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Contents

Thrice Monthly Volume 10 Number 8 March 16, 2022

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 8 March 16, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 8 March 16, 2022

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 8 March 16, 2022

Contents

ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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CASE REPORT

Escitalopram-induced hepatitis: A case report

Guillaume Wabont, Laurie Ferret, Nicolas Houdre, Antoine Lepied, Johana Bene, Etienne Cousein

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Abstract

BACKGROUND

The antidepressant escitalopram is widely prescribed for the treatment of depression. It is generally well-tolerated, and cholestasis is not mentioned in its summary of product characteristics (SmPC). We present a case of cholestatic and cytolysis liver injury due to escitalopram and a VigiBase® study.

CASE SUMMARY

A 68-year-old man was admitted to our emergency unit due to clinical jaundice associated with hepatitis, pruritus and dark urine. We tested the patient for the most common etiologies of jaundice, including hemolysis, viral hepatitis, cirrhosis, carcinoma, cholangitis, cholelithiasis and intrahepatic or extrahepatic obstruction. The etiological study was negative, and an adverse drug reaction was the sole possible explanation. The patient was receiving treatment with escitalopram. Two days after its withdrawal, pruritus was resolved. Ten days after withdrawal, clinical jaundice disappeared. It took a month and three weeks after withdrawal for the patient to have normalized liver function tests. To our knowledge, this is the first reported case of cholestasis where treatment with escitalopram was the only possible cause, with a highly probable causality. In addition, we determined whether escitalopram is associated with hepatotoxicity and cholestasis by performing a disproportionality analysis. All cases of hepatobiliary disorders induced by escitalopram and reported in the World Health Organization pharmacovigilance database (VigiBase®) were analyzed to characterize this toxicity. We found that patients treated with escitalopram had an increased risk of hepatitis [odds ratio (OR) = $1.938^{(1.186\text{-}3.166)}$] and cholestasis [OR = $1.866^{(1.279\text{-}2.724)}$] [OR (95% confidence interval)]. The median duration between the introduction of escitalopram and the occurrence of acute hepatitis and/or

cholestasis was ten days +/- seven days.

CONCLUSION
Although extremely rare, this case report, the review of the literature and the pharmacovigilance update confirm that escitalopram can cause drug-induced hepatotoxicity and cholestasis, generally within a week after initiation. Thus, escitalopram should be withdrawn immediately if an iatrogenic cause cannot be excluded. If its responsibility is ascertained, escitalopram should be consequently contraindicated. In addition, serotoninergic antidepressants in patients with non-severe depression are ineffective and harmful. Finally, the SmPC of escitalopram should be updated to alert for this risk and give clear clinical guidelines.

Key Words: Escitalopram; Hepatitis; Cholestasis; Pharmacovigilance; Case report

Core Tip: The antidepressant escitalopram is widely prescribed for the treatment of depression. The article consists of a unique clinical case, a review of the literature and a pharmacovigilance analysis. This is the first clinical case of escitalopram as the only possible drug causing hepatitis and cholestasis. This is also the first pharmacovigilance analysis conducted to qualify and quantify the risk of hepatitis and cholestasis when using escitalopram.

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INTRODUCTION

Depression is a common mental disorder worldwide and a leading cause of non-fatal health loss, affecting more than 264 million people[1].

Among the antidepressants, selective serotonin reuptake inhibitors are often prescribed as a first-line treatment. They increase the intrasynaptic levels of serotonin by inhibiting the neurotransmitter's reuptake into the presynaptic neuron. However, the benefits of antidepressants are known to be minimal or ever non-existent in patients with mild to moderate symptoms, uselessly exposing them to potential adverse drug reactions[2]. Drug-induced liver injury is a rare complication of antidepressants and is a concern mainly for tricyclic and tetracyclic antidepressants[3].

Here we present a case of cholestatic and cytolysis liver injury due to escitalopram, a selective serotonin reuptake inhibitor, and a VigiBase® study.

