

CYP2D6 polymorphism may contribute to Trazodone-induced hepatotoxicity: a rare case of drug-drug-gene induced liver injury

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Abstract

A 46-year-old female with a history of type I diabetes, alopecia areata and autoimmune hypothyroidism presented with a significant hepatocellular hepatitis. The top 3 differential diagnoses were drug-induced liver injury, autoimmune hepatitis and drug-induced autoimmune hepatitis. Considering the predisposition for immune-mediated conditions, we performed a liver biopsy to exclude an autoimmune hepatitis.

A temporal relationship between the onset of liver injury and the start of Trazodone and Escitalopram was observed. We report a case of Trazodone-induced liver injury in which pharmacogenomic testing identified a CYP2D6 gene polymorphism leading to CYP2D6 dysfunction and accumulation of Trazodone's potential hepatotoxic metabolite m-CPP, which elucidates the underlying pathogenesis. This case also presents an example of a drug-drug-gene interaction between Trazodone and the not-so-innocent bystander Escitalopram leading to an additional component of CYP2D6 inhibition.

This case highlights the potential benefit of targeted pharmacogenomic testing to minimise the risk of drug-induced liver injury. (*Acta gastroenterol. belg.*, 2024, 87, 332-335).

Keywords: Drug-induced liver injury, acute hepatocellular hepatitis, Trazodone-induced hepatotoxicity, CYP2D6 dysfunction, drug-drug-gene interaction, pharmacogenomics.

Introduction

Drug-induced liver injury (DILI) accounts for <1% of cases of acute liver injury, but is the most common cause for acute liver failure (ALF) (1,2). In contrast to the predictable course of intrinsic DILI, the course of idiosyncratic DILI (IDILI) is almost impossible to predict (2,3). It is one of the most challenging liver disorders faced by gastroenterologists because of the large variety of drugs used in clinical practice with potential hepatotoxic effects (3).

Trazodone is a triazolopyridine derivative and is commonly prescribed in clinical practice, mainly used as a sleep aid. Significant liver injury is exceptional and limited to a few cases with no well-established underlying pathogenesis (4).

Pharmacogenomics has made significant progress in the area of drug metabolism, evaluating the potential role of polymorphisms in genes encoding for enzymes involved in drug metabolism (5). CYPs are of particular importance since they are responsible for the metabolism of 70-80% of all drugs (5). Despite these advances in the identification of polymorphisms that

potentially contribute to the underlying mechanism of DILI, pharmacogenomic testing has not been routinely integrated into the assessment of DILI to detect interactions leading to hepatotoxicity (5).

To the best of our knowledge, this is the first case of Trazodone-induced hepatotoxicity in which a targeted pharmacogenetic testing could identify a CYP2D6-polymorphism contributing to the underlying pathogenesis.

Case history

A 46-year-old female with a medical history of type I diabetes, autoimmune hypothyroidism and alopecia areata, was referred to the hepatology clinic with significantly elevated liver enzymes noticed through routine biochemical check-up. She did not report any discomfort. Her vital signs were normal. Physical examination revealed a soft, nondistended abdomen. The patient did not use alcohol and did not smoke. Her current medications included Perindopril, Empagliflozin, L-thyroxine, Insulin aspart, Insulin degludec, Trazodone 100 mg/day (since August 2020) and Escitalopram 10 mg/day (since September 30, 2020). She reported no use of over-the-counter medication or herbal and dietary supplements. She had no underlying liver disease. There was no family history of autoimmune or liver diseases.

At first presentation (November 2020), a significant hepatocellular hepatitis was noticed (AST 1140 U/L, ALT 1129 U/L, ALP 159 U/L, GGT 266 U/L, R >5) (table 1). No arguments could be made to rule in acute liver injury or ALF. If we looked chronologically at the lab results of the past three years, elevated liver tests were first noticed on September 30, 2020 (table 1). Because of the possibility of an underlying AIH, autoantibody titres were determined (table 2). Except a positive ANF titre of 1/1280 (antiparietal cell antibodies), autoantibodies and IgG were negative. To rule out a viral hepatitis,

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Table 1. — Timeline liver test parameters

	04-03-2020	30-09-2020	24-11-2020	02-12-2020	05-01-2021	03-03-2021	12-03-2021	15-06-2021	28-09-2021	17-11-2021
AST (U/L)	16	193	1140	486	80	65	72	33	27	22
ALT (U/L)	17	379	1129	785	68	73	69	28	21	17
TBL (mg/dL)	/	/	/	5.33	1.06	0.49	0.64	0.17	0.23	/
DBL (mg/dL)	/	/	/	3.96	0.71	0.28	0.34	0.17	0.16	/
ALP (U/L)	66	72	159	165	108	77	75	65	72	80
GGT (U/L)	10	45	266	285	86	37	38	27	19	15

Bold = abnormal liver test; red = moment of first presentation to the department of gastroenterology and hepatology; green = full recovery of the liver test abnormalities.
 AST: aspartate aminotransferase; ALT: alanine aminotransferase; TBL: Total bilirubin; DBL: Direct bilirubin; ALP: alkaline phosphatase; GGT: Gamma-glutamyl transferase.

