Case Report

Oxcarbazepine-induced liver injury after sensitization by valproic acid: a case report

Hepatotoxicity associated with antiepileptic drugs (AEDs) is well recognized and ranges from mild increases in serum liver enzymes to potentially fatal liver failure (1). Valproic acid (VPA), which has been used to treat bipolar disorder since 1966, most commonly causes a mild, transient elevation in liver enzymes, although more severe hepatotoxicity has also been reported (2, 3). Oxcarbazepine (OXC), a newer AED that is also used for mood stabilization, can cause modest elevations in liver enzymes but has not been associated with hepatotoxicity (4, 5). Therefore, OXC is often used as a replacement for VPA when treating bipolar disorder in the setting of elevated liver enzymes. We present a patient in whom treatment with OXC caused liver injury following sensitization by VPA, suggesting that a washout period between medications may be necessary.

Case report

Mr. P is a 46-year-old man with a history of schizoaffective disorder, bipolar type, and a moderate intellectual developmental disorder who presented to a psychiatric emergency department (ED) with command auditory hallucinations and suicidal ideation. He had been taking VPA extended release 1000 mg daily for the past three years, as well as risperidone 4 mg daily and haloperidol decanoate 150 mg once monthly, with last administration eight days prior to presentation. His medical history was significant for hypothyroidism, treated with levothyroxine 88 µg daily. Mr. P reported no allergies, personal or family history of liver disease, or use of acetaminophen products, herbal supplements, teas, or alcohol. Mr.

**Objective:** The aim of the present case report is to describe a potential interaction between valproic acid and oxcarbazepine that resulted in hepatic injury.

**Methods:** We report the case of a 46-year-old man with schizoaffective disorder who was cross-titrated from valproic acid to oxcarbazepine because of liver injury.

**Results:** Initiation of oxcarbazepine four days after stopping valproic acid produced a significant elevation in liver enzymes that normalized with oxcarbazepine discontinuation and did not reappear with its reintroduction five days later.

**Conclusions:** Our findings suggest that a longer washout period or another agent should be considered when transitioning from valproic acid to oxcarbazepine.
P also denied any recent change in VPA dose or initiation of new medications.

Routine laboratory studies obtained in the ED revealed a mild transaminitis, with an alanine aminotransferase (ALT) of 163 U/L (normal 10–35 U/L) and an aspartate aminotransferase (AST) of 43 U/L (normal 8–38 U/L). His VPA level was low at 14.9 µg/mL (target range: 80–100 µg/mL). Antibodies for hepatitis A virus, hepatitis B virus, and hepatitis C virus, as well as serum levels of alcohol, aspirin, acetaminophen, and lithium were negative. Urine drug screen was also negative. All other laboratory studies, including thyroid function tests and blood count differential, were within normal limits. Given Mr. P’s persistent symptoms of bipolar disorder and elevations in liver function tests (LFTs), he was admitted voluntarily to an inpatient psychiatric hospital for adjustment of his mood stabilizers.

VPA was discontinued but Mr. P remained on risperidone 4 mg daily for mood stabilization and psychosis. Physical exam was unremarkable. Right upper quadrant sonogram showed cholelithiasis without evidence of cholecystitis. Given that the pattern of LFTs was not consistent with obstruction, a gastroenterology consultant felt that gallstones would not explain the laboratory abnormalities. By day five of hospitalization, Mr. P’s LFTs began to normalize [ALT 103 U/L, AST 24 U/L, and alkaline phosphatase (ALP) 106 U/L]. Mr. P had a history of elevated creatinine (1.5 mg/dL) during a prior lithium trial, and thus he was started on OXC 300 mg twice daily (BID). Clonazepam 1 mg every bedtime (QHS) was also added for anxiety, as well as propranolol 10 mg three times/day (TID) for akathisia.

After four doses of OXC, AST, ALT, and ALP increased to 658, 866, and 200 U/L, respectively. OXC was discontinued and LFTs subsequently trended down over the next five days. Additional laboratory studies ruled out drug-induced liver injury, viral hepatitis, Wilson’s disease, thyroid related disease and autoimmune hepatitis. LFTs, coagulation studies, a basic metabolic panel, and complete blood count were monitored daily.

On day 11 of hospitalization, given Mr. P’s consistent improvement in liver function, OXC was restarted at 300 mg BID and increased the following day to 300 mg in the morning and 600 mg QHS. No further elevations in LFTs occurred. On this dose of OXC, in conjunction with risperidone 4 mg daily, propranolol 10 mg TID, and lorazepam 2 mg QHS, Mr. P returned to his psychiatric baseline and was ready for discharge on day 14 of hospitalization.

Discussion

Mr. P initially presented with a mild transaminitis that improved with VPA discontinuation. Initiation of OXC four days after stopping VPA led to a significant elevation in LFTs that normalized after OXC discontinuation. After five days, OXC was reintroduced without elevation of liver enzymes. The time course of Mr. P’s LFT abnormalities (Fig. 1) suggests that liver injury with OXC was a result of his preceding VPA use rather than the effects of OXC alone. This is further supported by the Naranjo adverse drug reaction probability scale, which classifies the causal relationship as probable (6).

One possible mechanism by which VPA may have sensitized the liver to OXC is an imbalance in antioxidant enzymes and reactive oxygen species (ROS). Several studies have shown that VPA reduces levels of antioxidant enzymes, such as glutathione-S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase. OXC, on the other hand, has been reported to induce ROS (7). Therefore, through a pharmacodynamic mechanism, VPA may have suppressed the antioxidant enzymes necessary for neutralizing free radicals produced by OXC. The time between OXC discontinuation and re-initiation likely allowed for antioxidant enzyme regeneration, preventing subsequent LFT abnormalities.

It is also possible that an interaction between VPA and OXC was mediated by metabolism. OXC is rapidly metabolized via arylketone reductase to its pharmacologically active metabolite,
10-hydroxy-carbazepine (10-OH-CZ), which is primarily eliminated through glucuronidation (8). VPA is predominantly metabolized through β-oxidation at low doses and glucuronidation at higher, therapeutic doses, although several minor cytochrome P450-mediated pathways exist (9). While the involvement of glucuronidation in both drug pathways might suggest an interaction, this is not supported by clinical studies, which show no difference in drug levels with co-administration. In one study comparing patients taking VPA with healthy controls, there was no difference in levels of OXC or 10-OH-CZ following OXC administration (10). Another study similarly showed no change in OXC or 10-OH-CZ levels in patients on VPA compared to controls, as well as no difference in VPA levels in response to OXC dosing (11).

Excluding one prior report (12), OXC-induced liver injury has been seen only in the setting of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (13), which is not present in this case given the absence of characteristic skin findings and eosinophilia. Additionally, OXC has only been associated with elevated liver enzymes in less than two percent of patients (14). Mr. P’s elevated LFTs are also unlikely to have been caused by OXC alone, as his LFTs remained stable after re-initiation of OXC.

Conclusion

OXC is a commonly used mood stabilizer that may be considered by clinicians when patients experience intolerable side effects to first-line agents, such as lithium or VPA. Our experience with Mr. P. suggests that OXC may cause liver injury after recent treatment with VPA, and that clinicians may wish to consider another agent or a longer washout period.

Disclosures

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References
