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Fulminant hepatic failure in association with quetiapine: a case report

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Abstract

Fulminant hepatic failure is a serious disease with significant mortality and morbidity. Identifying the exact cause of hepatic failure and predicting prognosis is of paramount importance in managing such patients. Drug induced liver injury is a common but challenging entity to treat. The use of newer drugs and medications with previously unknown hepatotoxicity add to the challenges, the treating physicians face. Quetiapine is an antipsychotic that has rarely been linked to acute liver injury. In the present case report we describe a case of fulminant hepatic failure secondary to use of quetiapine. A 59-year-old Caucasian female with known Parkinson's disease was being treated with quetiapine for hallucinations. She was referred to our hospital with yellow discoloration of the sclera and later on developed clinical features suggestive of hepatic encephalopathy. The diagnosis of fulminant hepatic failure was made following admission to the intensive care unit. Her condition improved after discontinuing the offending agent and providing the standard supportive treatment. Our case emphasizes the importance of keeping an open mind in cases of fulminant hepatic failure. As drug induced hepatotoxicity is the most common cause of fulminant hepatic failure in many parts of the world, a consideration should be given to the medication(s) patient is receiving as the potential cause and a review of the list should be part of the clinical care.

Keywords

Acute liver injury; fulminant hepatic failure; quetiapine
Introduction

Fulminant hepatic failure (FHF) is defined by the rapid development of severe acute liver injury accompanied by synthetic dysfunction and the development of encephalopathy in an individual with either a previously normal liver or well compensated liver disease [1-2]. Proposed definitions of the time course for fulminant hepatic failure include the development of encephalopathy within eight weeks of the onset of symptoms in a patient with a previously healthy liver [1] or the appearance of encephalopathy within two weeks of developing jaundice, in a patient with or without previous underlying liver dysfunction [2]. Although, FHF can result from a wide variety of causes, drug induced hepatotoxicity are common causing high mortality with estimated 3.5 deaths per million people in the United States alone [3]. The reported short term survival is 49% although the outcome of FHF has significantly improved with the introduction of liver transplantation [4].

Quetiapine (Seroquel®, AstraZeneca) is an atypical antipsychotic agent used to control positive and negative symptoms in patients with psychosis [5]. It has a low side effect profile and is generally well tolerated in doses from 150-750 mg/day [6]. The common known side effects of quetiapine include a mild asymptomatic disturbance of liver enzymes, leucopenia, pancytopenia and thrombotic thrombocytopenic purpura [7-8]. Rarely neuroleptic malignant syndrome, hyperprolactinemia, myoclonus and cardiac arrhythmias have also been reported as adverse effects [9-12]. We describe a case of FHF caused by quetiapine, a rarely reported adverse effect of this drug associated with significant mortality if not identified and treated early [13-15]

Case report

A 59-year-old Caucasian female with a prior history of Parkinson’s disease was on carbidopa-levodopa combination for 3 years and oxazepam along with pramipexole for 6 months
before she developed hallucinations that were attributed to pramipexole therapy. Subsequently, pramipexole was discontinued and the patient was initiated on quetiapine to treat her hallucinations. She had received 6 weeks of quetiapine therapy before presenting to our hospital with the main complaint of feeling unwell for 3 weeks. Her symptoms were accompanied with nausea, vomiting, decrease appetite and abdominal pain for a few days duration. She had also noticed a yellowish discoloration of her sclera but no change in the color of urine or stool. There was no accompanying history of fever, chills or rigors. No risk factors or history suggestive of familial liver disease was provided. She was a non-smoker and denied drinking alcohol.

The general physical examination revealed a stable hemodynamic status with bilateral icterus but no pallor, cyanosis or lymphadenopathy. Abdominal examination demonstrated distention with tenderness in the right upper quadrant but no clinically detectable ascites or hepatosplenomegaly. No other stigmata of chronic liver disease were seen. Cardiovascular and respiratory system examinations were unremarkable. No abnormality was detected on the neurological examination.

Admission blood results showed normal hemogram, normal renal function tests including electrolytes but deranged liver function tests (alanine aminotransferase:71IU/L; aspartate aminotransferase:740IU/L; lactate dehydrogenase:737IU/L; gamma-glutamyl transferase:509IU/L; alkaline phosphatase:196IU/L; total bilirubin:244µmol/L and international normalized ratio of 2.7). Blood ethanol level was in the normal range. Viral serology tests for hepatitis A, B and C were reported as negative. A vasculitic screen was performed which revealed anti-nuclear antibody titer of 1:1600, positive anti ds-DNA but negative anti-liver kidney microsomal antibody. Tests for anti-neutrophil cytoplasmic antibodies showed negative result for anti myeloperoxidase but equivocal for anti-proteinase 3. Normal alpha-1 anti-trypsin levels (1.89 µmol/L) and other immunoglobulins were obtained (IgG: 34 g/L, IgA: 2.44 g/L and IgM: 1.5 g/L). Screening tests for Wilson’s disease and hemochromatosis were also negative.

Ultrasound of the abdomen showed a distended gall bladder with absence of stones and no free fluid in the abdomen. The liver and spleen sizes were reported as within normal ranges. Computerized tomography of the abdomen confirmed the absence of intra-hepatic biliary dilatation.

