

Case Report

Cholestatic Hepatitis Secondary to Carbamazepine Treatment with Ursodeoxycholic Acid - A Case Report

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Abstract

Background: Drug-induced hepatitis and several features of liver toxicity associated with the administration of carbamazepine have been reported; they involve non-immunoallergic hepatotoxicity and immunoallergic hypersensitivity syndrome. Ursodeoxycholic acid (UDCA) has liver protective effects and is indicated for hepatitis.

Case: An 18-year old patient with epilepsy and on carbamazepine 200 mg once daily was admitted to a hospital for generalised rash and significant elevation of liver enzymes. Carbamazepine was discontinued and replaced with leviteracetam 250 mg twice daily. Patient had cholestatic features of liver damage and UDCA 500 mg twice daily was given for 2 weeks until liver enzymes normalized.

Conclusion: Ursodeoxycholic acid treatment could be an alternative treatment for patient with carbamazepine-induced hepatitis.

Keywords: Carbamazepine, Drug-induced hepatitis, Liver damage Ursodeoxycholic acid, Leviteracetam

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INTRODUCTION

Carbamazepine (CBZ), an established antiepileptic drug, has clinical efficacy in the treatment of acute mania, stress disorders and neuropathic pain. Furthermore, the drug has been linked to more than 250 cases of clinically apparent liver injury including 18 deaths [1]. There are several features of liver toxicity due to carbamazepine and which involve non-immunoallergic hepatotoxicity and immunoallergic hypersensitivity syndrome. Ursodeoxycholic acid (UDCA) has liver protective effects and is generally indicated for acute and chronic hepatitis [2]. In non-immunoallergic liver injury, the use of UDCA has been reported as a prophylactic and treatment alternative [3].

CASE REPORT

An 18-year old girl with body mass index (BMI) of 16.0 was admitted in the Medical Ward, of Hospital Universiti Sains Malaysia due to drug-induced hepatitis. Patient presented with itchy rashes on all four limbs and trunk, high grade fever with chills, vomiting for five days, right upper quadrant pain and mild jaundice. Patient was diagnosed with complex partial seizure in 2008 and was on carbamazepine for the past one month. Previously, patient was on lamotrigine 200 mg twice daily but seizure was not controlled. Magnetic resonance imaging (MRI) revealed sclerosis at left temporal with mild lobe atrophy. Electroencephalography (EEG)

Table 1: Serial liver biochemistry over the period of hospital admission

Parameter	Normal	Day 1	Day 3	Day 4	Day 6	Day 7	Day 8	Day 10	Day 18
AST (U/L)	0-55	292	152	167	165	165	196	121	33
ALT (U/L)	0-55	654	380	392	334	348	378	354	98
Bilirubin (Umol/L)	5-21U	374	92	115	119	82	64	45	23
ALP (U/L)	40-150	129	280	315	501	621	689	583	237
Total protein (g/L)	66-83	74	48	48	50	56	67	74	73
Albumin (g/L)	35-52	44	28	28	29	33	38	41	43
Globulin (g/L)	25-44	30	20	20	21	23	29	33	30
PT (s)	10-35	13.3	13.1	13.1	12.9	12.5	12.5	12.8	12.8
APTT (s)	26-42	40.2	39.8	39.5	39.6	38.4	37.5	37.2	37.2

Key: AST = aspartate aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; PT = protrombine time; PTT = activated partial thromboplastin time

showed bimodal spikes with secondary generalization.

Carbamazepine was withdrawn and leviteracetam 250 mg twice daily started. Calamine lotion, hydrocortisone cream and loratadine 10 mg once daily were prescribed for her generalized body rash. Tablet ursodeoxycholic acid 500 mg twice daily was given on day-7 of hospital stay.

Liver enzymes showed the following levels: alanine transaminase (ALT), 654 U/L; aspartate transaminase (AST), 292 U/L; alkaline phosphatase (ALP), 374 U/L; and total bilirubin, 129 uMol/L. Albumin level became normal (from 29 to 33 g/L) on day 7, while autoimmune as well as hepatitis B and C screening was negative.

Rash and other complaints were resolved by day 5. The levels of ALT, ALP and AST rebounded to seven times the upper limits of normal on day 2 of UDCA initiation but gradually dropped to normal at the end of 2 weeks (Table 1). Patient was discharged and remained normal on one-week follow-up.

DISCUSSION

The typical features of liver toxicity caused by carbamazepine were shown similar in current patient of the study. The literature reports symptomatic treatment for the management of carbamazepine induces hepatotoxicity [1]. In contrast, current patient required treatment to normalise liver function parameters. Liver function abnormalities were most consistent with cholestatic reaction as evidenced by the > 3-fold elevation in alkaline phosphatase after 4 weeks of carbamazepine therapy.

The mechanism of liver injury in carbamazepine-induced hepatitis remains poorly understood, but it is believed that the drug is metabolized in the liver and excreted unchanged in the urine at a

level of about 12 % [4]. Carbamazepine is metabolized into several epoxides through oxidative metabolism. These epoxides have been associated with hematological toxicity and hepatotoxicity. In cholestatic liver disease, alteration in the pattern of bile secretion by hepatocytes results in intracellular accumulation of hydrophobic or toxic bile acids. This may lead to apoptosis and necrosis or tissue damage of the liver [5].

Ursodeoxycholic acid (UDCA) is a dihydroxy bile acid (3 α , 7 β dihydroxy-5 β -cholanolic acid). It is present in human bile as a hydrophilic non-toxic bile acid. UDCA has antioxidative, cytoprotective and anti-apoptotic effect by reducing cytolysis of hepatocytes. Furthermore, UDCA alter bile acid pool, thus altering the balance between toxic hydrophobic and non-toxic bile salts [3,6].

The initial slight incline of ALT and AST after commencement of UDCA treatment was quickly brought under control; but the significance of the secondary elevation is unclear. However, in the liver, UDCA is converted into active form via a metabolism and conjugation process. The active form undergoes entero-hepatic circulation to exert its action [7]. This may be the cause of the delayed effect of UDCA after the drug was started. Based on patient Naranjo's algorithm [8] score of 7, there is a 'probable' association between the event and carbamazepine.

CONCLUSION

Ursodeoxycholic acid treatment might be an alternative treatment for patients with carbamazepine-induced cholestatic hepatitis. Furthermore, ursodeoxycholic acid prevents further hepatocyte cell deaths and other complications. Further research in determining the causes of secondary elevation of ALT and AST after UDCA is, however, required.

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