Case Report

A Case of Carbamazepine-induced Severe Cholestatic Hepatitis: Case Report and Review of Literature

Suhas Ganesh, Lekhansh Shukla, Arun Kandasamy, Vivek Benegal

ABSTRACT

Carbamazepine (CBZ) is one of the widely prescribed drugs in the field of neuropsychiatry. We report a case of a 27-year-old female patient presenting with severe cholestatic hepatitis presenting after the initiation of CBZ. We establish the probability of drug-induced liver injury using Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method causality assessment scale, and the patient had high probability with a score of 9. We briefly review the literature in this field discussing the scope of the problem, etiopathogenesis, clinical manifestation, course, and management.

Key words: *Carbamazepine, cholestatic, Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method, hepatitis*

INTRODUCTION

Six decades have passed since the introduction of carbamazepine (CBZ) to the field of psychopharmacology, and to date, it remains one of the widely prescribed medications in the fields of both neurology and psychiatry. However, a few serious side effects and significant interaction with other medications often co-prescribed have resulted in this drug often being considered second line for many psychiatric conditions. Here, we describe a relatively rare case of serious hepatotoxicity in a young woman prescribed CBZ and establish the probability of adverse drug reaction using we used Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale.[1] We briefly discuss the existing evidence on CBZ-induced hepatotoxicity in the final section. An informed consent was obtained from the patient about the proposed documentation.

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Department of Psychiatry, Centre for Addiction Medicine, National Institute of Mental Health and Neuro Sciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Suhas Ganesh
Department of Psychiatry, Centre for Addiction Medicine, National Institute of Mental Health and Neuro Sciences, Bengaluru - 560 029, Karnataka, India. E-mail: suhasg90@gmail.com

CASE REPORT

A 27-year-old married female patient presented with history of episodic abnormal behavior, severe aggression during these episodes for 4 years, and history of alcohol use in dependent pattern for the past 6 years. The patient was also noted to have emotionally unstable personality traits. She was initially seen under neurology for the episodic abnormal behavior and was started on tablet CBZ started at 100 mg and increased up to 400 mg with provisional diagnosis of complex partial seizures. She was later admitted for 4 weeks for the treatment of alcohol dependence syndrome. On discharge, the patient was continued on tablet CBZ 400 mg/day, tablet baclofen 40 mg/day as anticraving agent, and multivitamin supplements.

Two weeks postdischarge patient presented to outpatient services with symptoms of generalized itching and scaly lesions all over the body, deep yellowish discoloration of the eyes, clay-colored stools, mild fever at onset, and loss of appetite. The patient had been abstinent on alcohol for nearly 6 weeks before these symptoms. Biochemical examination revealed total bilirubin of 17.2 mg/dl, direct bilirubin 13.1 mg/dl, indirect bilirubin 4.1 mg/dl, serum alkaline phosphatase 460 IU, serum glutamic oxaloacetic transaminase 120 IU, and serum glutamic pyruvic transaminase 100 IU. Renal functions, electrolytes, and hemogram were within normal limits with eosinophil count of 5% and total count of 8600/mm^3. Urine was strongly positive for bile salts and bile pigments. Ultrasonography of the abdomen did not show any abnormality. Serological markers for hepatitis B and C were negative. CBZ-induced cholestatic hepatotoxicity was considered, and the drug was discontinued. The patient underwent symptomatic management, and the above symptoms subsided within next 10 days. She was later started on tablet valproate for prophylaxis of seizures and in behavioral abnormalities. Tablet baclofen was continued as the anticraving agent without any further similar adverse reactions.

On CIOMS/RUCAM scale,[1] the patient scored a total of 9 suggesting high probability of drug-induced liver injury Table 1.

