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Case Report

Hepatotoxicity induced by clozapine: Case report and brief review



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ABSTRACT

Introduction: Antipsychotics are drugs that can produce transient elevations of hepatic enzymes. Clozapine is an atypical antipsychotic used in treatment-resistant schizophrenia and there is evidence that it can produce elevations of hepatic transaminases, expression of liver damage in a hepatocellular pattern.

Methods: Case report and non-systematic review of the relevant literature.

Case presentation: A 39-year-old woman with a diagnosis of paranoid schizophrenia attended the emergency department of a general hospital for nausea, vomiting and jaundice that appeared after the initiation of clozapine. There was no clinical improvement during hospitalisation, and death occurred after 44 days.

Literature review: Clozapine can increase the liver enzyme levels transiently and asymptotically; however, there are clinical criteria that recommend the withdrawal of the antipsychotic.

Conclusions: This is the third case reported in the literature of a fatal outcome of clozapine-induced hepatotoxicity.

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Hepatotoxicidad inducida por clozapina: reporte de caso y revisión breve de la literatura

RESUMEN

Palabras clave:

Enfermedad hepática inducida por medicamento

Antipsicóticos

Evento adverso

Introducción: Los antipsicóticos son medicamentos que pueden producir elevaciones transitorias de las enzimas hepáticas. La clozapina es un antipsicótico atípico usado en el tratamiento de la esquizofrenia refractaria a los antipsicóticos convencionales y existe evidencia que puede producir elevaciones de las transaminasas hepáticas, expresión de daño hepático con patrón hepatocelular.

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Métodos: Reporte de caso y revisión no sistemática de la literatura relevante.

Presentación del caso: Una mujer de 39 años con diagnóstico de esquizofrenia paranoide acudió a un servicio de urgencias de un hospital general por náuseas, vómitos e ictericia que apareció tras el inicio de clozapina. No hubo mejoría clínica de la paciente durante la hospitalización, que falleció a los 44 días de su ingreso.

Revisión de la literatura: La clozapina puede elevar las cifras de función hepática de manera transitoria y asintomática. Hay criterios clínicos para recomendar la suspensión de este antipsicótico.

Conclusiones: Este caso es el tercero en la literatura que registra un desenlace fatal tras un cuadro de hepatotoxicidad inducido por clozapina.

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Introduction

Clozapine is an atypical antipsychotic used preferentially in treatment-resistant schizophrenia.¹ It is reserved for this purpose because of its risk of agranulocytosis (absolute neutrophil count <500/ μ l), which has a prevalence of around 0.7%,² conditioning its use to be monitored with periodic blood cytology controls.

In general, all antipsychotics can raise hepatic enzymes. Of the typical antipsychotics, chlorpromazine is most commonly associated with hepatotoxicity.³ In this case, the injury type is cholestatic (decreased bile flow, which in this case does not imply any kind of obstruction).⁴ Within the atypical group, clozapine is the drug most associated with hepatotoxic effects.⁵ Up to 60% of patients have raised liver transaminases and 15%–30% have elevations up to two to three times the normal value.⁶ These elevations are often transient and asymptomatic, but there are cases in which clozapine-induced hepatotoxicity can be severe, as reported in different case series.³

The following case describes a woman with a diagnosis of paranoid schizophrenia who was admitted to an accident and emergency department for nausea, vomiting and jaundice, apparently triggered by clozapine, and who unfortunately had a fatal outcome due to hypovolemic shock. Due to the scarcity of records in Spanish on clozapine-induced hepatotoxicity, this report and review of the literature is relevant.

Case report

This concerns a 39-year-old woman, diagnosed with paranoid schizophrenia four years prior and with no family psychiatric history or drug use. Relevant medical history included abdominal surgery at the age of eight years for hepatic trauma due to a traffic accident (findings unknown) and hepatitis A in childhood. There is no record of subsequent liver problems. Furthermore, there was no additional consumption of any herbal or non-pharmaceutical product. Her psychopharmacological history included previous treatment with risperidone, haloperidol decanoate, olanzapine and quetiapine. Despite taking antipsychotic medication, her psychotic symptoms had not progressed favourably, so her treating doctor decided to

start her on clozapine 200mg from the first day of treatment. The patient showed clinical improvement of positive symptoms after four weeks of treatment, but suffered from orthostatic dizziness. Two months before her admission (eight weeks after taking clozapine), morning sickness manifested, but the psychotic symptoms were clinically stable, so it was decided to reduce the clozapine dose to 150mg/day. She also presented with sporadic vomiting one month before her admission. Due to these discomforts, she went to a gastroenterologist, who performed an upper gastrointestinal endoscopy, which revealed moderate erythematous chronic gastritis and bile reflux. The patient discontinued clozapine eight days prior to admission due to the symptoms. The patient was referred to the accident and emergency department of a general hospital for persistent nausea and vomiting, as well as jaundice. There is no information on when the jaundice started. There was no weight alteration or hyporexia.

