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A case report on hepatotoxicity associated with haloperidol

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Abstract

A 55-year-old male with a decade-long history of schizophrenia had severe psychotic symptoms and was prescribed haloperidol. Three weeks later, he began experiencing signs of liver malfunction, such as dark urine, exhaustion, nausea, and moderate right upper quadrant abdominal discomfort, which was accompanied by jaundice. Laboratory studies revealed high levels of AST, ALT, ALP, and total bilirubin in the liver. Tests for viral hepatitis and autoimmune markers were negative, and an abdominal ultrasound revealed no evidence of biliary blockage. In Drug Induced Liver Injury (DILI), the Roussel Uclaf Causality Assessment Method (RUCAM) assigns points for clinical, biochemical, serologic, and radiologic features of liver injury, resulting in a comprehensive assessment score that reflects the possibility that the hepatic injury was caused by a specific medication.

Keywords: Haloperidol, RUCAM, Hepatotoxicity

Introduction:

From a regulatory standpoint, Drug-Induced Liver Injury (DILI) is the primary reason for removing drugs from the market or imposing warnings and usage changes. DILI can be classed as predictable or unpredictable (idiosyncratic). Predictable instances frequently demonstrate

dose-dependent patterns with a short onset period (days) caused by the drug's or its metabolites' direct toxicity. [1-2]

A wide range of pharmaceuticals, comprising anaesthetics, anticancer treatments, antibiotics, antituberculosis agents, and antiretrovirals, in addition to various traditional and herbal remedies, can cause liver damage. Drug-Induced Liver Injury (DILI) includes an array of manifestations, which are characterized depending on the duration of injury and histological patterns as acute or chronic, hepatitis, cholestatic, or a mixed pattern of injury. [3]

Hepatotoxicity with antipsychotics, particularly phenothiazine derivatives like chlorpromazine, is rare and occurs at a rate of 1 in every 500 people. Significant elevations in liver enzyme test findings take place at a low rate (4%; range, 0-15%), and the emergence to hepatotoxicity is uncommon. Antipsychotics have been linked to minor and clinically inconsequential liver enzyme increases in 32% of patients (range: 5%-78%).[4]

We present a rare instance of hepatotoxicity related with haloperidol use. Haloperidol, a member of the Butyrophenone family, works as a first-generation antipsychotic. One of its most noticeable symptoms is the initiation of Extra Pyramidal Symptoms (EPS), which include movement disorders, for instance, dystonia, akathisia, tardive dyskinesia, and Parkinsonism. Antipsychotic prescription drugs are considered to block central dopamine D2 receptors, causing the start of EPS.[4]

Table 1 Dose of medications with chronological liver function test values

Time	Bilirubin (mg/dl)	SGOT (U/L)	SGPT (U/L)	ALP (IU/L)	GGT (U/L)	HALOPERIDOL (mg)	THP (mg)
8 week before Haloperidol started	0.2	28	40	80	19		
0	0.3	30	45	85	23	5 mg	2 mg
2 weeks	5	1211	1990	160	165	15 mg	2 mg
2 weeks 2 days	7.2	1075	1179	178	149	Withdrawn	Withdrawn
5 weeks	8.6	65	266	108	69	None	None
8 weeks	1.9	90	89	80	42	Restart	
9 weeks	1.3	81	90	75	41	10 mg	2 mg
10 weeks	2	94	111	99	42	10 mg	2 mg
11 weeks	2.2	99	115	95	40	15 mg	2 mg
Next day						Withdrawn	Withdrawn

We present a rare instance of hepatotoxicity related with haloperidol use. Haloperidol, a member of the Butyrophenone family, works as a first-generation antipsychotic. One of its most noticeable symptoms is the initiation of Extra Pyramidal Symptoms (EPS), which include movement disorders, for instance, dystonia, akathisia, tardive dyskinesia, and Parkinsonism. Antipsychotic prescription drugs are considered to block central dopamine D2 receptors, causing the start of EPS.[4]

