

Aripiprazole-induced Hepatitis: A Case Report

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Aripiprazole is an atypical antipsychotic that acts as a partial agonist of dopamine type 2 receptors as well as 5-HT_{1A} receptors. It is used in the treatment of schizophrenia and in type 1 bipolar disorder for mania. Because aripiprazole is well tolerated with few side effects it is used off-label in other psychotic disorders. The prevalence of abnormal liver function tests with antipsychotic use is 32%, with clinically significant effects in 4% of cases. No cases of aripiprazole-induced liver injury have been published. We report a 28-year-old female who presented with non-affective first-episode psychosis and who was treated with aripiprazole. Initially she was medicated with 10 mg per day, with an increase to 20 mg per day on the 12th day of hospitalization. Nine days after she became icteric, with nausea and had a vomiting episode. Laboratory analysis revealed a very high level of alanine aminotransferase, and minor to moderately high levels of aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and bilirubin. Aripiprazole was tapered and paliperidone was started with the improvement of clinical and laboratory findings.

KEY WORDS: First-episode psychosis; Psychosis; Aripiprazole; Transaminases; Hepatitis.

INTRODUCTION

Aripiprazole is an atypical antipsychotic drug that has a unique pharmacological profile. It acts as a partial agonist at D₂ receptors as well as serotonin 5-HT_{1A} receptors, together with antagonism at serotonin 5-HT_{2A} receptors [1]. Aripiprazole binds with high affinity to D₂ receptors with a lower level of intrinsic activity. Aripiprazole has been primarily used in the treatment of schizophrenia and in type I bipolar disorder for mania [2]. In addition to its antipsychotic and antimanic properties, the unique profile of aripiprazole provides high tolerability, potential preservation of cognitive functions, and subjective well-being [2]. The most commonly reported adverse effects at recommended doses (10–30 mg per day) include restlessness, sedation, extrapyramidal symptoms, blurred

vision, headache, fatigue, and nausea [3]. Atypical antipsychotics rarely induce severe liver toxicity. For all antipsychotics the mean percentage of patients with abnormal liver function tests is 32%, of which 4% are clinically significant (greater than three times the upper limit of normal alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma-glutamyltransferase [GGT] levels, and greater than two times the upper limit of normal alkaline phosphatase [ALP] levels) [4]. Chlorpromazine is the most common antipsychotic associated with severe toxicity [5]. To the best of our knowledge we report the first case of a patient with a psychotic disorder treated with aripiprazole who experienced toxic hepatitis. Written informed consent to publish this case was obtained from the patient.

CASE

A 28-year-old black female, with no previous psychiatric history, was admitted at the emergency department with persecutory and reference delusions that began two weeks before admission. She had also Capgras delusion, the patient had the idea that her brother was replaced by an identical impostor. Upon initial evaluation, the patient

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was anxious, suspicious, and claimed that some people were following her, including at the hospital. There were no known medical diseases. There was a history of cocaine inhaled use since she had 26-year-old, on average one line inhaled once per month. There was no history of other drug use, including alcohol. Physical and neurological examinations were normal. Psychiatric family history was unremarkable. Positive and Negative Symptom Scale (PANSS) revealed a score of 15 for the positive subscale, 7 for the negative subscale and 31 for the general psychopathology subscale. Routine laboratory tests on admission revealed no significant abnormalities, including negative urine toxicology and hepatitis B and C serologies. Electrocardiogram showed no significant alterations. According to her clinical presentation and investigations, the patient was provisionally diagnosed with brief psychotic disorder according to the criteria of Diagnostic and Statistical Manual of Mental Disorders 5th edition [6].

