Olanzapine-induced Liver Injury and the Correlation with Body Weight Gain: A Case Report

The liver is the vital organ metabolizing most substances. Hepatocellular, cholestatic, and steatotic injuries are main mechanisms associated with acute liver toxicity. Steatohepatitis may play a rôle in second-generation antipsychotic-induced hepatic decompensation [1]. Here, we present a 43-year-old female patient with schizoaffective disorder, who gained about 18 kg in body weight with liver decompensation after having received olanzapine for nine months.

Case Report

A 43-year-old female patient was hospitalized due to worsening of auditory hallucinations, depressed mood, and suicidal attempts with wrist cuttings. She had neither history of liver disease nor systemic illness. She started alcohol use in her teenage years without further tolerance nor dependence. At the age of 22 years, she developed psychotic symptoms including auditory hallucination, visual hallucination, and persecutory delusion during amphetamine intoxication. In the previous decade, she suffered from waxed and waned psychotic symptoms with abstinence from alcohol and other substances. The main diagnosis was revised as schizoaffective disorder, bipolar type after she developed depressive and manic episodes at the age of 39 years. She ever received various antipsychotic drugs, including risperidone, ziprasidone, aripiprazole, trifluoperazine, and quetiapine in combination with lithium carbonate. Before this admission, she had received olanzapine 20 mg/day, lithium carbonate 900 mg/day, and flurazepam 30 mg/day for nine months. In that period of time, she gained weight from 72.9 kg (body mass index [BMI] = 30.3 kg/m^2) to 91.8 kg (BMI = 38.2 kg/m^2) with increased appetite and chronic fatigue.

Upon evaluation, the patient had liver decompensation and dyslipidemia as serum alanine transaminase (ALT) level was 354 U/L (reference range, 5-40 U/L), aspartate transaminase 193 U/L (0-34 U/L), gamma-glutamyltransferase (GGT) 135 U/L (0-38 U/L), triglyceride (TG) 257 mg/dL (0-200 mg/dL), and low-density lipoprotein 146 mg/dL (0-130 mg/dL). The test for hepatitis B antigen and hepatitis C antibodies was negative. Abdominal ultrasonography reported no hepatomegaly nor cirrhosis.

Under the differential diagnosis of olanzapine-induced liver injury, the patient's olanzapine was discontinued and switched to aripiprazole directly. Due to limited treatment response under aripiprazole 30 mg/day, her antipsychotic drug was finally switched to risperidone at the dosage of 8 mg/day. Her liver function had been gradually improved within two months (Figure 1) and her body weight had also remarkably decreased (Figure 2) as well.

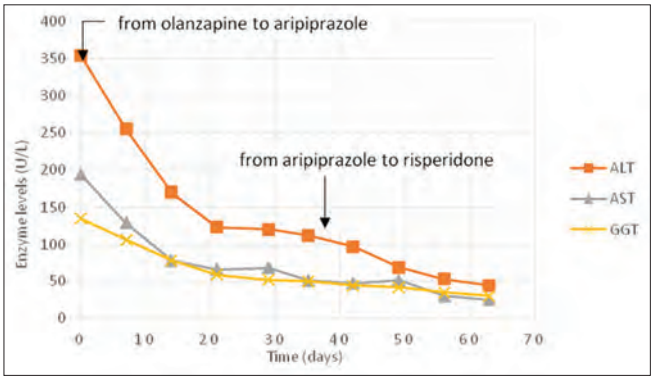

Figure 1. Changes in liver biochemistry during medication adjustment from olanzapine. ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; U/L, units/liter.

Comment

The patient fulfilled the criteria for drug-induced hepatotoxicity in the absences of serological evidence of viral hepatitis, chronic liver disease, and a temporal relation to the antipsychotic medication therapy. We applied the Roussel Uclaf Causality Assessment Method, a scoring system to determine drug-induced liver injury (DILI), to assess the likelihood of olanzapine hepatotoxicity and found a total score of 4, suggesting a possible adverse drug reaction [2, 3].

DILI is classified into three categories: hepatocellular, cholestatic, and steatotic liver injury. Hepatocellular injury accounts for 90% of drug-induced hepatotoxicity with elevated serum ALT; cholestatic liver injury is associated with high serum alkaline phosphate, but only slightly higher serum ALT levels; steatosis is relatively chronic with gradually increased fat accumulation in the liver, especially TG [1].

