Author's response to reviews

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Version: 2 Date: 30 August 2012

Author's response to reviews: see over
Fulminant hepatic failure in association with quetiapine: case report and literature review.

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Abstract:
Fulminant hepatic failure is a serious disease with significant mortality and morbidity. Identifying the cause of fulminant hepatic failure in managing these patients and predicting the outcome. Drug induced liver injury is a common but challenging entity. New medications and drugs with recently discovered hepatotoxicity require the clinician’s careful attention. Quetiapine is an antipsychotic that has been linked to liver toxicity in very few case reports. In this report we describe a case of fulminant hepatic failure secondary to quetiapine.

A 59 years old Caucasian female with history of Parkinson's disease was treated with quetiapine for hallucinations. Althohe presented to our hospital with jaundice and developed hepatic encephalopathy. The diagnosis of fulminant liver failure was made and she required admission to the intensive care unit. Her condition improved after discontinuing the offending agent and providing supportive treatment.

This case stresses the importance of keeping an open mind in cases of fulminant liver failure. Consideration should be given to drug induced liver injury as the potential cause. The patient’s list of medications needs to be reviewed carefully.

Introduction
Fulminant hepatic failure (FHF) is defined as the rapid development of severe acute liver injury with synthetic dysfunction and the appearance of encephalopathy within eight weeks of the onset of symptoms in a patient with a previously healthy liver [1]. It causes an estimated 3.5 deaths per million people in the United States [2]. Outcome of FHF has significantly improved with liver transplantation. Currently, the reported short term survival is 49% [3].

Quetiapine (Seroquel®, AstraZeneca) is an atypical antipsychotic agent proven to be effective in the control of positive and negative symptoms of psychosis [4]. It has a low profile of side effects and is well tolerated in doses from 150mg/day to 750mg/day [5]. Side effects of quetiapine include: mild asymptomatic disturbance of liver enzymes, leucopenia, pancytopenia and thrombotic thrombocytopenia purpura [6,7]. Neuroleptic malignant syndrome, hyperprolactinemia, myoclonus and cardiac arrhythmias have also been reported as rare adverse effects of quetiapine [8-11]. In this paper we describe a case of fulminant liver failure caused by quetiapine. There have been very few published reports describing hepatic toxicity, a potentially dangerous adverse event [12],[13],[14].

Case report
A 59 year old Caucasian female with 4 years history of Parkinson disease maintained on carbidopalevodopa for 3 years, oxazepam and pramipexole for the last 6 months. Six weeks prior to her presentation she developed hallucinations that were believed to be a side effect of pramipexole. Pramipexole was stopped and she received quetiapine to treat hallucinations. She presented to our hospital with a chief complaint of feeling unwell for 3 weeks. This was associated with nausea, vomiting, decrease appetite and abdominal pain for few days. She also noticed yellowish discoloration of her sclera but no change in the color of her urine or stool. She denied any history of fever, chills or rigors. She had no risk factors nor personal or family history of liver disease. She denied consuming tobacco or alcohol.
On physical examination she was haemodynamically stable. Her skin exam revealed jaundice but no pallor or cyanosis. There was no lymphadenopathy. Her abdomen was distended with tender right upper quadrant, no clinically detected ascites or hepatosplenomegaly, no other stigmata of chronic liver disease. Cardiovascular and respiratory examinations were unremarkable. Neurologically statues was also intact.

Lab investigations showed ALT 71 IU/L, AST 740 IU/L, LD 737 IU/L, GGT 509 IU/L, ALP 196 IU/L and T. Bilirubin 244 µmol/L. Initial INR was 2.7 which increased further during the course of her illness before it went back to normal levels (table 1). Viral serology tests for hepatitis A, B and C were negative. ANA titer was 1:1600, Anti DNA +VE, AMA, ASA and anti KLM were also negative. Anti MPO was negative and anti PR3 was equivocal. Alpha-1 antitrypsine was 1.89 µmol/L, IgG: 34 g/L, IgA: 2.44 g/L, IgM: 1.5 g/L. Screening tests for Wilson’s disease and hemochromatosis were negative. Ethanol level was normal. CBC, renal profile and electrolytes were within normal range.

Ultrasound of the abdomen showed distended gall bladder with no stones and there was no ascitis. Liver and spleen size were both within normal range. CT abdomen showed no intrahepatic biliary dilatation and no liver lesions.

The patient was admitted with suspicion of drug induced hepatitis. Quetiapine was stopped and she was continued on carbidopa-levodopa and oxazepam and managed conservatively. Within 48 hrs she became encephalopathic with confusion, astrexis, decreased level of consciousness and developed significant ascitis. She was transferred to the intensive care unit where she was managed and observed more closely. Liver transplant team was involved in her care and transplant work up was initiated. She did not require ventilator support. Spontaneous bacterial peritonitis was ruled out and blood and urine cultures were negative. Patient was treated with lactulose, spironolactone and furosemide. She was also started on methyprednisolone 20mg intravenously twice daily.

