Topiramate-induced acute liver injury: A rare adverse effect

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Abstract:
Idiosyncratic drug-induced liver injury (DILI) is damage to liver occurring at recommended dose of a drug in contrast to toxic or predictable DILI. Although it is common in first-generation antiepileptic drugs (AEDs), it is rare in newer AEDs such as topiramate. Topiramate commonly causes neurological adverse effects such as psychomotor slowing and somnolence. Hepatotoxicity by topiramate is rare and has been previously reported in combination with other drugs such as valproate and carbamazepine. Here, we report a case of topiramate-induced asymptomatic elevation of liver enzymes in an adult man diagnosed with alcohol dependence syndrome and alcohol withdrawal complicated with seizures.

Keywords:
Hepatotoxicity, liver injury, topiramate

Introduction
Idiosyncratic drug-induced liver injury (DILI) is an unintended response to a drug that occurs at the recommended dose for therapeutics or prophylaxis in contrast to predictable or toxic DILI.¹ It is defined as an elevation in serum alanine transaminase (ALT) or aspartate transaminase (AST) more than five times the upper limit of normal (ULN) without symptoms or an increase in alkaline phosphatase (ALP) or bilirubin more than twice the ULN with any rise in ALT and AST or AST/ALT less than five times ULN with symptoms.¹ More than 600 drugs and chemicals including first-generation antiepileptic drugs (AEDs) are known to cause hepatotoxicity but not the newer AEDs.¹ Here, we report a case of acute liver injury with topiramate which is infrequently reported as a single-inciting agent.

Case Report
A 31-year-old male presented to our hospital a year ago with a history suggestive of alcohol dependence for 10 years. He was then treated with benzodiazepines and was discharged on anticraving agent acamprosate. Subsequently, he had multiple episodes of withdrawal seizures for which he was started on topiramate and levetiracetam. Acamprosate was stopped as topiramate is known for its additional anticraving properties. After a year of abstinence since the last discharge, the patient stopped all medications. He restarted consuming alcohol at an average of 24 units per day for the last 2 months. He gave a history of multiple episodes of seizures during this time whenever he did not consume alcohol intermittently. The last episode of seizure was 10 days prior to the current admission and the last drink was 1 day prior.

The patient was diagnosed with alcohol dependence syndrome (ADS)-relapse and complicated withdrawal with seizures. He was started on multivitamin supplementation and lorazepam for symptomatic relief. A neurological opinion was sought in view of multiple seizures. Due to good response in the past, topiramate alone was restarted at a dose of 25 mg twice daily.

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daily. However, the duration of exposure to topiramate after having prescribed the last admission was not well defined as the patient reported of nonadherence. We were also unable to assess the cause of nonadherence as he was lost to follow-up and the possibility of any adverse drug reaction (ADR) that time could not be excluded.

The patient had some elevation of liver enzyme at baseline during the current admission [Table 1]; hence, as a routine treatment plan, liver function tests (LFTs) were repeated on the 3rd day of starting topiramate. The laboratory results revealed that the liver enzymes increased three times from the baseline. All other causes of liver injury including viral hepatitis were ruled out by a gastroenterologist. DILI was suspected. Lorazepam is known to be widely used in ADS and is less frequently associated with liver injury. Hence, the latter was suspected to be the cause as there are established case reports stating topiramate-induced DILI in conjunction with other hepatotoxic drugs, and in this case, there is an already existing baseline liver injury caused due to excessive alcohol consumption before admission. Therefore, topiramate was tapered and stopped within the next 2 days whereas lorazepam was continued at the same dose of 6 mg/day along with multivitamin suppletions. Repeat LFT was done on day 3 after the last dose of topiramate [Table 1], which showed a marked decrease in the liver enzymes. The patient was discharged. He was abstinent and coping well with further decrease in liver enzymes at the first follow-up visit after a week.

