CASE REPORT

Acute liver injury secondary to sertraline

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dr.chrislws@gmail.com**SUMMARY**

Sertraline is widely prescribed to treat depression and anxiety disorders. However, hepatitis secondary to its use is a rare entity. We report the case of a 26-year-old woman in her 20th week of pregnancy presented with nausea, vomiting, malaise and dark urine. This occurred 6 months after sertraline 50 mg daily was started for the treatment of depression. Three weeks prior to her presentation, the dose of sertraline was increased to 100 mg daily. The patient's liver biochemical profile demonstrated increased transaminases. The biopsy of the liver showed lobular hepatitis, with a mild prominence of eosinophils, suggestive of a drug-induced or toxin-induced aetiology. Extensive biochemical work-up failed to show any other pathology to account for her hepatitis. Liver function tests normalised after cessation of sertraline, indicating a probable association between sertraline use and acute hepatocellular injury in our patient.

BACKGROUND

Sertraline is a medication widely used in the treatment of depression. It is also approved for use in a range of psychiatric disorders including panic disorder, obsessive-compulsive disorder and post-traumatic stress disorder. Sertraline also has a role as an appetite suppressant in the management of obesity and weight reduction. Its main pharmacological action is to inhibit the presynaptic reuptake of serotonin.¹ It also has very weak effects on norepinephrine and dopamine neuronal uptake.² The usual dosing schedule of sertraline in the treatment of major depressive disorders is 50 mg daily, which can be gradually increased to a maximum of 200 mg daily, guided by the therapeutic response. Common side effects of sertraline include nausea, diarrhoea, insomnia and sexual dysfunction.²⁻³ Acute hepatitis secondary to sertraline use, however, is rare. A case of acute hepatitis secondary to sertraline use is described in this paper and the potential mechanisms for its occurrence are discussed. In view of the widespread use of sertraline, an awareness of this side effect is important among all clinicians to ensure early diagnosis of this potentially serious complication.

CASE PRESENTATION

A 26-year-old Caucasian woman, pregnant at 20 weeks gestation, was referred to our tertiary hospital with abnormal liver function tests (LFTs). These were ordered by her primary care doctor following an incidental finding of positive urobilinogen on a urine dipstick, performed routinely in pregnancy.

On further questioning, the patient reported a 12-week history of dark discolouration of urine associated with mild epigastric discomfort, significant vomiting and mild pruritus. There was no history of fevers, diarrhoea or recent travel and she had no risk factors for viral hepatitis.

Her history included depression that had previously been managed with desvenlafaxine 50 mg daily. This was changed to sertraline 50 mg daily, 4 weeks prior to conception (24 weeks prior to admission) due to more available data regarding its safety profile in pregnancy. Given its relatively low levels in breast milk, sertraline was also considered a relatively safe option for ongoing use, including in the postpartum period.⁴ Three weeks prior to admission, the sertraline dose was increased to 100 mg daily in view of optimising control of depressive symptoms. Other medications administered during this time included ranitidine and metoclopramide, which were used throughout the pregnancy. Gastro-oesophageal reflux was the main indication for ranitidine, which the patient had been taking for several years, while metoclopramide was prescribed at the start of gestation for pregnancy-related nausea. There was no history of antibiotic or herbal medication usage.

Her clinical examination was unremarkable, with no evidence of hepatosplenomegaly or stigmata of chronic liver disease.

INVESTIGATIONS

LFTs were significantly abnormal with a predominant transaminitis alanine transaminases (ALT) 700 U/L (ref 7–56 U/L), aspartate transaminases (AST) 410 U/L (10–50 U/L), alkaline phosphatase (ALP) 113 U/L (30–120 U/L), γ -glutamyl transpeptidase 26 U/L (7–64 U/L), bilirubin 25 μ mol/L (0–20 μ mol/L) which was consistent with acute liver injury. Other blood results including International Normalised Ratio were within the normal range.

A full blood screen was performed to determine the aetiology of the liver derangement. Serology for hepatitis A, B, C and E, Epstein-Barr virus and cytomegalovirus were negative. Hepatitis E PCR was also negative, and an autoimmune screen for antinuclear antibody, antismooth muscle antibody, antineutrophil cytoplasmic antibody, antimitochondrial antibody and antiliver kidney microsomal type-1 antibody and coeliac antibodies was also negative. In addition, iron studies, caeruloplasmin, serum copper, 24-h urinary copper and α -1-antitrypsin levels were within the normal range. An abdominal ultrasound was unremarkable, with no evidence of hepatic or biliary pathology. Suspecting drug-induced liver injury (DILI), sertraline was ceased.