The patient was admitted into the Psychiatric Department and started aripiprazole on a dosage of 10 mg per day and lorazepam 2.5 mg three times per day. During hospitalization the patient underwent cranial magnetic resonance imaging and an electroencephalogram with normal results. After 12 days of treatment the patient maintained reference delusions and the dosage of aripiprazole was then titrated to 20 mg per day, with a significant improvement on few days. On the 21st day of hospitalization the patient became nauseous and had one vomiting episode. Sclerotic jaundice was revealed on observation. Laboratory tests showed AST levels of 176 U/L, ALT 745 U/L, GGT 437 U/L, ALP 224 U/L, total bilirubin 1.14 mg/dl, direct bilirubin 0.79 mg/dl, and C-reactive protein (CRP) 0.66 mg/dl. Hepatitis A serology was negative. An abdominal ultrasonography did not detect any significant changes.

Aripiprazole was discontinued and paliperidone was started and titrated until reaching 6 mg per day. Lorazepam 2.5 mg three times per day was maintained. Close monitoring of liver laboratory results was carried out and a progressive normalization of the clinical picture and hepatic parameters was seen.

The patient was discharged after 35 days of hospitalization with a significant improvement in her psychiatric symptomatology. On discharge she scored on the PANSS scale, 9 on the positive subscale, 7 on the negative subscale, and 18 on the general psychopathology subscale.

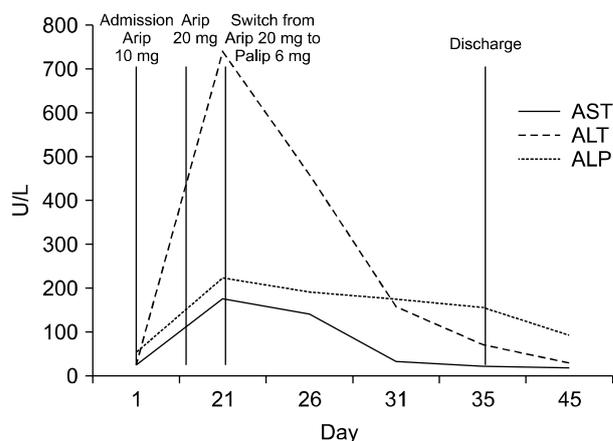


Fig. 1. Line graphic showing the evolution of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) over time. Arip, aripiprazole; Palip, paliperidone.

On discharge, liver function tests revealed AST levels of 22 U/L, ALT 72 U/L, ALP 155 U/L, GGT 252 U/L, total bilirubin 0.49 mg/dl, and direct bilirubin of 0.30 mg/dl. The patient is currently undergoing follow-up treatment at our outpatient clinic and maintains the remission of psychotic symptoms. Laboratory liver parameters on ambulatory tests showed complete normalization of all values. Figure 1 shows the patient liver function tests (ALT, ALT, and ALP) over time.

DISCUSSION

We describe a case report of a young female, with no previous psychiatric history, with non-affective first-episode psychosis. She was treated with aripiprazole 10 mg per day and titrated to 20 mg per day based on partial clinical response. Some days after, she developed a clinical picture characterized by nausea, vomiting, and jaundice. Laboratory results revealed high levels of AST, ALT, GGT, ALP, CRP, as well as total and direct bilirubin. Aripiprazole was switched to paliperidone with improvement in clinical and laboratory findings.

Atypical antipsychotics rarely induce severe drug-induced liver injury. The most common is asymptomatic elevation of the levels of the aminotransferases and bilirubin [4]. Severe drug-induced liver injury is rare. Clozapine is the atypical antipsychotic most associated with drug-induced liver abnormalities [7,8]. Drug-induced liver injury has also been reported with other atypical antipsychotics

such as risperidone [9,10], quetiapine [11,12], olanzapine [13,14], and ziprasidone [15]. Amisulpride and aripiprazole are atypical antipsychotics with lower rates for drug-induced liver injuries [5].

This is the first case report referring to a severe case of hepatic toxicity due to aripiprazole on usual doses. Despite the good tolerance and few side effects of aripiprazole, several case reports have revealed some rare, but relevant, side effects of the drug, including tardive dyskinesia [16], neuroleptic malignant syndrome [17], acute dystonia [18], parkinsonism [19], hypersexuality [20], priapism [21,22], neutropenia [23], skin rash [24], hypertension [25], hyperlipidemia [26], hypersensitivity pneumonitis [27], Raynaud's phenomenon [26], hyponatremia [28], and sialorrhea [29].