Discussion

Alcohol is known to cause derangements in LFT. However, it is unlikely to be the cause of elevated liver enzymes in our patient as he was admitted in the ward and was abstinent from alcohol for a week by which time LFTs usually come down. Despite alcohol abstinence we observed that the liver enzyme levels increased three times, the only trigger factor being topiramate which was started 3 days prior to LFT assay. This was followed by a rapid fall subsequent to stopping topiramate (de-challenge positive) making it the “probable” cause of liver injury according to the World Health Organization causality assessment. According to the Naranjo algorithm, the causality is “possible” with a score of 4.[2] According to the Schumock and Thornton preventability scale, the ADR is unpreventable,[3] and based on the Hartwig and Siegel Severity Assessment Scale, the severity of the reaction is placed at level 4 which involves withholding of the suspected drug and a prolonged hospital stay by at least 1 day.[2]

The Roussel Uclaf Causality Assessment Method (RUCAM) of a drug in liver injury[4] was also used and the R ratio calculated was 3.52 suggestive of mixed-type liver injury. Topiramate in this case was found to be the “possible” causal agent with a RUCAM score of 3. The temporal association of topiramate use and liver enzyme elevation, <50% fall in ALP, and exclusion of concomitant hepatotoxic drugs, alcohol use while on topiramate, and other causes of liver injury favors this causality assessment.

Topiramate is a sulfamate-substituted monosaccharide AED approved for partial seizures, generalized tonic-clonic seizures or Lennox-Gastaut syndrome in patients at least 2 years of age, and as prophylaxis for migraine in adults.[5] Topiramate is thought to act through one of the four mechanisms, namely, inactivates voltage-gated sodium channel in cerebellar granule neurons, activates hyperpolarizing potassium current, enhances postsynaptic Type A gamma-aminobutyric acid receptor, and limits activation of ε-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-kainate subtype of glutamate receptors.[6] The major adverse effects of topiramate are of central nervous system origin, most common being psychomotor slowing and somnolence.[6] However, there have been case reports on topiramate-associated hepatotoxicity in conjunction with other drugs such as valproate and carbamazepine.[6]

The mechanism by which topiramate causes liver injury is largely unknown except for an animal study postulating that it may be due to decreased antioxidant capacity of the organism as observed by decreased glutathione levels.[7] On the other hand, hepatotoxicity due to combination of drugs with topiramate is thought to be due to induction of CYP3A4 or inhibiting CYP2C19 increasing risk of valproate or other drug-induced hepatotoxicity.[6]

Table 1: Serum liver enzyme values and timelines

| Timeline       | Baseline values at admission* | 3 days after starting to piramate* | 3 days after last dose of to piramate* | 7 days after discharge – 1st follow-up |
|----------------|------------------------------|-----------------------------------|---------------------------------------|---------------------------------------|
| Date           | February 19, 2016            | February 25, 2016                  | March 01, 2016                        | March 07, 2016                        |
| AST (U/L)      | 210                          | 454                               | 162                                   | 96                                    |
| ALT (U/L)      | 161                          | 675                               | 468                                   | 277                                   |
| GGT (U/L)      | 508                          | 558                               | 417                                   | Not done                             |
| ALP (U/L)      | 101                          | 121                               | 109                                   | Not done                             |

*Protein values, bilirubin and coagulation workup were normal. AST=Aspartate transaminase, ALT=Alanine transaminase, GGT=Gamma-glutamyl transferase, ALP=Alkaline phosphatase
Conclusion

Topiramate is thought to be rarely associated with liver injury and by and large known to cause liver toxicity in conjunction with other anticonvulsants. Here, we report a case of acute asymptomatic elevation of liver enzymes in an adult caused solely by topiramate which, to the best of our knowledge, has not been reported before. Further to this, we recommend monitoring patients on topiramate for liver enzymes whenever feasible especially when on concomitant drugs labeled to cause liver injury.

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Conflicts of interest
There are no conflicts of interest.

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