Changes in Transaminases Over the Course of a 12-Week, Double-Blind Nalmefene Trial in a 38-Year-Old Female Subject

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A 38-year-old female was drinking 30 drinks/week before entering a 12-week, double-blind study of nalmefene for the treatment of alcohol dependence. Liver function tests (LFTs) were within normal limits at baseline and week 4, but on week 8, the ALT showed a 7-fold increase, and the AST showed a 4-fold increase from baseline. A decision was made to continue study medication based on the patient's positive response to this therapy (i.e., achieving complete abstinence) and no known dose-dependent association with liver toxicity in over 1300 patients treated with nalmefene for other indications. LFTs were repeated serially to assess the trend of the LFT values. The patient achieved total abstinence over the course of the study period and at the 3-month posttreatment follow-up was continuing to maintain these gains from the study program, and her LFTs had returned to normal. A gradual return to normal in ALT and AST, while treatment with nalmefene continued, does not support the role of nalmefene as an hepatotoxin. Relapse to drinking was excluded because of normal values for the γ-glutamyltransferase, and verification of sobriety by self-report, significant other, and breathalyzer. A virology panel ruled out the presence of viral hepatitis. Dietary intake before the elevation in LFTs contained elements that have established association with hepatocellular changes. The routine prescription of serial LFTs in alcoholism pharmacotherapy trials may be expected to reveal clinically nonsignificant elevations that could potentially be related to exogenous factors, such as dietary composition and should not be reflexively attributed to medication under investigation and/or drinking.

Key Words: Nalmefene, Hepatotoxicity, Alcohol Dependence, Adverse Drug Reactions, Pharmacotherapy.

Two recent independent, double-blind studies reported reductions in alcohol consumption and craving in alcohol-dependent patients randomly assigned to treatment with the opiate antagonist, naltrexone, relative to those treated with placebo. One potential risk of this new pharmacotherapy for alcoholism is its dose-dependent relationship to hepatic toxicity (DuPont Merck Pharmaceutical Co., data on file). This is of potential concern in a population characterized by chronic heavy alcohol use that may have resulted in liver damage. A newer opiate antagonist, nalmefene, has shown no dose-dependent association with hepatic toxicity in over 1300 patients treated for other indications (Baker Norton Pharmaceuticals, Inc., data on file). Furthermore, naltrexone is metabolized by oxidative pathways, whereas nalmefene is metabolized primarily by glucuronide (nonoxidative) pathways. Thus, nalmefene plasma levels may show less variability in relation to alcohol, which is known to stimulate hepatic microsomal activity and thereby accelerate drug metabolism. A double-blind pilot study of nalmefene in 21 alcohol-dependent patients found a significantly lower rate of relapse to heavy drinking and a greater increase in the number of abstinent days/week in patients randomly assigned to 20 mg twice a day (b.i.d.) of nalmefene relative to patients treated with 5 mg b.i.d. of nalmefene or placebo. Both nalmefene groups significantly reduced their number of drinks/drinking day. There were no significant changes in drinking outcome variables associated with placebo. A large-scale, double-blind study is currently underway to evaluate the safety and efficacy of nalmefene for alcohol dependence, with random assignment to 10 mg b.i.d., 40 mg b.i.d., or placebo.

CASE REPORT

Patient 11 is a 38-year-old female who was drinking 30 drinks/week before entering the 12-week, double-blind nalmefene study. The patient initially sampled alcohol at 13 years of age and met criteria for alcohol dependence at 33 years of age. Her longest period of abstinence since the onset of dependence was 7–10 days. Her preferred pattern of alcohol consumption before treatment was 4–8 drinks daily. Baseline physical examination, complete blood count, urinalysis, urine toxicology screen for drugs of abuse, and electrocardiogram were unremarkable. Liver function tests (LFTs) were obtained at baseline and monthly throughout the study, as specified in the study protocol. The patient's LFTs were within the normal range at baseline and week 4 of the study, but on week 8, the ALT showed a 7-fold increase; and the AST showed a 4-fold increase from baseline, as shown in Fig. 1. Complete blood count and urine toxicology showed no significant changes from baseline.

A decision was made to continue study medication based on the
The following hypotheses were considered as explanations for the elevation in LFTs occurring at week 8 of double-blind treatment: nalmefene induced the liver enzyme activity; the patient had resumed drinking; the patient was infected with a virus such as hepatitis or mononucleosis; an hepatotoxic agent was present in food or other substances consumed; or that a negative interaction had occurred between nalmefene and another agent. The gradual return to normal of ALT and AST, as shown in Fig. 1, while treatment with nalmefene continued, does not support the role of nalmefene as an hepatotoxin. Another hypothesis was that the patient may have had a relapse to drinking, but that was denied by the patient, and excluded because of normal values for the \( \gamma \)-glutamyltransferase (GGT), as well as weekly negative breathalyzer tests and verification of sobriety by her significant other.