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Figure 1 (H&E, ×200): Lobular (perivenular) inflammation with mild ballooning degeneration of hepatocytes. Lipofuscin accumulation and anisonucleosis of hepatocytes are also noted, indicative of hepatocyte regenerative changes. A Councilman body (arrow) is observed.

An ultrasound-guided liver biopsy was subsequently performed. Histopathology showed mild resolving perivenular (zone 3) hepatitis, with the presence of occasional eosinophils. In addition, lipofuscin pigmentation was moderately prominent, suggesting a resolving process. Of note, rubeanic acid staining for copper was negative. Although the appearance was non-specific, the overall finding of hepatitis with moderate eosinophilia was suggestive of a drug-induced or toxin-induced aetiology (figures 1–4).

There was a progressive worsening of LFTs until 1 week postcessation of sertraline, with the ALT peaking at 820 U/L, followed by a gradual improvement. Improvement in her biochemical markers was accompanied by a marked improvement in her symptoms.

DIFFERENTIAL DIAGNOSIS

Given the non-specific symptoms at presentation, a number of differential diagnoses were considered including viral hepatitis, autoimmune hepatitis and biliary pathologies. In addition, hereditary liver disorders including Wilson's disease and haemochromatosis were considered. These pathologies were, however, excluded through imaging and extensive biochemical investigations.

A review of the patient's medication history revealed that the patient was also taking ranitidine, which has potential hepatotoxic side-effects albeit rare.^{5 6} However, ranitidine was not thought to

Figure 2 (Periodic Acid-Schiff (PAS) stain, ×200): Perivenular lipofuscin suggestive of resolving hepatitis.

Figure 3 (H&E, ×400): Scattered eosinophils (arrow) and mild hepatocyte anisonucleosis.

be responsible for the presentation as the patient had been taking this medication for several years and therefore it was not ceased. The improvement in liver function shortly after cessation of sertraline, while all other medications were continued, further supports our diagnosis of sertraline-induced hepatitis.

The patient was pregnant at the time of presentation so pregnancy-related liver dysfunction was considered in the differential diagnosis. HELLP (Haemolysis, Elevated Liver enzyme, Low Platelet) syndrome was considered unlikely given the finding of a normal platelet count, and no evidence of haemolysis. The lack of significant pruritic symptoms and the time during the pregnancy on presentation (second trimester) made intrahepatic cholestasis of pregnancy less likely. The timing of symptoms was also inconsistent with the typical pattern of presentation for hyperemesis gravidarum and acute fatty liver of pregnancy. Importantly, the histological analysis of the liver biopsy was not supportive of pregnancy-related disorders of liver dysfunction. Use of the Naranjo Adverse Drug Reaction Probability Scale indicated that sertraline was the probable cause of the hepatocellular injury in our patient.⁷

OUTCOME AND FOLLOW-UP

At ongoing outpatient follow-up, the patient expressed significant improvement in her symptoms. Normalisation of LFTs

Figure 4 (H&E, ×100): portal tract (left) and venule (right). Mild perivenular (zone 3) ballooning is noted.

Figure 5 (A and B) Alanine transaminase and bilirubin against time showing gradual normalisation of liver function over time. Arrow denotes date of liver biopsy (note: day 0: date of admission).

occurred approximately 80 days after sertraline was discontinued (figure 5A and B).

The patient had an otherwise uneventful pregnancy and delivered a healthy male neonate at 39 weeks' gestation.

DISCUSSION

DILI is a potential adverse effect of pharmacological therapy. Assessing the true incidence of DILI can be challenging as a significant number of cases occur in asymptomatic patients and the diagnosis may be missed if LFTs have not been performed. A prospective study estimated the incidence of DILI among hospital inpatients to be 6.6 per 1000 patients per week.⁸

Data from the premarketing evaluation of sertraline hydrochloride suggest that the rate of asymptomatic elevations in serum transaminases (AST and ALT) secondary to sertraline use is 0.8%, with most cases occurring within the first 9 weeks of drug initiation.² Acute hepatitis secondary to sertraline is a rare entity with very few reported cases so far. In our patient, the biochemical abnormalities and histopathological results, in relation to the drug history, suggests sertraline-induced hepatitis as the likely cause of hepatitis. In addition, imaging and extensive biochemical investigations failed to demonstrate any other pathology to account for the liver derangement. The improvement

in LFTs shortly after cessation of sertraline, while all other medications were continued, is further supportive of our diagnosis of sertraline-induced liver injury.

