Liver toxicity of Naltrexone. a case study and review of literature

Abstract

Alcohol Use Disorder is becoming a growing problem worldwide. As a chronic and relapsing disease, it can cause multisystem changes and can lead to important damages specifically in the liver and the brain. Several efficacious pharmacotherapies are currently approved for relapse prevention and naltrexone is the most used one. Even if many studies have tested its safety, we should be very careful in monitoring liver tests, because, even if rarely, liver toxicity may occur as well. In this work, we present a case of a patient with Alcohol use disorders whom was offered relapse prevention therapy with naltrexone. A severe liver toxicity occurred in the third day of the treatment with naltrexone making us think that, were there are rules and there are exceptions too.

Keywords: alcohol use disorders, naltrexone, liver function test

Abbreviations: AUD, alcohol use disorders; LVT, liver function test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NTX, naltrexone

Background

Alcohol Use Disorder (AUD) is becoming a growing problem worldwide.1 As a chronic and relapsing disease, it can cause multisystem changes and can lead to important damages specifically in the liver and the brain.2,3 Liver remain the primary target for the detrimental effects of alcohol since ethanol is mainly metabolized by liver cells, through two major alcohol oxidizing enzymes, alcohol dehydrogenase and CYP2E1.4 Elevated liver tests due to toxic effects of ethanol are the most common laboratory findings in alcohol abuse. However, other organs, including brain, gut, pancreas, lungs and the immune system are also affected by alcohol. Vitamin deficiencies leading to serious problems such as Korsakoff syndrome5 memory impairment are frequent among those with alcohol use disorders. Alcohol may also serve to intensify the progression of viral infections, autoimmune diseases and cancer by increasing the oxidative stress, dysregulation in lipid and protein metabolism. Despite psychosocial approach, several efficacious pharmacotherapies as Naltrexone, acamprosate or disulfiram are currently approved for managing AUD. They target specific aspects of biology metabolism and neurobehavioral mechanisms responsible for craving or urge for alcohol.6

Naltrexone hydrochloride, an opioid antagonist or so-called “the anticraving “drug, inhibit the pleasurable feelings of alcohol by blocking the opioid receptor sites through different mechanisms.7,8 It blocks the dopaminergic effects of brain endorphins that are released following alcohol consumption.8 On the other hand, Naltrexone can enhance the sedative effects of alcohol, and reduce craving for alcohol, both when alcohol is consumed and in response to alcohol cues when alcohol is not consumed. At the usual daily dosage of naltrexone (i.e., 50 mg or less), approximately 10% of patients may experience nausea, vomiting, fivefold elevation in liver enzymes headache, sedation, or anxiety.9,10 Many studies suggest that hepatotoxicity can occur at higher (i.e., 300 mg) daily doses11 and it is rare at the typical 50 mg daily dose. That’s why naltrexone has been used with close monitoring in individuals with liver disease.12

Case presentation

A 42-year-old, widowed, unemployed, Hispanic, man with a history of severe alcohol dependence and marijuana abuse, presented to our department of Addiction Medicine to get help for his substance abuse related problems. He has previously been admitted to emergency treatment for management of alcohol intoxication and withdrawal, including several episodes of epigastralgia, vomiting, headache, delirium tremens. Despite he was always offered inpatient substance abuse treatment that was the first time he agreed to hospitalize. He had a history of 22 years of alcohol abuse and the last year, since the death of his wife, he had increased the amount of alcohol to 40 drinks/day and was enrolled in cannabis abuse.

A detailed physical examination was performed including the blood levels of glucose, alanine aminotransferase (ALT), aspartate aminotransferase AST, Gamma-Glutamyl Transferase (GGT), direct and indirect bilirubin, lipase, amylase, troponin I, and ammonia, renal-function tests, testing for hepatitis B and C viruses. The electrocardiogram was normal and the chest radiograph showed findings consistent with chronic bronchitis.

