OMCR

Oxford Medical Case Reports, 2017;11, 212–214

doi: 10.1093/omcr/omx067
Case Report

CASE REPORT

Levetiracetam-induced transaminitis in a young male with traumatic brain injury

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Abstract

Levetiracetam is a commonly prescribed antiepileptic drug for seizure prophylaxis in patients with traumatic brain injury (TBI). Levetiracetam metabolism has been reported to be non-dependent on hepatic cytochrome P450 (CYP450) isoenzyme system. Furthermore, levetiracetam and its metabolites are reported to be eliminated from systemic circulation via renal excretion. Therefore, due to its well-known renal clearance mechanism with no dosage adjustments recommended for hepatic impairment, levetiracetam is often chosen as the drug of choice in patients with suspected or ongoing hepatic dysfunction. Furthermore, monitoring of liver enzymes is often not considered to be critical in levetiracetam therapy. However, hepatotoxicity is still possible with levetiracetam. Here, we report on an 18-year-old male with TBI who developed transaminitis with levetiracetam therapy which resolved following the discontinuation of levetiracetam. A close monitoring of liver enzymes and early recognition of hepatotoxicity is still necessary and critical to preventing major sequelae stemming from levetiracetam-induced hepatotoxicity.

INTRODUCTION

Levetiracetam is a commonly prescribed anticonvulsant drug often used for seizure prophylaxis in patients suffering from traumatic brain injuries (TBIs) [1–3]. Levetiracetam metabolism has been reported to be non-dependent on hepatic cytochrome P450 (CYP450) isoenzyme system and its metabolites are reported to be eliminated from systemic circulation via renal excretion [4]. Additionally, levetiracetam does not require a titration period, making it easier to use [5]. Therefore, levetiracetam is often chosen as the drug of choice in patients with suspected or ongoing hepatic dysfunction. However, an induction of hepatic response is still possible with levetiracetam therapy. Here, we report on an 18-year-old male with TBI who developed transaminitis with levetiracetam therapy which resolved following the discontinuation of levetiracetam.

CASE REPORT

An 18-year-old previously healthy male was brought to the emergency department by emergency medical service with a TBI resulting from jumping off a moving vehicle while under the influence of alcohol (blood alcohol level of 0.249% w/v). He

Received: June 27, 2017. **Revised:** July 31, 2017. **Accepted:** August 22, 2017

Table 1: Chronology of events

Day number	Event
0	Admission #1
1	Levetiracetam initiated
13	Discharge #1
68	Admission #2
75	Discharge #2
101	Admission #3
105	Levetiracetam discontinued
106	Metoprolol initiated
108	Discharge #3
123	Admission #4
132	Discharge #4
143	Admission #5
159	Discharge #5

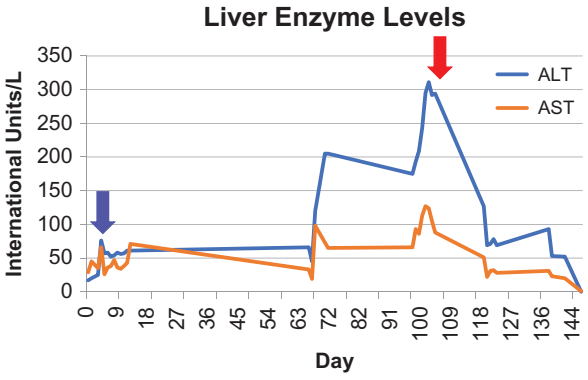

Figure 1: Trend of liver enzymes, alanine aminotransferase and aspartate aminotransferase. Blue arrow indicates the start of levetiracetam therapy (Day 1). Red arrow indicates discontinuation of levetiracetam (Day 105)

was found with Glasgow Coma Scale of 3 and was intubated on the scene. The CT scan of head revealed scattered intraparenchymal contusions. His admission laboratory findings included alanine aminotransferase (ALT) of 17 and aspartate aminotransferase (AST) of 29, both within normal limits, with AST:ALT ratio <2:1. Although acutely intoxicated during the initial admission, he did not have any significant past medical history or history of chronic alcohol use. The review of his complete past and present medication use did not reveal significant use of any medications. The patient did not have any family history of autoimmune or chronic liver diseases. The patient did not have any signs and symptoms of acute or chronic liver failure, either documented in the chart or noticed during clinical interview and physical exam. He did not demonstrate any clinical symptoms of iron overload such as hyperpigmentation, diabetes, arthropathy, hypogonadism and cardiomyopathy. The CT scan of the abdomen showed unremarkable findings in the hepatobiliary system. He was started on levetiracetam 500 mg PO BID for seizure prophylaxis. On Day 4, the laboratory results showed ALT of 76 and AST of 66. The patient was discharged on Day 13 to a skilled nursing facility with levetiracetam, albuterol, enoxaparin, tramadol and ondansetron. On Day 14, ALT was 61 and AST was 71.