Although there is no definitive biological marker to detect either relapse to drinking or alcohol dependence, GGT is regarded as the most sensitive marker for acute alcohol consumption.\(^9\) Verification of abstinence by negative breathalyzer and collateral informants, combined with GGT data, comprised the best available instruments to ratify abstinence.

A virology panel ruled out the presence of hepatitis A and B. When the increase in LFTs was noted at week 8, the patient was interviewed regarding use of concomitant medications. She reported initiation of decadron therapy and motrin 14 days before week 8 LFTs. These medications were prescribed by a private physician for an exacerbation of a preexisting right knee arthralgia. The concomitant medications were terminated by the prescribing physician 1 week after the elevation in LFTs was noted. Figure 1 demonstrates that LFTs decreased over time when the patient continued on nalmefene, but discontinued decadron and motrin. Nalmefene, decadron, and motrin, independently, have no dose-dependent association with elevation in liver enzyme activity. However, the possibility of an interaction effect by the medications on liver enzyme activity was not excluded.

At her week 10 study evaluation, the patient reported that a friend, with whom she had dined at a Mexican restaurant the evening before week 8 LFTs, had to have his inguinal hernia repair surgery rescheduled because of an elevation in LFTs that was significantly above the level previously obtained by his private physician. The patient and her friend had their LFTs analyzed on the same day by separate laboratories, with both laboratories reporting a comparable elevation. The patient's friend was not taking nalmefene, decadron, or motrin, thus ruling out the contribution of these medications, singly or in combination, in inducing liver enzyme activity. He was also found to have a negative serological test for hepatitis A and B. Therefore, the possibility of an hepatotoxic substance in their food composition the evening before the LFTs were obtained was found most plausible. Subsequent inquiry revealed that both the patient and her companion had consumed tomato-based salsa and burritos with hot pepper sauce. The patient and her companion denied any alcohol consumption. A review of the literature revealed that high doses of red chilli have been associated with hepatic histopathological changes in male mice, glycogen depletion, and anisocytosis of hepatocytes.\(^10\) Another animal study demonstrated histological changes in the liver and an increment of D-AST and inhibition of alkaline phosphatase in rats fed with garlic extract for 10 days.\(^11\) Differences across species and in duration of administration, and lack of information regarding comparability of dosage in these studies makes the applicability of these animal studies to the patient's LFT elevations impossible to assess. However, a potential association between dietary composition and liver enzyme activity in this case is intriguing.

The finding that a shared Mexican meal immediately preceded the elevation in LFTs of the patient and her friend supports the hypothesis that an hepatotoxic agent in food may have induced the liver enzyme activity. The elevation was not of clinical significance, although outside of the normal range, and both patients remained asymptomatic. If the patient's LFTs had not been routinely evaluated on a monthly basis, as part of the standard research protocol, the elevation would have undoubtedly passed unnoticed. However, given that this was an experimental medication protocol in alcohol-dependent subjects where repeated LFTs were obtained as both safety and outcome measures, an initial impulse was to attribute
the elevation in some way to the research medication or a return to drinking.

New pharmacotherapies under investigation for alcoholism offer the most promising adjunct to traditional therapies developed to date. LFTs are serially obtained in most alcoholism pharmacotherapy trials as both safety and outcome measures; for safety because of the association between alcoholism and liver disease and, at least one medication under investigation, naltrexone, is a dose-dependent hepatotoxin; as an outcome measure because self-report of reduced alcohol consumption in chronic alcoholics would presumably be validated by corresponding reductions in LFTs. However, this procedure subjects liver enzyme activity to a frequency of scrutiny that would not ordinarily be obtained. A danger of this procedure is that such a broad net is cast, that “normal” fluctuations in LFTs are captured in the data collection process and incorrectly attributed to the medication under investigation. Such an incorrect attribution could easily be made by a narrowly focused investigator or clinician, resulting in possible termination of a drug that is having a beneficial effect for the indication under investigation. This case study provides an example of a patient clearly benefitting from the intended purpose of the pharmacotherapy, but who was found to have elevations in ALT and AST during routine laboratory studies. Had it not been for the unusual circumstances of a companion, with no history of alcoholism and who was not taking study medication, showing a similar elevation following a meal shared with the patient that contained food elements associated with changes in liver activity, the patient may have been terminated from a medication that was associated with her longest period of abstinence since the onset of problem drinking. Also, a promising pharmacotherapy may have been incorrectly associated with hepatotoxicity as an adverse drug reaction.

The routine prescription of serial LFTs in alcoholism pharmacotherapy trials may be expected to reveal clinically nonsignificant fluctuations in LFT values that could potentially be associated with other ingested substances, including common elements in food. As new pharmacotherapies are developed for alcohol dependence, and more medically complex alcoholics are exposed to these medications in phase 3 trials and private practice settings, it is important that clinicians are properly informed about interpreting and managing minor elevations in measures of liver functioning. The investigator and clinician are encouraged to consider all possible etiologies for such LFT elevations, in lieu of reflexively making the attribution to an adverse drug reaction or a return to drinking.

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REFERENCES