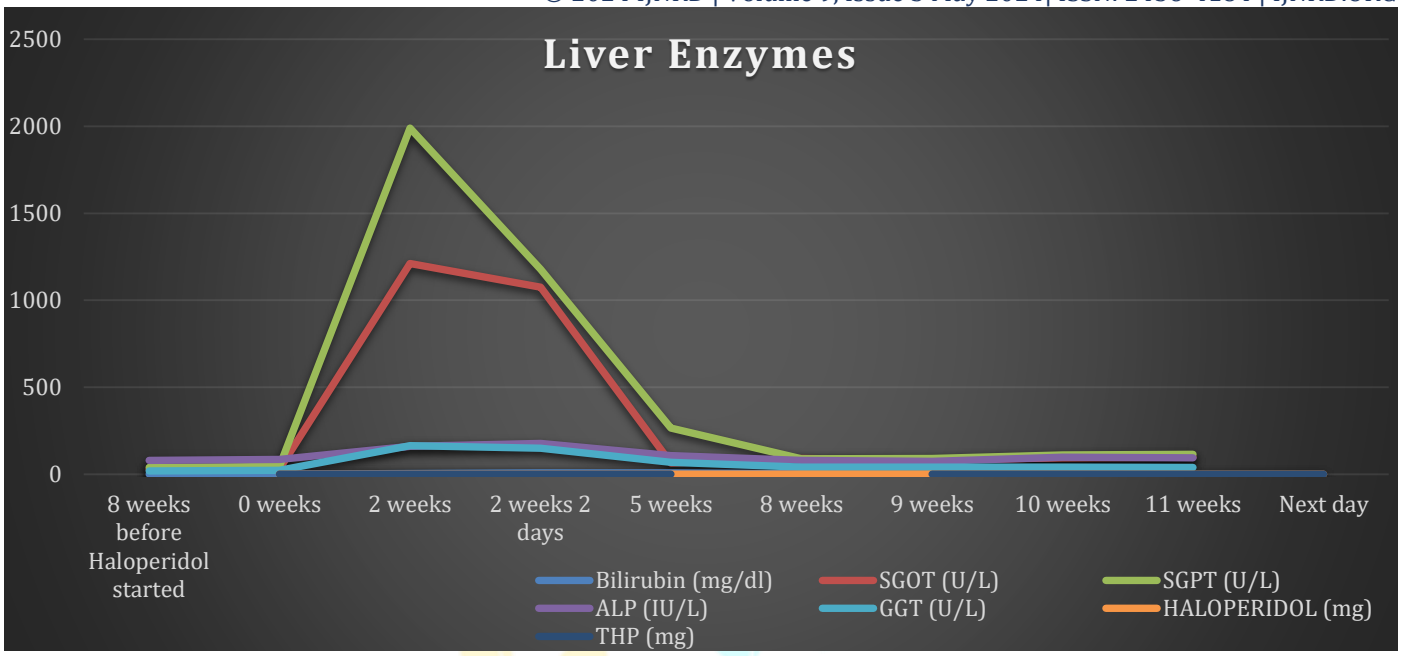

Figure 1: Graphical representation of liver enzymes

CASE PRESENTATION

A 55-year-old male with schizophrenia and a 10-year history of disease presented with deteriorating psychotic symptoms, including hallucinations and delusions. Upon admission, the patient was initially prescribed Olanzapine, subsequent to the diagnosis of paranoid schizophrenia. He refuted any record of alcoholism, illegal drug usage, or chronic liver disease. Following an appropriate trial and no improvement in symptoms, Risperidone was tried, but it also had a poor response.

The patient was started on Haloperidol at 5 mg and gradually increased to 15 mg BD (twice daily) over courses of action of two weeks. Although his psychotic symptoms improved, the patient developed jaundice (yellowing of the skin and sclerae), low appetite, lethargy, nausea, black urine, and mild right quadrant stomach discomfort by the second week. He denied experiencing fever, chills, or a loss of appetite.

In liver function tests, higher Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (GGT), alkaline phosphate (ALP), and bilirubin were all observed. The viral hepatitis serologies (A, B, and C) were negative, as were the autoimmune markers. Abdominal ultrasonography showed no evidence of biliary blockage.

At this moment, the patient was taking Haloperidol 15 mg and Trihexyphenidyl 2 mg. The patient had no prior diagnosis of chronic liver disease (CLD), and the baseline Liver Function Test (LFT) was within normal limits. All of his drugs were stopped over the next two weeks, and his LFT returned to normal, but his schizophrenia worsened and became unruly on the ward at times.

Because of his positive reaction to Haloperidol and an unsatisfactory reaction to Olanzapine and Risperidone, the patient was restarted on Tablet Haloperidol, starting at 5 mg and escalating to 15 mg over two weeks. Over the next two weeks, his LFT was calculated weekly; nevertheless, by the end of the second week, his liver enzymes began to rise again, requiring him to discontinue Haloperidol; he was then started on Tablet Aripiprazole, and he is currently doing better.