On physical examination the patient was found to have dry oral mucous membranes, with jaundiced (++) sclerae, skin and mucous membranes and epigastric and mesogastric pain on palpation. There was no evidence of liver enlargement. Axillary temperature was 37.5°C.

Her liver function tests on admission were glutamic oxaloacetic transaminase (GOT) 183 U/l, glutamic pyruvic transaminase (GPT) 268 U/l, with total bilirubin (TBil) of 3.5 mg/dl. Her complete blood count showed white blood cells of 7970/ μ l, with eosinophils of 40/ μ l (normal, 20–500/ μ l) and C-reactive protein of 1.3 mg/dl.

Abdominal ultrasound findings on admission showed a liver with regular contours, with increased parenchymal echotexture and no focal or diffuse lesions. The bile ducts and common bile duct were of normal calibre and without gallstones. The kidney ultrasound was normal. Her serology tests for hepatitis B and C were negative. She was diagnosed with an emetic syndrome and jaundice syndrome until clozapine-induced hepatotoxicity was ruled out, and she was admitted. Nasogastric feeding tube placement was indicated but, despite this indication, nausea and vomiting persisted for 13 days and the vomiting was bilious in content.

Fifteen days after admission, oral tolerance was tested with a liquid diet because she had gone two days without vomiting, but the nausea continued, so the nasogastric feeding tube was reinserted due to the reappearance of vomiting.

Table 1 – Evolution of laboratory tests.

	13/06	14/06	17/06	26/06	09/07	12/07	18/07	25/07
White blood cells (normal, 4000–10,000/ μ l)	7.97		4.73	5.18		4.48		1.00
GOT (normal, 5–35 U/l)	183		162		48	116	42.9	
GPT (normal, 5–45 U/l)	268		255	251	99	152	91	
GGT (normal, 5–49 U/l)		77			97	122	129	
Total bilirubin (normal, 0.2–1.2 mg/dl)	3.5		1.8	1.8	2.2		3.0	
Alkaline phosphatase (normal, 30–120 U/l)					216.9	224	199	
C-reactive protein (normal, 0–0.7 mg/dl)		1.3			0.46	0.49		
Platelets (normal, 150–400 $\times$ 10 ⁹ /l)	301		175	225		235		50

Other tests performed were: thyrotropin, 1.36 μ IU/ml (normal, 0.3–4.5 μ IU/ml); free T₄, 16.8 pg/ml (normal, 8.9–17.2 pg/ml); IgG, 1236 mg/dl (normal, 656–1351 mg/dl); ANA, 1/100 pattern DFS70 positive. Table 1 shows the evolution of liver function during hospitalisation. As can be seen, GOT and GPT were three times higher than the upper limit of normal in the patient one month after hospitalisation.

Other tests ordered were an abdominal CT scan one month after hospitalisation, which showed a liver of normal size, shape and location, with decreased density in the simple phase (without intravenous contrast) and with contrast; no focal lesions or bile duct dilatation were found, with a common bile duct of preserved calibre. The gallbladder was described as collapsed, with perivesical oedema and no gallstones. The conclusion was mild diffuse hepatopathy and perivesical oedema. Due to the suspicion of intestinal obstruction, she underwent an intestinal transit X-ray, which could not be completed due to vomiting induced by the contrast medium, and an upper gastrointestinal tract endoscopy, which showed a regular amount of mucous and bile in the stomach, the antrum with a mucosa of whitish mottled appearance, congestive, without erosions, and a congestive pylorus. It was concluded: antral congestive gastropathy and bile reflux.

From the time the patient was admitted, oral intolerance due to nausea and vomiting and jaundice persisted until day 42 of hospitalisation, when greenish vomiting appeared. Her glucose level was found to be 45 mg/dl with a prothrombin time of 20 s. One day later, her condition was complicated by encephalopathy and refractory multi-organ failure due to an upper gastrointestinal haemorrhage. The cause could not be determined due to the torpid progression of the patient, who died one day after the onset of the disease.

Discussion

Drug-induced hepatotoxicity refers to any damage to liver function from the ingestion of drugs, herbs or dietary supplements and ranges from asymptomatic raised liver enzymes to acute liver failure.⁷ Drug-induced hepatotoxicity can be classified as follows: direct, idiosyncratic or indirect.