In view of above findings and history, the patient was admitted with a probable diagnosis of quetiapine induced hepatitis. Quetiapine was discontinued but other medications i.e. carbidopa-levodopa and oxazepam were not stopped. The initial treatment was mainly supportive. However, within 48 hrs of admission, the patient demonstrated signs of encencephalopathy in the form of confusion, astrexis and impaired level of consciousness with the development of significant ascitis. She was subsequently transferred to the intensive care unit and the local liver transplant team was
consulted for probable transplant. After ruling out spontaneous bacterial peritonitis, the patient was treated with lactulose, spironolactone and furosemide. She was also initiated on methylprednisolone 20mg intravenously. Follow up abdominal ultrasound revealed splenomegaly, coarse liver parenchyma and ascitis but no focal lesions or cholelithiasis. The hepatic and portal circulations were patent on Doppler examination. Trans-jugular liver biopsy confirmed extensive confluent and bridging necrosis predominantly in the zone 3. The portal area contained mild to focally moderate mixed inflammatory cellular infiltrate consisting of lymphocytes, macrophage, eosinophils and a few polymorphonuclear cells along the boundaries of necrotic areas. The parenchyma showed variable degrees of hepatocellular degeneration and mild mixed inflammatory cellular infiltrate consisting mainly of lymphocytes and macrophage with few plasma cells and prominent kupffer cells. The overall histopathological picture was reported to be suggestive of an acute hepatitis with confluent and bridging necrosis, suspicious of drug induced liver injury.

The patient's clinical symptoms improved gradually accompanied by improvement in biochemical parameters over the course of her stay in the intensive care unit. The encephalopathy resolved completely with improvement in icterus, nutritional status and oral intake. Later on, she was transferred out of the intensive care unit to the general ward and put on a tapering dose of oral prednisone starting at 40mg/day.

She was discharged home in a stable condition approximately six weeks after the initial admission on 20mg prednisolone per day with a suggested tapering of 5mg every week. She was advised against taking quetiapine in future. Follow up blood results 8 weeks after discharge revealed mildly elevated liver enzymes (less than twice the upper limit of normal) with normal synthetic and excretory hepatic functions.

**Discussion**

Quetiapine is a dibenzothiazepine, an atypical antipsychotic agent that is known to have positive effect on positive and negative symptoms of psychosis [5]. Although its mechanism of action is poorly understood, it is thought to exert its effect through a combination of dopamine (D2) and 5-hydroxytryptamine-2 (5HT2) receptor antagonism. Quetaipine demonstrates a heterogenic antagonist activity in the brain with stronger antagonism of 5HT2 receptors compared to D2. It also have affinities for a range of other neurotransmitter receptors such as serotonin 5HT1a, D1, histamine-1 and adrenergic alpha-1 and alpha-2. It has however, no appreciable affinities for cholinergic muscarinic and benzodiazepine receptors [16]. It is metabolized via the hepatic mixed function oxidase system using the cytochrome P450 3A4 isoenzyme [5]. Quetiapine was considered to be a
non-hepatotoxic drug except for a mild and transient asymptomatic elevation of liver enzymes prior to the first published report of quetiapine induced FHF by El Hajj et al. in 2004 [13].

The most likely etiology of our case was quetiapine induced liver injury. Other possible etiologies such as viral hepatitis A, B and C, metabolic disorders including Wilson’s disease and vascular diseases such as Budd-Chiari syndrome were ruled out. The other diagnosis which is considered with such presentation is of ‘FHF of unknown etiology’ that accounts for 17% of FHF cases [18]. However, the temporal association between the commencement of the medication and the onset of her symptoms strongly indicates the possibility of quetiapine as the culprit agent. The other differential diagnosis that was considered was of autoimmune hepatitis due to the elevated anti-nuclear antibody level found in our patient. However, anti-nuclear antibody elevation is a non-specific finding and can also be seen in drug induced hepatic injury. Moreover, in absence of other serological markers and absence of findings on liver biopsy, an auto-immune etiology is very unlikely. Of note, acute liver injury secondary to autoimmune process or drug toxicity shows response to steroid therapy in both cases. Also, extensive zone 3 predominant necrosis (as seen in our patient) on liver biopsy is seen in drug induced liver injury [19]. Indeed, on the Roussel Ucafl causality assessment method/council for international organizations of medical sciences scoring system our patient scored 7 indicating probable causation of FHF by quetiapine [20-21].

In cases of FHF, the decision for liver transplantation is based on clinical judgment and utilization of prognostic criteria such as the King’s College criteria. For known acetaminophen induced FHF, the criteria include: disease etiology (cryptogenic/toxin), age (<10, >40), duration of jaundice (>1 week before the development of encephalopathy), serum bilirubin concentration of 18mg/dl and INR >3.5, our patient fulfilled only three of these five criteria [22]. Complete resolution except for minimal elevation of liver enzymes was the final outcome in our patient as opposed to mortality in two other cases of quetiapine induced liver injury reported in the literature [13]. One other case reported by Shpaner et al. showed improvement after quetiapine cessation, which may have been due to sub-fulminant rather than [15].

**Conclusion:**

Our case emphasizes the importance of keeping an open mind in cases of fulminant hepatic failure. As drug induced hepatotoxicity is the most common cause of fulminant hepatic failure in many parts of the world, a consideration should be given to the medication(s) patient is receiving as the potential cause and a review of the list should be part of the clinical care.
**Consent:**

The patient’s informed consent was obtained.

**Competing interest**

The authors declare that they have no competing interests.

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