Table 2. — Extended laboratory workup

Rule out	Parameters	Result
Hepatitis A	Hepatitis A IgM and Hepatitis A IgG	Both negative
Hepatitis B	Hep B surface antigen and Hep B surface antibody	Both negative
Hepatitis C	Anti-HCV	Negative
Hepatitis E	Hepatitis E IgM and Hepatitis E IgG	Both negative
Ebstein-Barr hepatitis	EBV IgM and EBV IgG	Both negative
Cytomegaly virus hepatitis	CMV IgM and CMV IgG	CMV IgM negative (0,5) and CMV IgG positive (138)
Autoimmune hepatitis	ANF, ENA-screening, IgG, anti-SMA, anti-SLA and anti-LKM, IgG	ANF (1/1280), Anti-LKM, SMA and SLA negative, normal IgG
Primary biliary cirrhosis	AMA-M2	Negative
Thyrototoxic hepatitis	T3, T4, TSH	Normal thyroid tests
Glycogenic hepatopathy	HbA1c, glycemia	Well controlled type 1 diabetes mellitus

viral serology was determined and was negative (table 2). Doppler ultrasonography of the abdomen showed normal liver echogenicity, with no biliary or vascular abnormalities. An elastography was performed and could rule out clinical significant fibrosis and steatosis.

Clinical, laboratory and ultrasonographic workup could exclude a viral hepatitis, Budd-Chiari syndrome, portal vein thrombosis, alcohol-related liver injury and hepatic ischaemia. The top 3 differential diagnoses were DILI, AIH or drug-induced AIH. Considering the fact that the autoantibody titres were not specific, the probability of an AIH or a drug-induced AIH was low. However, an autoantibody negative AIH was not excluded. At this point, a liver biopsy was performed to rule out an AIH. The liver biopsy specimen demonstrated the presence of centrilobular necrosis in zone 3. Portal tracts were intact without significant portal inflammation and without interface hepatitis. No significant amounts of plasma cells or eosinophilic granulocytes were present, which made an AIH less probable. The periportal parenchyma was intact without significant lobular inflammatory

infiltrate. There was no steatosis. Sirius red stain showed no fibrosis. These findings were most consistent with DILI (figure 1a+b).

We performed a pharmacological review. The only recent treatment changes were the start of Trazodone in August 2020 and Escitalopram on September 30, 2020. A temporal relationship was observed between the onset of liver injury and the start of Trazodone and Escitalopram. Trazodone undergoes extensive hepatic metabolism by the cytochrome P450 enzyme system (CYP3A4 and CYP2D6) and hepatotoxicity may be mediated by toxic intermediates of its metabolism (4). Trazodone is metabolised by N-dealkylation via CYP3A4 to its active metabolite m-Chlorophenylpiperazine (m-CPP) which is further metabolized by CYP2D6. There is evidence that m-CPP is the potential psychopharmacological hepatotoxic metabolite of Trazodone, causing hepatotoxicity (4-9).

We searched for significant drug-drug interactions. Interaction checkers UpToDate®, PHIL®, Clinical Pharmacology® and MedicinesComplete® do not report

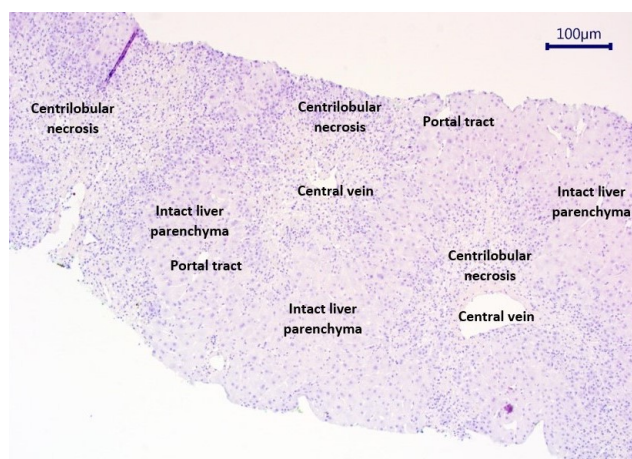


Figure 1a. — Haematoxylin-Eosin stain liver biopsy.

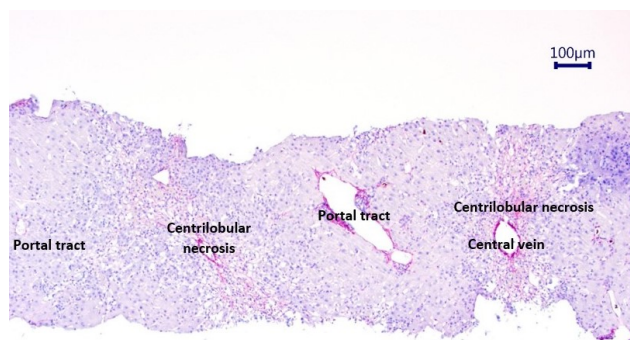


Figure 1b. — Sirius red stain liver biopsy showing no fibrosis.

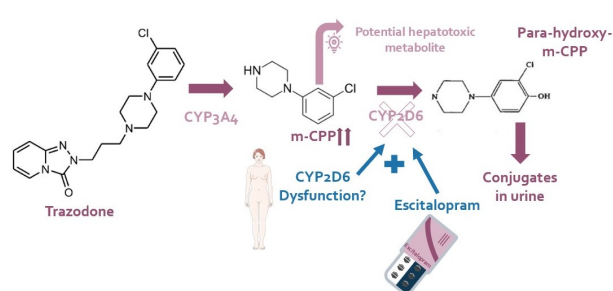


Figure 2a. — Hypothesis.

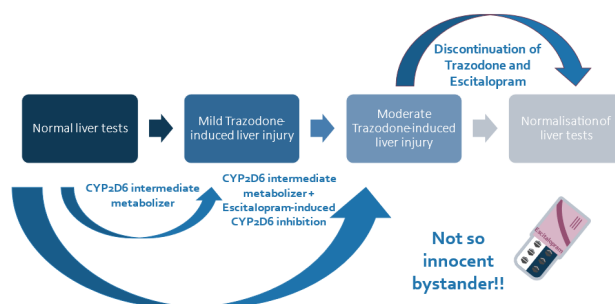


Figure 2b. — Confirmed hypothesis.

any interaction between Trazodone and Escitalopram. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) and a weak inhibitor of CYP2D6. Escitalopram may induce CYP2D6 inhibition and alter the concentration of m-CPP. Although interaction checkers could not demonstrate an interaction between Trazodone and Escitalopram, there may be a significant drug-drug interaction between the metabolite of Trazodone (m-CPP) and Escitalopram. This may have a more significant effect in patients with a genetic polymorphism in CYP2D6.

We hypothesized the following. Trazodone is metabolised by CYP3A4 to its potential hepatotoxic metabolite m-CPP, which is further catabolised by CYP2D6. Poor or intermediate CYP2D6 function as a consequence of a genetic polymorphism may lead to increased CYP2D6 substrate blood levels. Trazodone was started in August 2020. Shortly afterwards a mild hepatocellular enzyme elevation occurred and Escitalopram was added to the patients therapy. Escitalopram is a weak inhibitor of CYP2D6. This weak inhibition alone is less probable to cause significant liver test abnormalities due to accumulation of m-CPP, but in association with a genetic polymorphism in CYP2D6, it can be potentially responsible for significant hepatotoxicity. It is suspected that our patient is a poor or intermediate metaboliser of CYP2D6, but this required confirmation by targeted pharmacogenetic testing (figure 2a). Genetic testing resulted in the presence of an allele characterized by

decreased CYP2D6 activity (CYP2D6*41) and an allele characterized by a complete loss of CYP2D6 activity (CYP2D6*4). The patient is a confirmed CYP2D6 intermediate metabolizer. Our hypothesis could be confirmed (figure 2b). A CIOMS (Council for International Organizations of Medical Sciences) causality assessment score of ≥ 8 was given.

The initial step in the management of this DILI was discontinuation of the implicated drug, Trazodone. In this case, Trazodone and Escitalopram, were discontinued. Full recovery occurred after 4 months of discontinuation of the drugs and is an important criterion in the causality assessment. Escitalopram rechallenge did not trigger any recurrent liver test abnormalities. The pharmacogenetic variant in the CYP2D6 gene causes variability in drug response and susceptibility to toxicity. We have educated our patient on drugs that potentiate CYP2D6 inhibition and drugs that are a substrate of CYP2D6 and should be avoided. This is a form of precision medicine reflected in an individualised approach to prescribing medication.