CASE PRESENTATION

Chief complaints

The 68-year-old Caucasian male patient, was prescribed escitalopram 5 mg/d by his general practitioner for a minor depressive episode; the posology rose to 10 mg/d one week later. The patient developed clinical icterus with pale stools and dark urine three days later, without any pain or hyperthermia.

History of present illness

The patient was admitted to the emergency unit three days later. He was then transferred to the gastroenterology and hepatology unit, where an etiologic investigation was performed[4].

The moderate daily intake of alcohol (less than 10 g/d) and the absence of damaged hepatocytes, cirrhosis or carcinoma excluded hepatocellular jaundice.

History of past illness

The patient had no history of past illness, chronic treatment or known allergies.

Personal and family history

No notable personal or family history.

Physical examination

A physical examination was unremarkable, except for palpable hepatomegaly, eliminating an obstructive cause. Etiologies such as cholangitis, pancreatic carcinoma or edema, cholelithiasis and trauma were not found.

Laboratory examinations

Normochromic and normocytic anemia, a subtle inflammatory syndrome, cholestasis with conjugated hyperbilirubinemia and cytolytic hepatitis were observed (Table 1). The presence of conjugated bilirubin and the absence of hemolysis excluded pre-hepatic jaundice. A viral cause was improbable due to the absence of hyperthermia, and human immunodeficiency virus (HIV), hepatitis viruses (HAV, HBV, HCV, HEV), cytomegalovirus (CMV) and herpes simplex viruses (HSV) serologies were negative. Autoantibodies and serum immunoglobulin levels were not screened.

Imaging examinations

Hepatic ultrasonography was unremarkable.

FINAL DIAGNOSIS

Considering the lack of probing results from the etiologic investigation and the spontaneous resolution of symptoms after treatment was withdrawn, the only possible remaining cause was drug-induced cholestatic and cytolytic hepatitis due to escitalopram.

TREATMENT

Treatment with escitalopram was immediately stopped.

OUTCOME AND FOLLOW-UP

The chronopathology was as follows: The symptoms started to appear ten days after initiation of treatment. Pruritus resolved two days after escitalopram withdrawal. Clinical jaundice disappeared ten days after withdrawal. Liver function tests normalized a month after withdrawal. It should be noted that bilirubin levels normalized more rapidly than transaminase levels, which is not common in clinical practice, especially in drug-induced liver injury (DILI)[5]. However, we are unable to explain this phenomenon.

DISCUSSION

Case report description

We used the Roussel Uclaf Causality Assessment Method (RUCAM) to quantify the strength of the association between cholestatic hepatitis and treatment with escitalopram[6,7]. The RUCAM comprises seven criteria: The time to onset of reaction after drug start, clinical course, risk factors, concomitant drugs with hepatotoxic properties, non-drug causes, and published information on hepatotoxicity and the response to any new administration to the suspected drug. The RUCAM score ranges from -8 to +14. A higher score means a higher probability of DILI as it is collapsed into the following five-category scale: Highly probable (> 8), probable (6-8), possible (3-5), unlikely (1-2), and excluded (≤ 0).

According to the RUCAM, the iatrogenic cause of both hepatitis (10/14) and cholestasis (9/14) in our case was highly probable (Supplementary material).

Literature review

Eligible studies were identified through electronic searches of Medline and Embase (1966 to May 2020), using different sets of keywords. The first set consisted of "escitalopram" and "citalopram"; the second set of "cholestasis" and "hepatitis", the third one (optional) of "iatrogeny" and "drug-induced".

In addition, we reviewed the reference lists in the articles. Voican *et al*[3] wrote a review for clinicians on antidepressant-induced liver injury. Helmut *et al*[11] described a case of cholestasis and acute hepatitis three weeks after introducing citalopram in a 56-year-old woman. Milkiewicz *et al*[12] described a case of cholestasis and acute hepatitis two months after introducing citalopram 10 mg/d (posology rose to 20 mg/d one month later). Finally, Ng *et al*[13] described a case of cholestasis two weeks after the introduction of escitalopram and olanzapine in a 56-year-old woman.