On Day 68, the patient was re-admitted for sepsis secondary to a urinary tract infection. He was confirmed to be on the same medications since his discharge on Day 13. On Day 69, his ALT was 66 and AST was 33. On Day 75, ALT was 205 and AST 65. The evaluation of hepatitis A, B and C panels demonstrated positive hepatitis A virus IgG and negative hepatitis A virus IgM, hepatitis B surface and core Ag, hepatitis B core and surface antibodies, and hepatitis C antibodies. The patient was discharged back to the skilled nursing facility on Day 75.

On Day 101, the patient was re-admitted for sepsis and the ALT was 175 and AST was 66. On Day 106, the ALT was further elevated to 311 and AST was elevated to 124. At that point, levetiracetam was discontinued and he was started on phenytoin 25 mg PO TID. At discharge on Day 108, the ALT was 294 and AST was 88.

The patient was admitted a fourth time, on Day 123, with ALT of 127 and AST of 51, which further dropped to ALT of 69 and AST of 28 on discharge on Day 132. The patient was admitted for a fifth time for sepsis, and his laboratory results showed ALT of 53 and AST of 23. His liver function tests (LFTs) stayed within normal limits throughout the duration of his admission on Days 143–159. The chronology of events and patient's transaminase levels are summarized in Table 1 and Fig. 1, respectively.

DISCUSSION

Our patient demonstrated a clear time correlation between the initiation and cessation of levetiracetam and the elevation and normalization of LFTs. Although the patient was intoxicated immediately prior to admission, his liver enzyme panel was normal on admission and he did not meet the criteria for the diagnosis of alcohol use disorder. Furthermore, his hepatitis antibody panel was negative. Sepsis can certainly cause elevation in liver enzymes due to hypoxic damage and reperfusion injury [6] but our patient demonstrated normalization of ALT and AST following the discontinuation of levetiracetam, even during his subsequent fourth and fifth admissions for sepsis. Metoprolol has been reported to cause elevation in LFTs and thus hepatitis [7] but the timing of metoprolol and the transaminase levels in our patient do not correlate. The metoprolol regimen was started immediately following the discontinuation of levetiracetam, at the peak of ALT and AST levels. The ALT and AST levels continue to decrease throughout the course of metoprolol therapy. The patient did have in-patient orders for acetaminophen as needed for fever, but his dose was low and infrequent. All other potential contributing factors including concurrent in-patient and out-patient medications, chemical or infection induced liver damage, or autoimmune disorders, as well as any family history of any autoimmune or liver disease were ruled out.

According to the package insert, the bioavailability of levetiracetam is 100%, with 66% of the dose being renally excreted unchanged [4]. As for the metabolism of levetiracetam, it has been reported to be 'not dependent on any liver cytochrome P450 isoenzymes' [4]. Therefore, while requiring dosage adjustment based on renal function, no dosage adjustment based on hepatic function is recommended for levetiracetam [4], often making it a drug of choice in hepatic impairment. However, an induction of hepatic response is still possible with levetiracetam exposure. Levetiracetam therapy in one patient during the controlled trials was discontinued due to LFT or 'LFT abnormalities' [4]. In addition, although no meaningful changes in mean LFTs were observed during the controlled trials, levetiracetam has been reported to cause alterations in LFTs and hematologic laboratory parameters [8]. Tan *et al.* [9] reported elevated LFTs and fulminant liver failure potentially stemming from levetiracetam. Syed and Adams [10] also reported on potential liver failure stemming from levetiracetam use. Furthermore, Sethi *et al.* [1] also reported on levetiracetam-induced asymptomatic transaminitis. Interestingly, all but one of those cases reports

on levetiracetam-induced transaminitis are in the context of TBI and none in the context of unprovoked seizures. Therefore, it may be prudent to investigate any potential link between TBI, levetiracetam and elevated liver enzymes. In conclusion, levetiracetam induced alteration of hepatic function has been reported in few cases and a close monitoring of liver enzymes and early recognition of hepatotoxicity is critical to preventing levetiracetam-induced hepatotoxicity.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

None.

AUTHOR CONTRIBUTIONS

V.R., M.S., J.R. and M.A. organized and prepared this article.

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