# Hepatotoxicity to Risperidone

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The liver is the organ responsible for the metabolization of multiple drugs, among them psychotropic drugs. Drug-induced hepatotoxicity is an important and prevalent clinical problem worldwide, and with the growth in new prescriptions and over-the-counter drugs, it is one of the primary reasons for the failure of new drug candidates.[1]

Drugs can produce hepatotoxicity and other side effects by different reactions that can be divided into type A intrinsic reactions, which are dependent and predictable, and type B idiosyncratic reactions, which are unanticipated, not strictly dose dependent, and generally detected in postmarketing of approved medications.[2,3]

Hepatotoxicity is characterized by the elevation of serum liver enzymes, with or without an increase in bilirubin, defined as alanine aminotransferase (ALT) 5 times above the upper limit of normal, alkaline phosphatase (ALP) 2 times above the upper limit of normal, or ALT 3 times above plus bilirubin 2 times above the upper limit of normal.[1,4]

There are 3 main subtypes of liver damage: hepatocellular injury when the ratio of ALT to ALP is superior to 5 (characterized by cellular necrosis and inflammation, clinically presenting with malaise and exhaustion), mixed injury when the ratio is between 2 and 5 (combines features of both the hepatocellular and cholestatic patterns), and cholestatic injury when it is below 2 (results from the accumulation of bile in the hepatocytes due to insult to the bile ducts).[4]

Psychiatric patients represent a particular population in the sense that they often have multiple comorbidities such as alcoholism and drug abuse and are often polymedicated, which are factors that increase the incidence of liver disorder. Additionally, a significant percentage of psychiatric patients already have known liver disease with reduced hepatic reserve, making them more vulnerable to drug-induced hepatotoxicity, with severe consequences for their heath.[1,4] Liver failure can interfere with different stages of drug pharmacokinetics, affecting drug concentrations, duration of action, and effectiveness, which can lead to complex clinical management problems.[1]

Risperidone is an atypical antipsychotic metabolized by the liver via cytochrome P450 isozyme 2D6 to an active metabolite, 9-hydroxyrisperidone. It can also cause mild and transient serum enzyme elevations in up to 30% of patients on long-term therapy. Acute liver injury is an uncommon side effect. There are currently, to our knowledge, 10 cases of acute liver injury described in the literature.[5,6] This case report details the clinical course of a patient with schizophrenia who developed a likely risperidone hepatocellular hepatotoxicity.

## Case Report

A 44-year-old woman with a diagnosis of schizophrenia and no past medical history was admitted to an inpatient psychiatric unit after an exacerbation of mental illness in the community, secondary to medication nonadherence. The patient was admitted due to disorganized behavior associated with persecutory delusions, such as violence toward her neighbors, cutting the electric cables of her building, and starting bonfires inside her apartment. On psychiatric examination, she presented disorganized speech with derailment, auditory hallucinations, kinesthetic hallucinations, and passivity experiences. There was an impairment in social and occupational function.

The patient had been previously hospitalized 2 times in the last 15 years, the first time with a first episode of psychosis and the second time due to psychotic symptoms associated with substance use disorder including alcohol and cocaine. The patient had a history of multiple substance abuse, including alcohol, inhaled cocaine, and marijuana for a period of 5 years, ceasing the substance use during the last hospitalization (9 years ago). Current abstinence was confirmed by a urine toxicology screen, indicating that cocaine, marijuana, alcohol, or any other illicit substance were not present in her urine.

She was committed to the hospital involuntarily under the Portuguese Mental Health Law. Upon admission to the inpatient psychiatric unit, screening examinations were performed. The electrocardiogram showed no significant alteration, and the blood analysis had no alterations, with an ALT of 19 U/L, AST of 20 U/L, γ-glutamyltransferase (GGT) of 16 U/L, lactic acid dehydrogenase (LDH) of 145 U/L, and polymerase chain reaction (PCR) of 0.040 mg/dL.

She was treated with risperidone, with slow dose titration (from 2 mg on day 1 to 10 mg by day 10 of the hospitalization) to avoid intolerance and side effects that could compromise future adherence to treatment. Chlorpromazine in low doses (75 mg a day) was added on day 6 due to psychomotor agitation and then slowly reduced at day 9 of hospitalization to 25 mg a day and stopped on day 11.

On day 14, the patient started feeling malaise, exhaustion, and nausea, with diffuse abdominal pain and no appetite. The blood analysis indicated an ALT concentration

increase to 1,483 U/L and an AST concentration increase to 658 U/L, GGT of 97 U/L, PCR of 8.39 mg/dL, and bilirubin values within normal limits. An abdominal echography was done with no alterations.

Internal medicine consultation was made, and the clinical hypothesis of toxic hepatitis likely due to medication was proposed, followed by suspension of risperidone 10 mg. The next day, the ALT and AST concentrations decreased to 735 U/L and 153 U/L, respectively. The gastrointestinal symptoms presented by the patient also improved, with a resolution of abdominal pain and exhaustion. The patient still presented nausea and decreased appetite for the next 3 days. In the following 15 days, the hepatic markers decreased and normalized. Other atypical antipsychotic medication was introduced.

## Discussion

Medications commonly used in psychiatry account for a significant portion of those implicated in hepatotoxicity. They are the second most important group of pharmacology agents that can cause hepatotoxicity, implicated in 16% of drug-induced hepatotoxicity.[1] Antipsychotics are some of the most prescribed drugs in psychiatry, so understanding their possible effects on the liver is crucial for safer prescriptions.

The reaction presented by our patient was referred to the Portuguese Drug Monitoring System, and the connection of risperidone to the reaction was considered likely. Precautions in the use of antipsychotics in clinical practice are advised, and regular blood analysis should be performed to evaluate for possible side effects.

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