Among first-generation antipsychotic agents, chlorpromazine-induced liver injuries are mostly reported as cholestasis type. For second-generation antipsychotic drugs, the most related liver injury may follow a primary hepatocellular pattern, whereas atypical antipsychotics induced weight gain with subsequent metabolic changes including insulin resistance and metabolic syndrome, also leading to nonalcoholic fatty liver disease and steatohepatitis [4, 5].

Several case reports exist for olanzapine-induced liver injury. The patterns of serum enzyme elevation range from hepatocellular to mixed or even cholestatic type. The time to onset of liver injury with olanzapine varies widely, from a few weeks to three years. Many cases have shown rapid resolution following olanzapine discontinuation [2, 6].

In our case, the liver injury pattern was more likely to be hepatocellular type according to the profile of liver

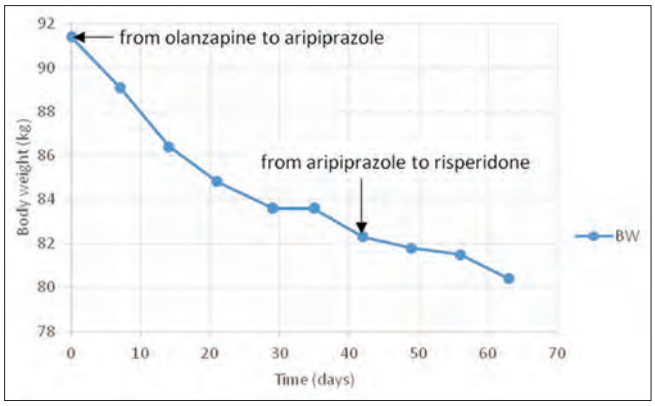

Figure 2. Change in body weight during medication adjustment from olanzapine. BW, body weight; kg, kilograms.

function tests and abdominal sonography. Although weight gain is a risk factor for nonalcoholic fatty liver disease or steatohepatitis, we did not favor these diagnoses due to the absence of hepatomegaly, remarkable fatty liver, acute onset of clinical presentation, or relatively high elevated liver enzyme levels. But the change pattern of body weight after stopping olanzapine use was compatible with that of liver enzymes, implicating the possible relation between weight gain and drug-induced hepatitis (Figures 1 and 2). Even though the rôle of weight gain in second-generation antipsychotic-induced hepatotoxicity is not yet explored, a recent animal study suggested that olanzapine disturbs hepatic lipid metabolism and the increased free cholesterol may be toxic to the liver cells. Furthermore, metabolic changes caused by olanzapine may sensitize the liver to injuries caused through the use of high-fat diet; underlying obesity or liver disease can also aggravate olanzapine-induced side effects [7, 8].

In a newly developed open access website established by the National Institute of Health (http://livertox.nih.gov), the risk of hepatotoxicity induced by medications is categorized in A to E according to all published case reports and case series in the previous decades. In this classification system, olanzapine was listed in categories B (12-49 of reported cases), risperidone in categories C (4-11 cases), and aripiprazole in categories E (no convincing reports) [9]. In our patient, we first switched olanzapine to aripiprazole considering the risk of liver injury [1, 9] and metabolic change [10]. As shown in Table 1, risperidone could be regarded as a compromise choice in clinical efficacy and side effect [1,9,10].

In summary, baseline laboratory testing including liver function tests and metabolic profiles is recommended before starting an antipsychotic agent. If serum ALT levels are elevated three times more than the upper limit during antipsychotic use, drug-induced liver damage should be considered, and the psychotropic agent is suggested to be reduced or switched to another with low hepatotoxicity. Our case implies that rapid weight gain may be associated with possible hepatotoxic effects of atypical antipsychotics.

Table 1. Comparison of categorization of implicated liver injury, mechanism of hepatotoxicity, and likelihood of weight gain between atypical antipsychotics

Drug	Categorization of implicated liver injury	Mechanism of hepatotoxicity	Likelihood of weight gain
Clozapine	B (12-49 cases)	Immunoallergic, chronic steatosis	High
Olanzapine	B (12-49 cases)	Immunoallergic, chronic steatosis	High
Risperidone	C (4-11 cases)	Immunoallergic, chronic steatosis	Moderate
Quetiapine	C (4-11 cases)	Unspecified	Moderate
Ziprasidone	D (1-3 cases)	Unspecified	Low
Aripiprazole	E (no convincing reports)	Unspecified	Low

Adapted from the work of Diogo TC et al. 2017 [1], Slim M et al. 2016 [9], and Dayabandara M et al. 2017 [10]

(This case report was approved by the institution review board of Taoyuan Psychiatric Center for publication (protocol number = R20191111-2, date of approval = November 18, 2019). Written informed consent from the patient was obtained for the purpose of publication.)

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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