CASE REPORT

Flupirtine drug-induced liver injury in a patient developing acute liver failure

David Noiva Perdigoto,^{1,2} Pedro Amaro,¹ Manuela Ferreira,^{1,2} Luis Tomé^{1,2}

¹Department of Gastroenterology, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal
²Faculty of Medicine, Coimbra University, Coimbra, Portugal

Correspondence to

Dr David Noiva Perdigoto,
 davidperdigoto@gmail.com,
 dperdigoto@hotmail.com

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SUMMARY

A patient is admitted with complaints of recent onset nausea, discomfort, jaundice and blood tests that reveal severe hepatitis. At the time, she had been taking medication with *Hypericum perforatum* (St John's wort) for 6 months, and 6 weeks before this event, she took flupirtine maleate. A few days after being admitted, she developed encephalopathy progressing to acute liver failure (ALF) requiring unsuccessful liver transplantation. The patient was ultimately diagnosed with drug-induced liver injury (DILI). In this context, while *H. perforatum* could interfere with other medication or trigger DILI itself, flupirtine appears to have triggered the DILI, given its liver toxicity capacity. DILI is one of the major ALF causes and can jeopardise patient's life. Accordingly, all efforts to reduce medication potentially hazardous to the liver are recommended.

BACKGROUND

Flupirtine is a centrally acting non-opioid analgesic with additional muscle relaxant properties.¹ This pharmacological agent acts through activation of G-protein regulated, inwardly rectifying potassium channels which result in the stabilisation of membrane-resting potentials in neurons. This cellular effect explains its associated relaxing capacity on muscle tone.²

Flupirtine has been used over the last 30 years as an alternative medication to non-steroidal anti-inflammatory and opioid analgesics. Initially, it was mainly prescribed in Germany, where it was produced. Recently, its reach expanded to other European countries, as well as Brazil and China.^{1,3} At that time, it was considered a safe analgesic, even with an indication to be used as an alternative to the other options. Over the last 7 years, however, there has been a surge in the number of publications reporting potential side effects of this drug.^{3–6} Despite the recent data, flupirtine is still a commonly prescribed analgesic.

CASE PRESENTATION

A 42-year-old, otherwise healthy woman presents at the local emergency department (ED) complaining of nausea, vomiting, malaise and jaundice over the previous 4 days.

Nausea and general discomfort started 7 days before going to the ED. One day later, she went to a local clinic because she was also feeling anxious. She was prescribed with escitalopram 20 mg once a day, alprazolam 0.25 mg at afternoon and 0.5 mg at

night. Three days later, escitalopram was reduced to 5 mg once a day and alprazolam to 0.5 mg at night by her assistant doctor. No further medication was introduced.

Two days later, her condition did not improve and she was still feeling ongoing nausea, started vomiting and developed jaundice. At the ED, she also pointed out that she had been feeling quite asthenic for the last 4 months, but she denied weight loss or anorexia. Besides, she noticed recent presence of dark urine but declared no other symptoms such as fever or pruritus.

When asked about her medical history, she described having been diagnosed with depression a couple of years before that was treated at that time but did not recall the drugs' names. She also reported being diagnosed with hepatitis A during her childhood. She advised that she had a history of penicillin allergy.

As for her chronic medication, she had been taking an oral contraceptive composed of gestodene 75 µg and ethinylestradiol 2 µg for several years. She was also taking Ansiotine, a multivitamin product belonging to the group of complementary and alternative medicine (CAM) that she started daily 6 months ago. Ansiotine's main elements are: *Griffonia simplicifolia*—100 mg, corresponding to a 25% extract of 5-hydroxytryptophan; *Paullinia cupana* (Guaraná)—100 mg; *Hypericum perforatum* (St John's wort)—50 mg, corresponding to 0.15 mg of hypericin and other components, such as L-glycine, L-glutamine, L-tyrosine, choline and other oligoelements.

Additionally, the patient had recently taken the analgesic flupirtine maleate (Metanor) for lower back pain. Six weeks before this acute event, she took flupirtine 100 mg twice a day during 1 week and then stopped.

The patient lived with her husband and children, used to drink tap water and had no contact with sick animals or known potentially transmittable diseases. Noticeably, she mentioned that 2 months earlier, several students in her school were diagnosed with viral gastroenteritis.

She denied smoking habits, alcohol drinking or taking any recreational drugs. She had not received blood transfusions, and she did not have any behavioural risk factors. She did all the standard vaccinations including hepatitis B vaccine.

Physical examination: in the ED, the patient collaborated with history taking and showed no objective signs of disorientation. She had no fever (tympanic temperature 36.5°C), a heart rate of 70

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Table 1 Laboratory tests in the emergency department

Parameter	Value
Haemoglobin (g/dl)	14.0
Leucocytes/Eosinophils ($\times 10^9/L$)	10.2/0.2
Platelets ($\times 1000/\mu L$)	226
Prothrombin time (seconds), control=14.0	42.9
INR	3.67
Activated partial thromboplastin time (seconds), control=28.0	38.0 (ratio 1.36)
Blood urea nitrogen (mg/dl) N: 7.94–20.9	5
Creatinine (mg/dl) N: 0.55–1.02	0.63
Sodium/Potassium (mmol/L) N: 136–146/3.5–5.1	136/3.7
Glucose (mg/dl) N: 60–109	121
Corrected (albumin) calcium (mg/dl) N: 8.8–10.6	9.4
Total protein/albumin (g/dl) N: 6.6–8.3/N: 3.5–5.2	6.1/3.3
LDH (U/L) N: 125–220	911
AST 3545 (U/L) n<31	3545
ALT (U/L) n<34	4767
AP (U/L) N: 40–150	135
γ GT (U/L) n<38	71
Total bilirubin (mg/dl) N: 0.3–1.2/direct bilirubin N: 0.1–0.5	11.7/7.3
Creatine kinase (U/L) (n<145)/C reactive protein (mg/dL) N:0–0.5	15/0.89
Arterial blood gas test (FiO ₂ 21 %): pH, N: 7.35–7.45	7.47
pO ₂ (mm Hg) N: 83–108 / pCO ₂ (mm Hg) N: 35–45	97.4 / 35.6
HCO ₃ ⁻ (mmol/L) N: 21–29 / Actual base excess (mmol/L) N: –3–+3	25.5 / 2.2
Oxygen saturation, N: 94–100 / Lactate (mmol/L) N: 0.50–2.00	97.8% / 1.28

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; γ GT, gamma-glutamyltransferase; INR, international normalised ratio; LDH, lactate dehydrogenase; N, normal value.

bpm, respiratory rate of 18 cycles per minute, blood pressure of 107/61 mm Hg and O₂ peripheral blood saturation of 98%. She had sclerotic and skin jaundice, hydrated mucosa and no cyanosis or rash. After detailed physical examination including neurological observation, no other significant findings were detected.

INVESTIGATIONS

At the ED, she was submitted to general complementary diagnostic evaluation. The laboratory tests results are expressed in [table 1](#).

An ECG and chest radiography showed no alterations.

Abdominal Doppler ultrasound: liver without morphological alterations. Collapsed gall bladder without lithiasis. No dilatation of intrahepatic and common biliary ducts. Portal vein, hepatic artery and hepatic veins without significant findings, namely without visible thrombus signs; absence of ascites.

Afterwards, more tests were requested, revealing a blood coagulation factor V: 31% (N: 50–150) and factor VII: 9.1% (N: 50–150). Pregnancy test was negative.

The patient was admitted to the gastroenterology intensive care unit (ICU) with the diagnosis of acute severe hepatic insufficiency with a high risk of imminent progression to acute liver failure (ALF).

In the first hours of admission, the investigation progressed with the following determinations:

Paracetamol (acetaminophen) serum values: <2.0 μ g/mL.

Alcohol and benzodiazepines serum screening: not detected.

Serum ammonia: 127 μ mol/L (N: 18–72).

Table 2 Bacterial and viral specific laboratory tests

Hepatitis A virus	IgG positive, IgM negative
Hepatitis B virus	HBsAg and HBcAb negative HBsAb value: 0.53 UI/L
Hepatitis C virus	Ab negative, RNA negative
Hepatitis E virus	IgG and IgM negative
HIV 1 and 2	Ag and Ab negative
Cytomegalovirus	IgG and IgM negative
Epstein-Barr virus	IgG positive IgM negative
Herpes simplex virus 1 and 2	IgG and IgM negative
Varicella-Zoster virus	IgG positive IgM negative
Leptospirosis' Ab	IgG and IgM negative

Antinuclear, antismooth muscle, antiliver kidney microsome, antisoluble liver antigen and antiliver cytosol type 1 antibodies: all negative. Immunoglobulins (all classes): normal values. Ceruloplasmin, 0.31 g/dL (N: 0.20–0.60), serum copper: 1.61 mg/L (N: 0.80–1.54). An abdominal CT angiography was performed and showed no significant vascular alterations.

Ab, antibody, Ag, antigen.

Specific viral and bacterial laboratory tests that are summarised in [table 2](#).

Antinuclear, antismooth muscle, antiliver kidney microsome, antisoluble liver antigen and antiliver cytosol type 1 antibodies: all negative.

Immunoglobulins (all classes): normal values.

Ceruloplasmin: 0.31 g/dL (N: 0.20–0.60), serum copper: 1.61 mg/L (N: 0.80–1.54). An abdominal CT angiography was performed and showed no significant vascular alterations.

DIFFERENTIAL DIAGNOSIS

The patient presented with acute hepatitis with considerable hepatic insufficiency. During admission, she developed type A encephalopathy progressing to ALF.

Facing the patient's hepatitis pattern, one must consider the three most likely conditions, as well as the less common causes. Ischaemic, viral or toxic/drug-induced hepatitis justify most cases when the transaminases values are higher than 1000 U/L. Although the lactate dehydrogenase value was quite high (4 $\times$ the normal upper value) in this specific case the ischaemic aetiology was, ab initio, unlikely because of the patient's age and absence of cardiovascular comorbidities. Besides, she was not taking any potential hypotensive medication, and there was no history of any recent clinical event that could have led to a significant period of hepatic ischaemia. Acute viral hepatitis or chronic reactivation was excluded because she was immune to hepatitis A and hepatitis B, C, E, and other hepatotropic virus like cytomegalovirus, Epstein-Barr virus and herpes simplex virus 1 and 2 were also ruled out.

Other infrequent events that can progress to severe hepatitis are acute bile duct obstruction, which was excluded by the initial abdominal Doppler ultrasound that also allowed ruling out Budd-Chiari syndrome. Moreover, an angiographic CT scan confirmed the absence of Budd-Chiari syndrome.

Autoimmune hepatitis and Wilson's disease were considered as possible causes because they might occur in female patients of this age. However, Wilson's is more frequent in younger patients and considering the liver enzymes pattern, imaging absence of chronic liver alterations, normal ceruloplasmin and just slightly elevated serum copper values, while not enough to rule out completely the disease, made Wilson's an extremely remote hypothesis. Additionally, in the patient's context, none of the main features typically associated with Wilson's disease

presentation as ALF were observed: absence of anaemia, the transaminases pattern was very elevated (both >2000 U/L), the aspartate transaminase/alanine transaminase ratio was less than 1 and acute kidney injury was not present.⁷ Similarly, an autoimmune hepatitis inaugural flare was ruled out as extremely unlikely because the immunoglobulins values were normal and all the specific autoantibodies were negative. There was no history of alcohol drinking (confirmed by the family), and any other potential liver toxins were excluded.

The patient had no fever or skin rash, and the laboratory tests showed absence of any cytopaenia or eosinophilia. These are findings that might support the diagnosis of drug-induced liver injury (DILI). Nevertheless, their presence is not mandatory, and, in fact, eosinophilia is only common when DILI occurs in association with a drug allergy component.

Thus, after ruling out other aetiologies, the most probable diagnosis was DILI caused by medication or CAM.

TREATMENT

Supportive therapy and close surveillance were carried out at an ICU. The patient developed ALF with progressive global deterioration, and 7 days after admission, was submitted to an urgent liver transplant.

OUTCOME AND FOLLOW-UP

The patient's general status has deteriorated significantly with accelerated progression to stage 4 encephalopathy on the sixth day after admission. During the early pretransplant management, the patient did not fulfil criteria of systemic inflammatory response syndrome, showed no sepsis signs, and no sympathomimetic amines were needed to keep an adequate median arterial pressure value. The patient had no renal dysfunction or failure requiring haemodialysis. Airway protection with orotracheal intubation was executed.

The patient was submitted to an emergent liver transplant on the seventh day after admission. During surgery, an unexpected severe ischaemic colitis with consequent perforation was noticed and required colectomy. Noteworthy, a CT angiography was done 4 days before and had shown no imaging signs consistent with intestinal ischaemia. Additionally, in the day preceding liver transplantation, the patient developed slight leucopaenia, $3.7 \times 1000/\text{mm}^3$ (N: 4–10) and had a minor procalcitonin elevation of 0.92 ng/mL (N: 0–0.5) but had normal C reactive protein, no fever or hypothermia and no ischaemic colitis signs such as haematochezia. The evolution was unsuccessful, and the patient died 1 day later due to uncontrolled septic shock. The liver explant presented extensive necrosis not allowing an aetiological pathological diagnosis.

