrease in liver enzymes 3 weeks after withdrawal. The patient remained well and balanced with her new anxiolytic treatment.

A month later, a follow-up liver function test showed yet again an elevation of serum ALT and AST. A thorough questioning of the patient revealed that no additional medication or potentially toxic substances, such as medicinal herbs or alcohol, had been taken. The decision of the withdrawal of the contraceptive drug was taken according to the discrimination of the only drug she was taking. The patient followed a physical contraceptive method. A normalization of ALT and AST was obtained after 3 weeks. Consecutive tests done within 3 months after the drugs discontinuation were normal (Table 1).

Table 1: The evolution of transaminase levels in our patient

	ALT	AST
Day 1	251	74
Withdrawal of escitalopram		
Week 3	102	29
Week 7	151	61
Withdrawal of the COCs		
Week 10	106	45
Week 13	20	21
Week 17	14	16
Week 22	15	13

ALT: alanine transaminase; AST: aspartate transaminase; COCS: Second-generation combined oral contraceptives

DISCUSSION

Drug-induced liver injury is often challenging to diagnose, relying on the exclusion of other potential causes. It can be classified based on the pattern of hepatic injury as hepatocellular, cholestatic, or mixed (Aithal *et al*., 2011). A detailed drug history, considering the timing of liver injury and recovery after discontinuing the implicated agent, can aid in diagnosis. In this case, the patient had no clinical presentation. Imaging and tests were negative for viral, auto immune, and metabolic liver diseases. While liver biopsy is not always necessary, it can be useful when there is uncertainty and other potential causes need to be ruled out. DILI typically shows nonspecific findings on liver biopsy. The RUCAM scoring system helps clinicians determine the likelihood of a DILI diagnosis (Danan & Benichou, 1993). The pathophysiology of DILI is attributed to direct, indirect, or idiosyncratic hepatotoxicity. It involves genetic factors, the drug's physicochemical and toxicological properties and its interactions with host and environmental factors (Chen *et al*., 2015).

In this case, the antidepressant escitalopram, which is metabolized by the liver, may have led to hepatotoxicity due to toxic intermediates (von Moltke *et al*., 2001). There is limited literature on DILI related to escitalopram. Recently, Wabont G *et al*., described a cholestatic and cytolysis liver injury due to escitalopram one week after its introduction, whereas Ng *et al*., reported a case of cholestasis due to escitalopram in a 56-year-old woman appeared two weeks after the drug was initiated (Ng *et al*., 2019; Wabont *et al*., 2022). It must be noted that this patient was also on olanzapine, which is another antidepressant that may cause cholestasis and hepatitis (Domínguez-Jiménez *et al*., 2012). In our case, escitalopram was introduced one year prior to the liver injury discovery as the patient was asymptomatic and only a fortuitous lab test revealed the abnormal transaminase. The absence of consent for biopsy limited

further investigation and histologic characterization of the liver injury in our patient.

The intriguing part of this case was the elevation of the transaminases after their decrease following escitalopram discontinuation. The normalization of the enzymes could have been obtained after a longer period, but we judged the withdrawal of the second-generation COC levonorgestrel/ethinylestradiol based on the need to eliminate all potential contributing factors to the liver injury. To our knowledge, only three cases described a levonorgestrel/ethinylestradiol combination oral contraceptive related DILI (Elouni *et al*., 2010; Stannov *et al*., 2019). All of them confirmed the liver injury by a biopsy, and one included a re-challenge. Elouni *et al*., suggested that its toxicity might be connected to the implication of estrogen, which may be impacting the hepatic transporters and the biosynthesis of bile acids (Yamamoto *et al*., 2006).

Studies suggested that comedication may alter drug hepatic safety, though data on how it impacts drug-induced liver injury is limited (Suzuki *et al*., 2015). In 2004, de Abajo and al reported that using two or more potentially hepatotoxic drugs increases the risk of acute liver failure by a factor of 6 in comparison to using one in the British population (de Abajo *et al*., 2004). A synergetic interaction between escitalopram and oral levonorgestrel/ethinylestradiol might have caused the abnormal elevation of liver enzymes, but their second rise after the discontinuation of the antidepressant remains a question of interest.

One of the first case studies to report the hepatotoxicity of escitalopram was of a 49 year old female patient presenting a severe toxic hepatitis of prolonged course, with 2 episodes of spontaneous reactivation despite drug withdrawal (Del Val Antoñana *et al*., 2008). The complete normalization of the liver enzymes was sustained at week 20 after the drug discontinuation. This fluctuation in transaminase levels also remained unexplained in this case.

In DILI cases, the cessation of the causative agent usually leads to recovery within days to weeks, often without further treatment. Yet, the course of recovery can be unpredictable, and prolonged or worsening liver function despite stopping the drug can create clinical uncertainty. Our case emphasis this aspect of DILI management and the complexity of toxicity mechanisms especially when multiple potentially hepatotoxic medications are involved.

CONCLUSION

DILI is a complex condition that requires careful assessment and consideration of various factors and their potential synergistic effects in causing liver injury. Our case emphasizes the importance of healthcare providers being aware of the potential for DILI linked to one of the most prescribed antidepressants. The fluctuating liver enzyme levels in our patient highlights the unpredictable nature of DILI, emphasizing the need for vigilant monitoring during long-term medication therapy.

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