Fulminant hepatic failure (FHF) refers to the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver or had well-compensated liver disease. The potential causes of FHF are numerous, but viral or toxin-induced hepatitis are the most common. Clozapine-induced hepatotoxicity has rarely been reported in the literature, occurs via an unknown mechanism and results in liver biochemical abnormalities that are usually of no clinical significance. In approximately 30% to 50% of patients treated with clozapine, there is an asymptomatic rise in serum aminotransaminase levels; however, there are no current guidelines for routine monitoring of liver function tests and liver enzymes during its use. Fatal fulminant hepatitis has only been reported in three patients receiving clozapine. A case of fatal FHF that occurred in a schizophrenic woman who began clozapine therapy shortly before her illness developed is described.

Key Words: Clozapine; Fulminant hepatic failure; Schizophrenia

CASE PRESENTATION

A woman in her fifth decade was examined by the gastroenterology service because of jaundice. She was admitted to hospital under the care of the psychiatry service due to increased delusions and a decreased ability to function independently. She had a history of paranoid schizophrenia with catatonic features and passive-aggressive behaviour. She also had type 2 diabetes and a gynecological malignancy that had been treated surgically one year earlier. Her medications before hospitalization included levothyroxine, risperidone and olanzapine, but she had a longstanding history of poor compliance. She denied having a history of alcohol use, smoking or intravenous drug use. She had no known history of liver disease.

Her regular antipsychotic medications were not continued after hospital admission and she was started on clozapine with the dose titrated from 150 mg daily to 300 mg daily. Baseline laboratory results collected on admission included a normal platelet count, normal liver enzymes and liver function tests. Her predmission laboratory investigations were also normal, including an alanine aminotransferase (ALT) level of 60 U/L and an aspartate aminotransferase (AST) level of 26 U/L (ALT normal at less than 38 U/L). Six weeks after initiation of clozapine, the patient complained of mild nausea and right upper quadrant pain, and was noted to have developed jaundice. She subsequently developed nausea, emesis and anorexia. Her physical examination revealed severe drowsiness with easy rousability and no asterixis. She had a mildly distended soft abdomen with tenderness in the right upper quadrant. There were no stigmata of chronic liver disease. Laboratory results obtained 8.5 weeks after clozapine initiation revealed a white blood cell count of 7.5×10⁹/L, AST 890 U/L, ALT 1668 U/L, direct bilirubin 273 µmol/L, albumin 27 g/L, international normalized ratio 2.9 and creatinine 54 mmol/L. Her clozapine was immediately discontinued. An abdominal ultrasound with Doppler assessment of
Clozapine-induced fatal fulminant hepatic failure

Figure 1) A Liver biopsy stained with hematoxylin and eosin demonstrating hepatocyte necrosis with some periportal sparing, mild chronic inflammation, marked bile stasis and relative preservation of portal to central vein relationships; B High-powered view of a portal triad; C Reticulin stain demonstrating immature fibrosis and collapse of the reticulin framework

DISCUSSION

Clozapine-induced FHF is an uncommon, but recognized, complication of clozapine therapy (2). Well-documented side effects limiting clozapine use include agranulocytosis, seizures, orthostatic hypotension, hypertension and drowsiness. From a gastrointestinal perspective, documented side effects include abnormal liver function tests, constipation, bowel ischemia and ascites (3,4). There have been five cases of clozapine-associated hepatitis reported in the literature (4-7) and, to the best of our knowledge, the present case is only the second documented report of a patient with FHF leading to death as a result of treatment with clozapine (2).

The mechanism of clozapine-induced liver injury is unclear. The drug is metabolized in the liver via the cytochrome P450 pathway. It has been suggested that patients who experience drug-induced hepatitis with any medication may be vulnerable to clozapine-induced acute hepatitis (8). Icteric hepatitis with accompanying nausea has been documented four times and zone 3 necrosis was demonstrated on liver biopsy in one case (7,9). Fulminant hepatitis with encephalopathy and coagulopathy has rarely been reported (2).

It has been suggested that regular monitoring of liver enzymes is not necessary, given that the incidence and risk of serious clozapine-induced hepatotoxicity is low. Approximately 40% of subjects receiving clozapine have ALT or alkaline phosphatase levels twice the upper limit of normal (10,11). Recovery from clozapine-induced hepatitis appears to occur in the majority of patients when the medication is stopped (4). In retrospect, documentation of abnormalities in liver enzymes along with a worsening clinical picture and earlier cessation of clozapine may have prevented the present patient from developing fatal FHF. Therefore, our experience should be of interest to clinicians prescribing clozapine.

IMPLICATIONS FOR CLINICAL CARE

Asymptomatic transaminitis is commonly associated with clozapine therapy. However, caution is advised for patients with elevated liver enzymes who are receiving clozapine because the transaminitis may be the earliest manifestation in the development of FHF. Unfortunately, it is not possible to reliably predict which patients will progress to hepatic failure. Nevertheless, it may be prudent to diligently follow biochemical liver tests in patients receiving clozapine to monitor for early evidence of the development of FHF and possibly death.
REFERENCES