DISCUSSION

Identifying a drug or CAM as the cause of ALF in this case is a quite complex issue because several agents were involved and must be considered. First, oral contraceptives can cause intrahepatic cholestasis with jaundice and pruritus, but DILI progressing to ALF is uncommon. Additionally, the patient took this class of contraceptive for several years and never experienced alterations in liver enzymes before.

Escitalopram and alprazolam were initiated together just after the patient started feeling ill. Because the patient had history of depression, she could have had previous treatment with this selective serotonin reuptake inhibitor (SSRI) antidepressant and a new exposure to the drug could have triggered a fast onset idiosyncratic DILI. However, since the patient

was already feeling ill when she started the antidepressant therapy and the time between the onset of medication and jaundice was very narrow (4 days), this hypothesis is unlikely. In general, all SSRI, and particularly escitalopram, are considered very low-risk drugs for the development of DILI. Similarly, benzodiazepines are considered a low-risk class for DILI occurrence.^{8–11}

The patient was taking *H. perforatum* during the 6 months before her visit to the ED. This herb is known for its ability to interact with several types of medication. Acting as a cytochrome P450 (CYP) inducer, particularly CYP3A4, *H. perforatum*'s ability to significantly reduce the plasma concentration of some drugs is well documented.^{12–14} On the contrary, an upregulation of the drug effect can happen through CYP 3A4 or CYP 2B6 conversion of prodrugs into their active metabolites.¹⁵ All the data underscore that there are still several St John's wort medication interactions that need to be characterised.

Scores have been developed to help in the assessment of causality of DILI and herb-induced liver injury (HILI).¹⁶ The formerly denominated Council for International Organizations of Medical Sciences Method is now called the Roussel Uclaf Causality Assessment Method (RUCAM).¹⁶ This score for *H. perforatum* as the potential HILI trigger is only 2 (1: >90 days' time frame, –2: concomitant drug known as hepatotoxin with compatible time to onset, 2: other causes ruled out, 1: reaction published but unlabelled).¹⁷

The patient took flupirtine for 7 days, 200 mg/day, 6 weeks before. This drug has been described in several studies^{3 5 6} as a potential medication leading to DILI. In addition, ALF due to flupirtine has already been reported.¹⁸ The R value, commonly used to identify the type of DILI, was 156 in this case, representing a severe hepatitis typical of hepatocellular-type DILI ($R > 5$) and often seen in flupirtine cases.³

In this case, the RUCAM score for flupirtine as the potential DILI trigger was 6 (2: 5–90 days time frame, 2: other causes ruled out, 2: reaction labelled). This makes this drug a probable cause (between 6 and 8). Among all scores, the RUCAM is still the most notable. However, it is important to highlight that none of them has an ideal accuracy.^{19 20}

The role played by *H. perforatum* in potentially interfering with other medication is unknown and cannot be completely excluded, while its role as the primary injury trigger¹⁷ seems to be unlikely (RUCAM of 2).

DILI caused by flupirtine leads to a hepatocellular-type pattern (R values commonly higher than 20) with extensive perivenular necrosis. The histological extent of liver necrosis correlates well with serum transaminases levels.⁴ The time between drug intake and injury is quite variable ranging from 11 days to 24 months.^{3 4} HLA-DRB1*16: 01-DQB1*05: 02 was recently identified as a risk factor for flupirtine-induced DILI (human leucocyte antigen genotyping not available in this case).²¹ The prognosis is usually favourable, but ALF requiring liver transplantation has been described.^{4 18}

In conclusion, because DILI is always an exclusion diagnosis,²² we assume that, after excluding other potential aetiologies, DILI due to flupirtine was the most probable cause of ALF in this case.

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Competing interests None declared.

Learning points

- ▶ Drug-induced liver injury (DILI) is a major cause of acute liver failure and may be associated with a poor prognosis.
- ▶ DILI is an exclusion diagnosis, so all the other causes must be first meticulously ruled out.
- ▶ Flupirtine can potentially be a trigger of DILI and must be used with discretion.
- ▶ St John's wort may be a harmful complementary and alternative medicine and prudence must be advised.
- ▶ Drug–drug interaction can lead to DILI. Therefore, combined medication should be carefully used, and awareness of potential adverse events should be raised.

Patient consent Obtained.

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