Table 1 C-reactive protein and liver test levels (D0: Day when escitalopram was withdrawn)

Date	C-reactive protein (mg/L)	Total bilirubin (μmol/L)	Conjugated bilirubin (μmol/L)	Unconjugated bilirubin (μmol/L)	Alanine transa-minase (IU/L)
D - 22	< 5.00	4			
D0	8.20	101	65	36	80
D + 1	7.80	109	66	43	77
D + 3	15.00	117	69	48	72
D + 4	13.90	115	71	44	69
D + 16		84	46	38	58
D + 20		50	24	26	
D + 29	6.90	25	11	14	43

Few cases have proved that hepatic cholestasis can rarely be caused by citalopram[11,12]. Since citalopram is a racemic composed of 50% R-citalopram and 50% escitalopram, it was plausible that such a rare adverse event could be due to escitalopram. Only recently, Ng *et al*[13] described a case of cholestasis due to escitalopram in a 56-year-old woman: The first clinical signs of cholestasis appeared two weeks after escitalopram was initiated. The RUCAM score showed a probable iatrogenic cause. The patient was treated with other drugs, and olanzapine was introduced four days before escitalopram. Olanzapine is also labelled as a cause a cholestasis[14], and up to 28% of patients experience elevated hepatic enzymes. Therefore, in the case presented by Ng *et al*[13], it may well have participated in hepatic toxicity. In our case, escitalopram was the only drug taken by the patient, and thus its sole contribution to hepatic toxicity is certain, making this case unique.

Milkiewicz *et al*[12] have made assumptions on the pathophysiological mechanism involving the hepatocellular redistribution of multidrug-resistant protein 2, one of the key canalicular proteins responsible for transporting several organic anions, including bilirubin glucuronides, from the hepatocyte to bile. However, the exact mechanism of such hepatotoxicity remains unclear and needs to be investigated.

Pharmacovigilance analysis of hepatitis and cholestasis induced by escitalopram was investigated using Vigibase®, which is the most extensive pharmacovigilance database. It contains more than 24 million individual case safety reports (ICSRs) submitted by national pharmacovigilance centers from countries all over the world within the World Health Organization pharmacovigilance program.

We used Vigibase® to describe the characteristics of the hepatobiliary disorders associated with escitalopram[8]. We searched for all ICSRs presenting at least one adverse drug reaction from a defined list related to escitalopram with a minimal set of data (Table 2), submitted from the 14 November 1967 to 7 May 2020. A total of 481 ICSRs were analyzed, but only 127 ICSRs matched our specific criteria of cholestasis and/or hepatitis (Table 2), presumably caused by escitalopram. For each of those 127 ICSRs, we collected the following data: Age and sex of the patient, time between the introduction of escitalopram and the hepatobiliary disorder, withdrawal of escitalopram, necessity for hospitalization and the recovery from hepatobiliary disease after it was diagnosed.

We also performed a disproportionality analysis from the data extracted from Vigibase® between the adverse reactions "hepatitis acute (PT)" or "cholestasis (PT)" and escitalopram treatment using the case/non-case method. The strength of the association was quantified by crude reporting OR with their 95% confidence interval[9,10]. Statistical methods are detailed in Supplementary material.

Statistical significance was defined as a *P*-value threshold of 0.05. Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC, United States).

With regard to the 127 ICSRs included for the characterization of hepatitis or cholestasis secondary to the intake of escitalopram, most of the patients were women (64.6%). The median (interquartile) age was $35^{(49\text{-}62.75)}$ years old.

The mean duration between the introduction of escitalopram and the occurrence of hepatitis or cholestasis was ten days +/- seven days.

Cases of cytolytic hepatitis (28 ICSRs - 22.0%) seemed to be more frequent than cases of cholestasis (19 ICSRs - 15.0%). Only 2 ICSRs (1.6%) corresponded to mixed cholestatic and cytolytic hepatitis.

The toxicity of escitalopram did not seem to be dose-dependent: In almost half of cases the prescribed posology was 10 mg/d (49.0%), followed by 20 mg/d (17.6%), 5 mg/d (8.6%) and 15 mg/d (5.5%).