Repeat abdominal US revealed coarse liver parenchyma and ascitis but no focal lesions, cholelithiasis or biliary tree was normal. Her spleen measured 14.2 cm. Doppler studies demonstrated patent hepatic and portal circulation with no evidence of thrombosis. Trans jugular liver biopsy revealed free intrahepatic pressure of 21/13 (18) mmHg, wedge pressure 25/22(23) mmHg and histologically reported as extensive confluent and bridging necrosis predominantly in zone 3. The portal area contained mild to focally confluent mild mixed inflammatory cellular infiltrate consisting of lymphocytes, macrophage, eosinophils and few polymorphs 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 that may contain ceroid. The overall histopathological picture was suggestive of an acute hepatitis with confluent and bridging necrosis, suspicious of drug induced liver injury. (Figure 1)

The patient showed gradual improvement both clinically and biochemically (table 1) while on steroids and off quetiapine (table 1). Her encephalopathy resolved completely. She became less jaundice and her nutritional status and oral intake improved. She was transferred back to the ward and switched to a tapering dose of oral prednisone starting at 40mg/day.

She was discharged home in a stable condition six weeks after admission on prednisone 20mg/day to be tapered at 5mg weekly and advised not to be treated with take quetiapine any more. Further follow up weeks later revealed mildly elevated liver enzymes less than twice the upper limit of normal but.
Nonetheless, she had normal synthetic and excretory hepatic function and was clinically asymptomatic.

Discussion:

Quetiapine is a dibenzothiazepine, an atypical antipsychotic agent that is proven to be effective in the control of both positive and negative symptoms of psychosis [4]. Although its mechanism of action is poorly understood, it is proposed to exert its effects through a combination of Dopamine (D2) and Serotonin (5HT2) receptors antagonism with more affinity to the later receptors. Moreover, heterogenic antagonist activity has also been reported for quatepine including neurotransmitter receptors in the brain. *It has activity on many neurotransmitter receptors including serotonin 5-HT1a and 5-HT2, dopamine D1 and D2, histamine H1 and adrenergic alpha 1 and alpha 2. However, it appears to have no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors* [15].

It is metabolized via the hepatic mixed function oxidase system by the cytochrome P450 3A4 isoenzyme [4], yet, well up to the first case report of possible quetiapine induced subfulminant hepatic failure by El Hajj et al [12], quetiapine seems to otherwise have a safe hepatotoxic record a part from well documented mild and transient asymptomatic elevation of liver enzymes [16]. **The first report of quetiapine induced subfulminant hepatic failure by El Hajj et al in 2004 [12]. Prior to that quetiapine was thought to be safe from a liver standpoint and only cause mild and transient asymptomatic elevation of liver enzymes [16].**

The most likely etiology of this patient’s presentation was quetiapine induced liver injury. Other possible etiologies of FHF including viral hepatitis A, B and C, metabolic disorders such as Wilson’s disease and vascular diseases such as Budd – Chiari Syndrome have all been objectively ruled out. FHF of unknown etiology where all other known causes have been excluded accounts for 17% of FHF cases [17]. This is far less likely to apply to our patient who was on quetiapine, especially in view of the temporal association between the commencement of this medication and the onset of her symptoms. The other differential diagnosis that should be considered for our patient is autoimmune hepatitis, giving the fact that her ANA was elevated and autoimmune hepatitis can present with FHF. However, ANA elevation is not specific and can be seen in drug induced hepatic injury. This is further supported by *Autoimmune hepatitis was less likely without the presence of the absence of other serological markers and or findings of autoimmune hepatitis on liver biopsy (figure 1). Her response to steroids may have complicated the matter and shift the balance towards autoimmune hepatitis but this is again non specific as steroids can still induce remission or clinical response in drug induced liver injury disease.* On the other hand the patient was taken off quetiapine at the same time of initiating steroids and the withdrawal of quetiapine may have been behind the dramatic response in our patient rather than steroids though combination of both is most likely the case. *The extensive zone 3 predominant necrosis seen on liver biopsy supports the diagnosis of drug induced liver injury (figure 1).*

**Drug induced liver injury was supported by putting all the facts together, the clinical presentation, the temporal association between the drug and onset of the symptoms and the evolution of her condition and analyzing the whole case in view of the criteria of drug induced liver disorders** [18]. Furthermore, by applying the Roussel Ucalf causality assessment method/Council for international organizations of medical sciences (RUCAM/CIOMS) scoring system [19,20] our patient scored 7 indicating probable causation of FHF by quetiapine.
In cases of fulminant live failure the decision to consider liver transplantation is based on clinical judgement and utilization of prognostic criteria such as the King’s College Criteria. For none acetaminophen induced FHF, the criteria includes: 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 [21]. Although work up for transplant was initiated it was not needed as she responded very well to withdrawal of offensive drug and possibly the steroids as well as other conservative management. Complete resolution except for minimal elevation of liver enzymes was the outcome in our patient compared to death in two other cases of drug induced liver injury in association with quetiapine reported in the literature [12]. A third case from Texas showed improvement after quetiapine was withdrawn, this may be explained at least in part by the different spectrum of complications that occurs in fulminant versus subfulminant hepatic failure [14].

Conclusion:

This was a case of fulminant hepatic failure secondary to quetiapine that recovered after withdrawal of that agent. Nonetheless, it emphasizes the importance of close clinical monitoring when starting this medication and keeping high index of suspicion when investigating patients with drug induced liver injury.

Consent:

The patient’s informed consent was obtained.

Competing interest

The authors declare that they have no competing interests.

Authors Contribution:

FA analyzed and interpreted the patient data, reviewed the literature and wrote the manuscript. TA was a major contributor in reviewing and writing the manuscript. All authors read and approved the final manuscript.

References:


