Short-term Naltrexone Use Associated with Delayed-onset Fever and Hepatotoxicity: A Case Report

The use of naltrexone for treating alcohol use disorder is clinically common and has also been recommended in the 2018 American Psychiatric Association practice guideline for the pharmacological treatment of alcohol use disorder patients [1]. The recent APA practice guideline further recommends that naltrexone be offered to patients with moderate to severe alcohol use disorder, (a) who have a goal of reducing alcohol consumption or achieving abstinence, (b) who prefer pharmacotherapy or have not responded to nonpharmacological treatment alone, or (c) who have no contraindications to use it [1, 2].

Few research have shown the relationship between naltrexone and fever. In 1998, a study showed a possible mechanism of μ-opioid antagonist-induced fever [3]. Bolton et al. reviewed 76 trials in 2019, and found only one report describing fever adverse events [4].

Although the effect of naltrexone on the liver is still unclear [4], the risk of hepatotoxicity with naltrexone use has long been well-known. Medication package inserts also alerted us about the elevation of blood alanine aminotransferase (ALT) levels under the usage of high-dose naltrexone (300 mg/day) (www.ksph.gov.tw/dfiles_pdf/ Naltrexone.pdf). Here, we present a patient who used standard-dose naltrexone (50 mg/day) for a week in a restricted psychiatric ward, and he developed late-onset fever with correlating ALT elevation.

Case Report

A 60-year-old male patient was admitted due to excessive alcohol consumption, with a relapse of alcoholic neuropathy affecting both legs. On admission, he was found to have a high glutamyl transpeptidase (γ-GT) level, possibly to indicate his recent alcohol abuse. This was his second admission to the psychiatric ward for similar problems, after an interval of about half a year.

On admission, the patient started to receive beta-blockers, sedatives (lorazepam, clonazepam, and flurazepam), as well as low-dose quetiapine (100 mg/day) for alcohol withdrawal and insomnia symptoms, along with thiamine supplements for treating neuropathy. On day 14, he asked for adjuvant pills to help fight the craving for alcohol use. After discussion, we prescribed naltrexone 50 mg/day for a week (days 14-21), which was tolerable without fatigue or gastrointestinal symptoms. Nevertheless, on days 24–26, a spiking fever of up to 39.2°C was observed (Figure 1). The fever persisted for 3 days. He did not show any obvious signs of infection, and the result of a physical examination was unremarkable in finding. We did a clinical workup for fever with suspecting having biliary tract infection (BTI) initially.

Blood survey showed elevated blood aspartate aminotransferase (AST), ALT, and alkaline phosphatase. Blood C-reactive protein levels were elevated mildly, but no leukocytosis was found. Hepatitis B and C virological tests showed inactive results. We arranged abdominal sonography and consulted a GI specialist to rule out BTI. The result revealed gall bladder sludge, liver cirrhosis, and splenomegaly, without obvious gall bladder wall thickening or biliary tract dilation. After discussion, BTI was less likely. Chest X-ray films showed no obvious pneumonia patch, and severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test was negative in finding. The result of a routine urine examination revealed no signs of infection. On day 25, we prescribed the empirical antibiotic ceftriaxone 2 gm/day despite the absence of a definite infection source. The fever was subsided on day 27. We observed a relevant ALT curve with the fever course in the day-by-day laboratory follow-up (Figure 1). The patient's fever was improved without signs of toxicity during the period of fever.

Discussion

In this patient, no obvious infection was confirmed through various infection tests. Thus, drug-associated fever must be considered. We reviewed the patient's medications on the ward and focused on naltrexone use for the risk of hepatotoxicity. The COMBINE Study in 2006 already reported a rate of about 2% of naltrexone users with blood-elevated AST/ALT levels of up to five times the normal blood level (6/309 people) [6]. In earlier studies, when naltrexone was tried to treat obesity

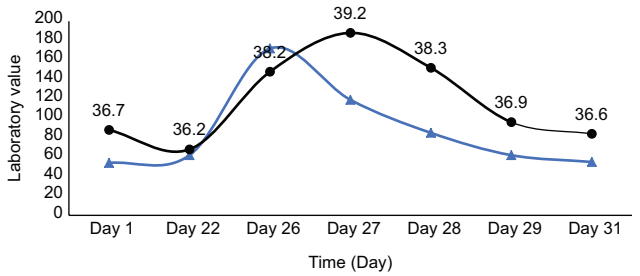

Figure 1. Laboratory data day-by-day during the fever episode. The line with triangle signs denotes the changes of blood levels of alanine aminotransferase (ALT). The line with solid circle signs is the body temperature in Celsius.

at a high dose (up to 300 mg/day), the risk of hepatotoxicity was reported and confirmed [7, 8].

Naltrexone is considered to be safe and tolerated. One study in 2006 [9], Kim et al. focused on higher doses (mean dose being 142 mg/day) and longer duration of naltrexone use (mean duration being 328 days) in 41 patients with the impulse-control disorder, and reported normal AST/ALT blood levels. In another study in 2006 [10], Yen et al. monitored 74 Taiwanese alcoholic patients using naltrexone 50 mg/day for three months, and reported no obvious blood liver enzyme level elevation. This finding showed that Taiwanese people might not be specifically vulnerable to naltrexone. In this case report, we suggest that abnormal liver function and concomitant fever episodes may occur in patients receiving standard doses of naltrexone.

The major limitation was the low-level evidence, with the present study being a single case report, and reports with larger samples are required to confirm the risk. Moreover, the possibility of hospital-acquired infection or other benzodiazepine-related hepatotoxicity cannot be fully ruled out. (The institutional review board at Chang Gung Memorial Hospital approved the publication of this case report [IRB protocol number = 202201423130 and date of approval = September 22, 2022] without the stipulation of obtaining signed informed consent from the patient.)

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Conflicts of Interest

All authors deny actual or potential conflicts of interest when writing this article.

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