Case Report

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Last drink was consumed around 9 hours before presenting at the hospital. Regular assessment of withdrawal symptoms was made using Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar), and the patient score was lower than 12 (the highest score was the first 24 hours of hospitalization). To prevent withdrawal complication as seizures, we used Lorazepam, a short acting benzodiazepine with no active metabolite in the liver. We applied a symptom-monitoring regime of benzodiazepine, associated to vitamin therapy and liver protectors. We began with 8mg/day and we stopped lorazepam the seventh day (Table 1). The withdrawal symptoms were managed only with lorazepam, and there was no need to add other anticonvulsant.

At admission liver function tests (LFTs) were elevated but less than 2-fold increase. ALT was 60 UI/L (normal values <41UI/L) AST 75 UI/L (normal Values <39UI/L) and GGT 122 UI/L (normal Values <61UI/L). After analyzing all the data, we excluded immune hepatitis, chronic viral hepatitis, severe dyslipidemia, obesity or other toxic drugs. And the main cause of elevated liver function test was alcohol abuse. The fourth day the ALT and AST turned to normal, while GGT values decreased and we began Naltrexone 12.5 mg/day. But, the fifth day occurred a 3-fold increase referring normal values of ALT and AST and a slightly increase of GGT. Despite the changes, after informing the patient and with his consensus, we decided to continue the medication with the same dosage. But, the toxicity become more severe and the third day of Naltrexone treatment a 10-fold elevation of liver test was observed, and we decided to stop the medication (Table 2). A further elevation of liver tests occurred the day after stopping naltrexone, due to the metabolism of the drug, a gradual return to normal in ALT and AST values was observed and we choose alternative treatment with accomprasate and psychotherapy for relapse prevention.

Table 1 Lorazepam dose during alcohol withdrawal

| Lorazepam Dose | 1st day of Hospit. | 2nd day of Hospit. | 3rd day of Hospit. | 4th day of Hospit. | 5th day of Hospit. | 6th day of Hospit. | 7th day of Hospit. |
|----------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                | 4x2mg             | 4x1.5 mg          | 3x1 mg            | 2x1mg             | 1mg               | 0.5mg             | 0                 |

Table 2 Liver tests variation during hospitalization, prior Naltrexone therapy, during and after stopping Naltrexone

| 1st day Ntx | 4th day Ntx | 5th day Ntx | 6th day Ntx | 7th day Ntx | 8th day Ntx | 10th day Ntx | 15th day Ntx | 21 day from admission at Hospit. |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-----------------------------|
| ALT U/L     | 60          | 39          | 124         | 410         | 569         | 502         | 278         | 101             | 35             |
| AST U/L     | 75          | 38          | 131         | 389         | 515         | 475         | 252         | 86              | 40             |
| GGT U/L     | 122         | 80          | 90          | 187         | 268         | 223         | 159         | 68              | 61             |

Discussion

The efficacy and the side effects of alcohol relapse prevention therapy are well studied. The oldest prescribed drug, disulfiram can induce hepatotoxicity and liver failure. Additionally, about 28% of the reported cases of disulfiram-induced hepatotoxicity resulted in death. Despite its limitations, it may be promising in patients with co-morbid alcohol dependence and post-traumatic stress disorder, or those with co-morbid cocaine- and alcohol-dependence.

Other options treatment as Naltrexone, are the drug of choice in alcohol dependent patients. Most of the studies highlight his safety, and there are few works, most of them case reports, who share the approach in naltrexone induced liver toxicity. In their study Pföhl DN and Allen JI conclude that asymptomatic and reversible elevations of serum transaminase values were seen only with high dosages of naltrexone (300mg/day) and in patient over 40 years old. While in one of his works, Salvato shed light on the idea that the elevation of LVT (Liver Function Test) could potentially be related to exogenous factors, such as dietary composition, lipid profile and should not be reflexively attributed to Naltrexone and/or drinking. Naltrexone toxicity is studied as well in patients with comorbidities like HIV or hepatitis C and is observed that it can be safely used even in this high risky category of patients. Naltrexone can be a good, safe and beneficial option treatment for alcohol use disorders patients. But we should always perform a careful monitoring of liver test, to check for dangerous liver toxicity. Then, were there are rules, there are exceptions too.

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The written informed consent of the patient was obtained, for the publication of his case.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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