Discussion

To the best of our knowledge, this is a first published case of Trazodone-induced liver injury in which targeted pharmacogenomic analysis identified a genetic CYP2D6 polymorphism that contributed to the underlying pathogenesis. We further hypothesized a drug-gene interaction

between Trazodone and the not-so-innocent bystander Escitalopram leading to additional CYP2D6 inhibition and potentiation of hepatotoxicity.

Our hypothesis was formed by detailed pharmacological review combined with consulting LiverTox® and evidence search in the current scientific literature. LiverTox® indicates that liver test abnormalities can occur with Trazodone, but are often mild and rarely require dose modification or discontinuation (4). Rare instances of ALF from Trazodone have been reported (4). Nefazodone, an antidepressant similar in structure and mechanism to Trazodone, was approved for use in 1994, but has currently a black box warning for hepatotoxicity because of multiple reports of ALF (4,6). In our case, Trazodone could possibly be involved in this hepatotoxicity.

We took a closer look at the metabolism of Trazodone. Trazodone is metabolised by CYP3A4 to m-CPP. Literature suggests that CYP2D6 plays a major role in the further metabolism of m-CPP. Najibi et al. found that Trazodone's reactive metabolite m-CPP was toxic towards rat hepatocytes. The study showed that co-administration with a CYP2D6 inhibitor results in an increased hepatotoxicity. Excessive dosage of m-CPP may be associated with hepatotoxicity. This is probably the main reason why Nefazodone was withdrawn from the market in 2004 given its clear causative link with hepatotoxicity (4,9).

M-CPP shows a large variability in clearance and bioavailability. Co-ingestion with inducers or inhibitors of the CYP2D6 enzyme could interfere with the elimination of m-CPP. Inhibitors of CYP2D6 metabolism can alter serum concentrations of drugs that are dependent on CYP2D6 for elimination. In this case, Escitalopram (weak inhibitor of CYP2D6) may induce CYP2D6 inhibition and alter the concentration of m-CPP. Genetic polymorphism of the CYP2D6 gene as well could alter the plasma concentration of m-CPP (6-8). The specific effect of CYP2D6 inhibition on CYP2D6 substrate blood levels varies widely among individual patients because of variability in CYP2D6 function due to genetic polymorphisms. Poor, intermediate, extensive, and ultrarapid CYP2D6 function types have been characterized and varies strongly between different ethnic groups (8). This led us to the targeted pharmacogenomic testing that identified a CYP2D6 gene polymorphism leading to CYP2D6 dysfunction and accumulation of Trazodone's potential hepatotoxic metabolite m-CPP. In this case Escitalopram is the not-so-innocent bystander by inducing an additional component of CYP2D6 inhibition. A limitation of this case is that we weren't able to perform a m-CPP dosage to strengthen our hypothesis because m-CPP dosing is not available in Belgium.

We performed a causality assessment. In our opinion, the CIOMS has limited applicability in this case. This scale was developed to demonstrate a causal relationship between a single drug and hepatotoxicity. There is support that Trazodone and its reactive metabolite m-CPP

are causative for hepatotoxicity. There is insufficient evidence that Escitalopram is hepatotoxic in itself in this case, but there is a role of Escitalopram in exacerbating hepatotoxicity by additional CYP2D6 inhibition. This assumption was supported by a negative rechallenge. For these reasons, the score item "concomitant therapy" was assigned a 0 score.

This case highlights the potential clinical benefit of pharmacogenomic testing; if pharmacogenomic knowledge is integrated into the assessment of DILI, the detection of important drug-(drug)-(gene) interactions may be beneficial for a personalized approach to drug selection and dosing to minimize the risk of DILI.

Conflict of interest

The authors have no potential conflict of interest relevant to this manuscript to be reported. This work did not receive any funding. This manuscript has not been published or been accepted as a full article.

Author contributions

Kymentie Ferdinande: case report initiation and development, writing of the manuscript.

Lynn Declerck and Laetitia Missiaen: pharmacological review, writing part of the manuscript, proof-reading of the manuscript.

Céline Melis: provision and explanation of pathological images. Proof-reading of the manuscript.

Laurence Seynhaeve: proof-reading of the manuscript, patient counselling.

Charlotte De Vloo: proof-reading of the manuscript.

Jochen Decaestecker: treating physician of the patient, case study development, supervisor of all parties, proof-reading of the manuscript.

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