Table 1: Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method causality assessment for drug-induced liver injury

Item	Condition (cholestatic/mixed)	Score
Time to onset - from the beginning of the drug	Initial treatment, 5-90 days	+2
Course	>50% decrease within 180 days	+2
Risk factors	Presence - alcohol, age <55 years	+1
Concomitant drug	Incompatible with time to onset	+0
Exclusion of other causes of liver injury	All causes in Groups 1 and 2 ruled out	+2
Previous information on hepatotoxicity of the drug	Reaction labeled in product characteristic	+2
Response to re-administration	Not done	+0
Total score		+9

Items and scoring adapted from CIOMS/RUCAM. 0 or lower: Relationship with the drug excluded, 1-2: Unlikely, 3-5: Possible, 6-8: Probable, >8: Highly probable. CIOMS – Council for International Organizations of Medical Sciences; RUCAM – Roussel Uclaf Causality Assessment Method

DISCUSSION

Scope of carbamazepine-induced hepatotoxicity

Benign elevation in aminotransferases and gamma-glutamyltransferase (GGT) is found in 1%–22% of patients receiving CBZ; however, this is rarely associated with histological changes.[2] Clinically significant hepatotoxicity is a relatively rare occurrence with a frequency of 16/10,000 treatment years.[3] The time course of such an occurrence is often within 6 months with a median time of 5 weeks[4] after treatment initiation but may extend up to several years.[5]

Etiopathogenesis

Benign enzyme elevation results from hepatic enzyme induction rather than from hepatocellular injury.[2] Clinically, evident hepatic injury resulting from CBZ has been at least partly attributed to its metabolism in the liver. CBZ primarily metabolized by CYP3A4 enzymes induces its own metabolism to ring hydroxyl metabolites including 2 and 3 hydroxyl CBZ, 10, 11 CBZ-epoxide. This process involves unstable immunoactive arene oxide intermediates. These result in formation of haptans which lead to immune-mediated injury.[6] A second hypothetical model of liver injury established among animal studies has been depletion of glutathione which is important in the scavenging of reactive oxygen species in the liver.[7] While hypersensitivity was proposed as the most common underlying etiological mechanism in the past, recent evidence suggests a hypersensitive reaction in only about 30% of the cases with CBZ hepatotoxicity.[8] In Southeast Asian populations, an association has been found with HLA-B × 1502 for hypersensitivity syndromes with CBZ.[9]

Clinical pathological manifestations

Nature of liver injury could be either cholestatic or hepatocellular or mixed and might even result in granulomatous hepatitis.[8,10] Patients with hypersensitivity-related injury often present with fever, loss of appetite, flu-like symptoms, rash, edema, lymphadenopathy, and icterus within 2 months

of initiation. Elevated white blood cell counts and peripheral and liver tissue eosinophilia are common in hypersensitivity-associated liver injury. Specific syndromes like drug-induced rash, eosinophilia and systemic symptoms have been described with CBZ.

Patients with hepatotoxicity without immune-allergic manifestations may present with symptoms of acute hepatitis up to 6 months. Aminotransferase elevation in either case is often above threefold of normal range, and unusually elevated levels of GGT and alkaline phosphatase suggest a cholestatic picture. Rarely, this might progress to acute fulminant hepatitis with fatal outcomes. Histologically, there are case reports describing vanishing bile duct syndrome,[11] hepatocellular necrosis, and granulomatous hepatitis.[4]

Course and prognosis

CBZ hepatotoxicity is often more severe among children as compared to adults. Cholestatic forms often respond to stoppage of medications with resolution of symptoms within 5–7 days. Those with hepatocellular forms have poorer outcomes, and hepatocellular necrosis predicts fulminant course and mortality.[4]

Management

Stopping the drug is the only definitive treatment in CBZ-induced hepatotoxicity. Rechallenge often results in emergence of rapid and severe liver injury and hence not recommended. Corticosteroids have been used in hypersensitivity-related and hepatocellular forms of CBZ hepatotoxicity. N-acetylcysteine has been used in either form to prevent secondary damage by reactive oxygen metabolites due to glutathione depletion.[7] Ursodeoxycholic acid has been reported to be useful for the treatment of cholestatic hepatitis caused by CBZ.[12] Severe fulminant liver failure has warranted liver transplantation.

CONCLUSIONS

CBZ, a widely used medication in the field of neurology and psychiatry, can result in both benign and severe forms of liver injury though in a small but significant minority of patients. High index of suspicion and early monitoring will prevent serious adverse event of hepatotoxicity. Discontinuation of the drug with symptomatic management will result in improvement in almost all patients with cholestatic/mixed hepatic injury.

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Conflicts of interest

There are no conflicts of interest.

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