RUCAM (Roussel Uclaf Causality Assessment Method), formerly referred to as CIOMS (Council for International Organisations of Medical Sciences), is a widely accepted tool for quantitatively assessing causality in cases of suspected drug-induced liver injury (DILI) and herb-induced liver injury (HILI). RUCAM is a structured, standardised, validated,

hepatotoxicity-specific diagnostic technique that assigns scores to particular important items, resulting in final quantitative gradings of causation for each suspect drug/herb in a case report. [5]

RUCAM was introduced in 1993 and is currently frequently utilized in determining the causality of drug-induced liver injury, both in the published literature and in support of regulatory decisions regarding drugs involved in hepatic injury [6]. Using RUCAM in our patient, the total score was 7, (0 or less indicates that the drug is "excluded" as a cause; 1 to 2 indicates that it is "unlikely"; 3 to 5 "possible"; 6 to 8 "probable"; and greater than 8, "highly probable"), indicating that Haloperidol is the most likely cause of our patient's deranged liver function [Table 1].

DISCUSSION

Mr. Y had developed clinical jaundice two weeks after starting Haloperidol. Any neuroleptic, including haloperidol, can cause asymptomatic changes in liver function. Liver damage caused by hepatic Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), or Glutamate Dehydrogenase (GDH) elevations, besides cholestatic Alkaline Phosphatase (ALP) and bilirubin elevations, has been described.

GLDH is found in the mitochondria of liver cells, and an increase in its levels in the blood is associated with liver cell injury. Serious liver cell damage is well studied and characterized in Chlorpromazine medication, which affects around 1% of individuals. Despite the fact that some case reports have been reported, the incidence of liver impairment caused by antipsychotics such as Haloperidol is extremely low.

The precise mechanism of haloperidol-induced hepatotoxicity remains unknown. It is thought to be idiosyncratic (unpredictable), with either direct hepatotoxicity or immune-mediated causes. The incidence is considered to be quite low, at roughly 0.002% [7]. In most cases, it has been stipulated that such rise of liver enzymes is a benign event, and that discontinuing antipsychotics is rarely necessary, with careful monitoring until transaminases approach 100 U/L [Figure 1].

Björnsson attempted to categorize drugs based on their likelihood to produce liver damage. [8] This classification is established on the basis of published case reports of particular medications and has five categories (category A, 50; category B, 12-49; category C, 4-11; category D, 1-3; category E, none). Haloperidol is classified as category B, with 25 case reports as of May 2015, none of which caused fatalities or re-challenges [8].

In a case reported by Fuller et al. [9], a patient diagnosed with schizophrenia presented with symptoms of anorexia, nausea, vomiting, lethargy, fever, and lower extremities rash 5 weeks after starting Haloperidol. His total bilirubin level was 4.2 mg per 100 ml, with SGOT at 100 IU per litre and SGPT at 130 IU per litre. Following withdrawal of Haloperidol, examination revealed a widespread red erythematous macular rash across the lower limbs and palms. On examination of the abdomen, there was minor pain in the right upper quadrant but no liver or splenic enlargement.

The pathological view after liver biopsy was that the alterations represented a hypersensitive reaction, primarily cholestatic but possibly hepatocellular. All symptoms vanished in a few weeks, and liver function tests returned to normal [9]. In another example, Fuller et al documented a 25-year-old female who developed jaundice four weeks after starting Haloperidol at a dose of 10 to 15 mg. After a thorough examination, medication Haloperidol-

induced intrahepatic cholestasis was discovered. After four weeks of stopping Haloperidol, her liver function test recovered to normal [9].
Dincsoy and Saelinger observed malaise, fever, jaundice, widespread pruritus, unexplained abdominal pain, and dark urine in a 16-year-old male after starting haloperidol for 5 weeks. The combination of hepatic dysfunction, jaundice, and eosinophilia that developed 5 weeks following haloperidol and benztropine mesylate therapy in this patient was highly indicative of a drug-induced hypersensitivity reaction [10].
In our case, symptoms appeared after two weeks of using Haloperidol, which corresponds to the latent period mentioned in earlier case reports. Also, the drop in liver enzymes within two weeks of discontinuing Haloperidol is consistent with earlier case reports. The unique aspect in our instance is an increment in liver enzymes within one week of re-challenge, albeit continuance beyond that period is ethically unacceptable, therefore re-challenge up to the prior dose and duration was not possible. Nonetheless, symptoms of positive re-challenge with objective proof by RUCAM are sufficient to consider Haloperidol as the causative agent for our patient's abnormal liver function tests.
This instance emphasizes the necessity of monitoring liver function tests in haloperidol patients, particularly during the early stages of treatment. Early identification and withdrawal of the medication can help prevent serious liver damage.

CONCLUSION

This case report highlights an uncommon but potentially serious consequence of haloperidol medication. Although it is uncommon, doctors should be aware of haloperidol-induced hepatotoxicity and follow patients for any signs and symptoms of liver impairment.

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