The vast majority of cases included in the international pharmacovigilance database lacked data such as the chronology of healing after the withdrawal of escitalopram. However, from our case, we can hypothesize that clinical recovery occurs within a few days and biological normalization within a few

Table 2 Search criteria in Vigibase® (characterization of hepatitis or cholestasis)

Adverse drug reactions list for extraction	The minimal set of data needed for extraction
Cholestasis and jaundice (HLT); Hepatic and hepatobiliary disorders NEC (HLT); Hepatic enzymes and function abnormalities (HLT); Hepatobiliary signs and symptoms (HLT); Cholestatic liver injury (PT); Drug-induced liver injury (PT); Hepatitis (PT); Hepatitis acute (PT); Hepatitis toxic (PT); Hepatocellular injury (PT); Hepatotoxicity (PT) HLT and PT from the MedDRA® hierarchy	Patient age above 18 years old; Patient gender specified in the ICSR

HLT: High-level term; PT: Preferred term; ICSR: Individual case safety report; NEC: Necrotizing enterocolitis.

Table 3 Reporting odds ratio of acute hepatitis and cholestasis in Vigibase® in patients receiving escitalopram

	OR	95% CI	*P* value
Acute hepatitis	1.938	1.186-3.166	0.0083
Cholestasis	1.866	1.279-2.724	0.0012

OR: Odds ratio; CI: Confidence interval.

weeks.

Among the 9372588 ICSRs included in the disproportionality analysis, 13071 involved escitalopram. Most of the patients were women (69.3%). Patient age was mainly between 45 and 64 years old (57.0%) followed by 65 and 74 years (21.3%), 18 and 44 years (13.9%), and ≥ 75 years (7.8%). A signal was found between acute hepatitis or cholestasis and exposure to escitalopram (Table 3).

Cholestasis is not mentioned in the summary of product characteristics (SmPC) of escitalopram in the EU or the United States. It should be noted that the American SmPC mentions a risk of delayed hyperbilirubinemia when taking escitalopram, with no further notice (incidence not known). Hepatitis is mentioned in both the European and American SmPC of escitalopram, with an unknown incidence.

Approximately two-thirds (64.6%) of the cases of hepatitis or cholestasis related to escitalopram found in Vigibase® concerned female patients. At first sight, this might indicate gender-based differences in the hepatic toxicity of escitalopram. However, it is well established that depression has a higher prevalence in women than in men: A recent United States national data study found a similar ratio[15]. Furthermore, the exact ratio applies to the number of cases of adverse drug reactions notified with escitalopram (69.3% of cases were female patients): It is unlikely that the hepatotoxicity of escitalopram differs according to gender.

The pharmacovigilance analysis confirmed that escitalopram could rarely cause acute hepatitis and cholestasis. However, the ICSRs in Vigibase® lack data, especially the course of clinical recovery and biological normalization after escitalopram withdrawal. Therefore, when confronted with hepatitis or cholestasis due to escitalopram, health practitioners must spontaneously report it to their local or national pharmacovigilance center and provide as many details as possible.

An interesting aspect of our case is that the general practitioner prescribed escitalopram for a minor depressive episode. A psychiatrist reexamined the patient during his hospitalization and diagnosed mild depression, with no need for an antidepressant drug. Thus, our case highlights something well established: Antidepressants are minimally helpful, if not useless and dangerous, in patients with mild to moderate depressive symptoms[2]. General practitioners and physicians should be aware of the ineffectiveness and harm of serotoninergic antidepressants in patients with non-severe depression.

CONCLUSION

Our case illustrates how inappropriate prescriptions can have severe consequences on both patients (*e.g.*, hospitalizations) and the health care system (evitable social security costs).

Although extremely rare, escitalopram can cause drug-induced hepatitis and cholestasis, generally within a week after initiation. Therefore, physicians must be aware of this rare but severe adverse effect. The SmPC of escitalopram should be updated to alert for this risk and give clear clinical guidelines. In the case of hepatitis or cholestasis, if an iatrogenic cause cannot be excluded, escitalopram must be immediately withdrawn and then contraindicated if its responsibility is ascertained.

FOOTNOTES

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