The direct, or intrinsic, mechanism is known to be related to accumulation of the drug after ingestion, as well as direct damage of its metabolites in the liver. It is dose-dependent and predictable, and the latency period is short (1–5 days) after high therapeutic doses or supratherapeutic doses, such as in the case of intentional or accidental overdose.⁸

The idiosyncratic mechanism is the most common mechanism and is neither dose-dependent nor predictable, relying

on the uniqueness of the individual.⁹ This type of hepatotoxicity results from immune-mediated liver injury or direct cell damage.^{10,11} Hepatotoxicity by this mechanism is initiated by exposure of the hepatocyte to some form of stress, although there are also other factors that sensitise this cell and amplify cell damage.¹² Protective mechanisms are involved, such as glutathione, which has the function of scavenging reactive oxygen species¹³ and the activation of anti-oxidative genes and their proteins mediated by the nuclear factor-erythroid 2 related factor 2 (Nrf2) protective pathway.¹⁴ Impairment of these protective mechanisms can lead to hepatocyte damage (protein dysfunction, impaired regulation of drug transporters, mitochondrial toxicity and lysosomal damage). The formation of reactive drug metabolites and covalent binding can lead to immune activation of T cells.¹⁵

In the idiosyncratic mechanism, a hypersensitivity syndrome may occur, characterised by the emergence of rash, eosinophilia and the development of autoantibodies, and manifests after a short latency period (one to six weeks). Although this mechanism is not fully understood, it is postulated that the hypersensitivity reaction is type I due to an increase in immunoglobulin E, angioedema and skin rash in some cases.^{16,17} Another hypothesis is the stimulation of T-lymphocytes, with a subsequent increase in interleukin 5, which promotes the production of eosinophils.¹⁸

Based on laboratory findings, the idiosyncratic mechanism can be classified as hepatocellular, cholestatic and mixed^{19,20}:

- Hepatocellular pattern: GPT $\geq$ 3 times the upper limit of normal and a GPT/alkaline phosphatase (ALP) ratio $\geq$ 5 times. It is the most common manifestation of idiosyncratic liver injury.²¹
- Cholestatic pattern: ALP $\geq$ 2 times the upper limit of normal and a GPT/ALP ratio $\leq$ 2 times. This pattern is related to bile secretion impairment, such as that caused by chlorpromazine, which leads to cholestasis.^{3,22}
- Mixed pattern: GPT $\geq$ 3 times the upper limit of normal, ALP $\geq$ 2 times the upper limit of normal and a GPT/ALP ratio <5 and >2 times.

The third mechanism described is indirect liver injury through increased risk of metabolic syndrome, which in turn increases the risk of non-alcoholic fatty liver disease, characterised by hepatic accumulation of triglycerides.²³ Antipsychotics, especially atypical agents, are associated with weight gain, hyperphagia, hyperglycaemia, insulin resistance, type 2 diabetes mellitus and dyslipidaemia.²⁴

Table 2 – Antipsychotics and hepatotoxicity.

Antipsychotics	Number of cases	Fatal injury	Category
Typical			
Chlorpromazine	>100	1	A
Haloperidol	25	0	B
Atypical			
Clozapine	27	1	B
Olanzapine	28	0	B
Quetiapine	11	1	C
Risperidone	6	0	C
Ziprasidone	3	0	D
Aripiprazole	–	–	E

A: the drug causes clinically apparent direct or idiosyncratic liver injury. More than 50 cases have been reported.

B: the drug is very likely to cause clinically apparent idiosyncratic liver injury. Between 12 and 50 cases have been reported.

C: the drug is likely to cause idiosyncratic liver injury. Fewer than 12 cases have been reported.

D: it is a rare cause of liver injury. Fewer than 3 cases have been reported.

E: there is no evidence that the drug has caused liver injury. There may be single case reports, but they are largely unconvincing.

E': the drug has not been proven to cause liver injury.

X: it is unknown if the drug has caused liver injury. Applies to drugs that are newly introduced or rarely used in clinical medicine.

Modified from Chalasani et al.²⁰ and Björnsson et al.²⁶

Of the atypical antipsychotics, clozapine is the one most associated with impaired liver function, usually raised transaminases, pointing to liver injury with a hepatocellular pattern.⁵ It should be noted that, in addition to clozapine, another of the most hepatotoxic antipsychotics is chlorpromazine, while the least hepatotoxic are aripiprazole and ziprasidone.^{3,5,25} Table 2 summarises the main antipsychotics and their hepatotoxicity classification.