With the exceptions of sulpiride, amisulpride, and paliperidone, the majority of antipsychotics are hepatically metabolized via the cytochrome P450 system (CYP) [30]. CYP2D6 and CYP3A4 are the enzymes that metabolize most antipsychotics, although clozapine and olanzapine are metabolized via CYP1A2. The variability of the risk of induced liver injury is determined by the relative importance of CYP enzyme isoforms for the metabolism of different antipsychotics leading to different interactions and pharmacogenetic influences [30].

There are three major mechanisms through which antipsychotics can be associated with liver injury: hepatocellular, cholestatic, and via nonalcoholic fatty liver disease [4]. The most frequent drug-induced hepatotoxicity is hepatocellular injury which is responsible for approximately 90% of liver injuries. In this case the antipsychotic metabolites have a direct toxic effect on hepatocytes [5,31]. It is associated with very high serum ALT and with a smaller or even no increase of ALP. The second mechanism is the impairment of bile secretion leading to cholestasis by antipsychotics or their metabolites [31]. This cholestatic category liver injury is associated with high levels of ALP with only slightly higher levels of ALT. The third mechanism is injury to the liver via an increased risk of metabolic syndrome leading to nonalcoholic fatty liver disease [32]. In our patient, we believe that the hepatocellular mechanism was the major cause, given the very high levels of ALT (22.5 times the normal upper limit) and moderate or minor levels of AST (greater than five times the upper limit), ALP (more than two times), and GGT (more than eleven times).

As mentioned, the patient has inhaled cocaine use for 4 years with a mean average use of one time per month. Cocaine has possible hepatotoxic effects [33]. On this patient this theoretical cause for the liver injury is quite implausible. There was a temporal relationship with the aripiprazole use, with no previous signs or symptoms of liver injury before its use.

There are no established guidelines for the management of preventive and therapeutic strategies concerning antipsychotic-induced liver injury. Some authors recommend evaluating liver function before starting antipsychotics [34,35]. If there is evidence of liver injury, weekly monitoring of liver function should be carried out, together with the use of lower doses of antipsychotics, or those with minimal hepatic metabolism (e.g., amisulpride) [36]. If there are no abnormalities shown by these tests then annual monitoring of liver function for all patients taking antipsychotics is sufficient. The only exception is for those patients taking clozapine, when it is advisable to test every six months [36]. More frequent monitoring is needed for patients with high use of alcohol or other substances [4]. If liver tests become altered after starting antipsychotics (e.g., aminotransferase greater than three times the normal upper limit or ALP greater than two times the upper limit of normal), assessment for signs of hepatic disease should be conducted and either discontinuation of the medication or referral should be considered [37]. For minor abnormalities on liver tests below the referred thresholds, antipsychotic discontinuation is not required but monitoring is advisable [4]. Our patient presented with severe changes, specifically for ALT, which was greater than 22.5 times the upper limit of normal values. As a result of this, we decided to switch to paliperidone, which is not metabolized via CYP and safe to use in liver injury patients. This change of medication resulted in a progressive normalization of liver function tests.

In conclusion, this is the first report of aripiprazole-induced liver injury, in this case, hepatitis. Despite good tolerance and few side effects, aripiprazole can also lead to severe drug-induced liver injury. We along with other authors suggest that it is necessary a precaution to monitor liver function in patients with known hepatic disease or using other drugs that could provoke liver injury (such as alcohol), before starting atypical antipsychotics and on a regular basis thereafter.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Ricardo Coentre. Data acquisition: Lígia Castanheira, Elsa Fernandes. Writing—original draft: Lígia Castanheira, Elsa Fernandes, Ricardo Coentre. Writing—review & editing: Lígia Castanheira, Elsa Fernandes, Pedro Levy, Ricardo Coentre.

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