Hepatotoxicity from sertraline is rare and appears to occur less commonly than with other selective serotonin reuptake inhibitor.⁹ To date there have been fewer than 10 published cases of sertraline-related hepatotoxicity in the English medical literature.^{10–17} A review of previous cases revealed highly diverse clinical presentations ranging from asymptomatic liver derangement to fulminant hepatitis.¹⁸ Common symptoms include abdominal pain and jaundice, and varying patterns of liver injury including hepatocellular, cholestatic and mixed pattern dysfunction.^{13–15} In sertraline-induced hepatic injury, liver function typically improves soon after sertraline cessation. However, the time to normalisation of liver function is variable and has been reported at 6 months following cessation of the drug.¹³ Our case is consistent with previously reported cases, with a time to resolution of 2.5 months postcessation of sertraline.

While the mechanism by which sertraline causes hepatotoxicity is still not fully understood, a number of theories have been suggested. Proposed mechanisms include hepatotoxicity from sertraline or one of its metabolites, or an accumulation of

sertraline in the body, through inhibition of its own metabolism.^{14–18} Recently, Li *et al*¹⁹ postulated that mitochondrial dysfunction could play a role in sertraline-related liver injury through rapid cellular depletion of ATP in hepatocytes, while also interfering with mitochondrial metabolism in a number of ways including the inhibition of mitochondrial respiration complexes. The theory of an immunologically mediated hepatitis has also been suggested and is supported by the presence of eosinophils on liver biopsy and the idiosyncratic nature of the reaction.¹⁴ In a case report of a 23-year-old woman who developed hepatotoxicity from sertraline, Persky and Reinus¹⁴ noted that inadvertent rechallenge with sertraline resulted in a prompt rise in ALT, suggestive of an anamnestic response. In the case of our patient, although recurrence following intentional rechallenge with sertraline would further support our diagnosis, this was not performed given the medical risks involved.

Similar to a number of antidepressants, sertraline has an inhibitory effect on cytochrome P450 2D6, although this effect is considered relatively weaker at lower doses of sertraline.^{20–21} As many drugs are metabolised through this pathway, sertraline has the potential of causing accumulation of other drugs, which can in turn cause hepatotoxicity, or exacerbate the hepatotoxicity caused by sertraline.¹⁴ For example, in a recent report of sertraline-induced hepatotoxicity, Brahmania *et al*¹⁵ proposed this as the potential mechanism of hepatic injury in their patient who was on sertraline as well as hormone replacement therapy with progesterone. In our patient, the temporal relationship between sertraline initiation and symptoms, as well as the biochemical and symptomatic improvement following discontinuation of the drug, strongly point towards sertraline-induced hepatotoxicity. Of note, however, our patient was also on ranitidine, and inhibition of cytochrome P450 2D6 by sertraline leading to increased levels of ranitidine, could have been a further potentiating factor in the sertraline-mediated liver injury. As for metoclopramide, it is only considered to be a weak inhibitor of cytochrome P450 2D6.²² Therefore, although contribution from these factors is theoretically possible, this is unlikely to have been of major clinical significance as ranitidine is only a minor substrate of cytochrome P450 2D6.

In summary, sertraline-induced liver toxicity remains rare and is still incompletely understood. Its diagnosis is challenging and

requires the exclusion of other potential causative aetiologies including viral, autoimmune and hereditary liver conditions. A thorough medical history, including a full drug history, is essential in the diagnosis of DILI. The diagnosis of sertraline-induced hepatotoxicity requires a high index of suspicion and awareness of the condition should be raised among all clinicians, in particular psychiatrists and general practitioners. If suspected, discontinuation of the medication is advised while other more common causes are excluded.

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Learning points

- ▶ Acute liver injury from sertraline is a rare entity and can be challenging to diagnose.
- ▶ Increased awareness of this condition is important given the widespread use of sertraline in both the primary care setting and specialist environment.
- ▶ A thorough review of the drug history is a key component in approaching the patient with acute hepatitis.
- ▶ Given that drug-induced liver injury can have significant morbidity and mortality, discontinuation of a potentially hepatotoxic drug should be considered while more common causes are excluded.

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