Raised liver function tests with clozapine are dose-dependent and usually occur at 200–400 mg/day.²⁷ Raised liver enzyme levels to clinically significant ranges occurs 5–8 weeks after starting clozapine, with a mean time of 34.2 days.^{28,29} Raised transaminase levels normalise spontaneously without

clozapine dose reduction in about half of patients at approximately nine weeks. When clozapine is reduced or stopped, hepatic enzymes return to normal in 4–6 weeks.^{27,29,30}

While there is no specific scale to assess the severity of clozapine-induced liver injury, the severity of drug-induced liver injury in general is shown in Table 3.

Regarding clozapine dosage, the literature recommends starting with 12.5 mg/day, with gradual increases of 25–50 mg/day up to 300 mg/day after 2–3 weeks, to reduce dangerous adverse effects such as orthostatic hypotension, seizures, myocarditis and neuroleptic malignant syndrome.^{32,33}

Clinical guidelines are not specific about monitoring hepatic enzymes. The Maudsley Prescribing Guidelines in Psychiatry³³ recommend a baseline liver function test and another at 4–6 months of clozapine treatment.

Moreover, in the event of clinical symptoms such as general malaise, fever, abdominal pain, nausea, vomiting, rash, dark urine or jaundice, hepatic enzymes should be checked and clozapine discontinued if GPT, GOT and GGT values are above three times the normal value or ALP or total bilirubin are >2 times the normal value.^{5,34–36} Acute fulminant hepatic failure has been described, which fortunately is extremely rare, with only two cases (0.001%) published.^{37,38}

In our case, the diagnosis of clozapine-induced hepatotoxicity was based on the patient's clinical history and the ruling out of other possible causes. Although the patient had a positive ANA test, the reported DFS70 pattern (fine and dense mottling, molecular weight 70 kDa) is found in healthy individuals.³⁹

The patient was admitted with GPT values six times the upper limit of normal, GOT five times the upper limit of normal and total bilirubin in the jaundice range, with no evidence of obstruction by stones. This is considered severe liver injury. The presentation was hepatocellular based on the marked increase in GPT, ultrasound findings and subsequent ALP controls, which did not show values >2 times the upper limit of normal. Despite discontinuing clozapine, hepatic enzymes did not normalise and there was no clinical improvement.

Table 3 – Severity of drug-induced liver injury.

Severity	Description
Grade 0: no liver injury	Tolerance to the drug without any hepatotoxic reaction
Grade 1: mild liver injury	Raised serum levels of GPT and/or alkaline phosphatase, total bilirubin <2.5 times the upper limit of normal, INR < 1.5 There may be fatigue, asthenia, nausea, anorexia, right upper abdominal pain, jaundice, pruritus, rash or weight loss
Grade 2: moderate liver injury	Raised GPT and/or alkaline phosphatase, with total bilirubin ≥ 2.5 times the upper limit of normal or INR ≥ 1.5 The symptoms described can be exacerbated
Grade 3: severe liver injury	Raised serum levels of GPT and/or alkaline phosphatase, total bilirubin ≥ 5 times the upper limit of normal, with or without INR ≥ 1.5
Grade 4: acute liver failure	Evidence of coagulation abnormalities indicated by INR ≥ 1.5 or prothrombin activity <40%, signs of hepatic encephalopathy and total bilirubin ≥ 10 times the upper limit of normal or daily elevation ≥ 1 mg/dl within 26 weeks after the onset of drug-induced liver injury Ascites and dysfunction of other organs may occur
Grade 5: lethal	Death due to drug-induced liver injury or need for liver transplantation for survival

Taken from Yu et al.³¹

Liver function tests should have normalised within one month of stopping clozapine. It is hypothesised that the history of childhood abdominal trauma and the initial dose of clozapine 200 mg/day without prior titration were related to hepatotoxicity. Although the patient experienced one of the most common gastrointestinal adverse effects of clozapine – nausea – from the first month of treatment, the persistence of nausea and the occurrence of vomiting should raise red flags and prompt immediate testing of hepatic enzymes.

Conclusions

The reported case concerns clozapine-induced hepatotoxicity. This conclusion was reached on the basis of presenting symptoms, ruling out other possible causes, the physical examination and laboratory findings. According to the literature reviewed, this is the third case with a fatal outcome. After having reviewed the literature, we recommend:

- Liver panel testing should be taken into consideration before starting clozapine. The next check-up should be after 4–6 months of treatment.
- If the patient exhibits clinical symptoms with clozapine, such as jaundice, fever, rash, malaise, nausea and vomiting, the liver panel should be checked for raised hepatic enzymes. If they are >3 times the normal value, clozapine should be discontinued. Otherwise, the clozapine dosage can be continued and the liver panel can be continuously assessed.
- Progressive titration of clozapine is recommended, starting at 12.5 mg/day. It should be increased by 25–50 mg/day to 300 mg/day after 2–3 weeks.

Conflicts of interest

The authors have no conflicts of interest to declare.

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