Disulfiram Use in Patients With Abnormal Liver Function Test Results

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Background: Concern about the precipitation of severe hepatitis by disulfiram often causes clinicians to avoid using this effective treatment in patients who have elevated baseline transaminase levels, even though no empirical evidence has so far shown severe hepatotoxicity to be related to such laboratory abnormalities. This study examines the effects of disulfiram in alcohol-dependent patients with elevated liver function test results and/or serologic evidence of hepatitis C virus (HCV) infection.

Method: Hepatitis serologies and baseline transaminase levels were obtained for 57 male alcoholics starting treatment with disulfiram. Sequential liver function test results were obtained for up to 12 weeks while subjects took disulfiram.

Results: Although subjects with elevated baseline transaminase levels and serologic evidence of HCV infection were the most likely to evidence marked elevations in transaminase levels while taking disulfiram, most subjects took disulfiram without other adverse consequences. In only 1 subject did elevations appear directly related to disulfiram.

Conclusion: Monitoring of liver function test results is warranted for patients taking disulfiram and permits most patients with moderately elevated transaminase levels to take it safely.

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Disulfiram is a widely used potentially effective pharmacologic treatment for alcohol dependence.[1,2] While typically viewed as a safe agent, disulfiram causes rare but potentially fatal hepatotoxicity.[3] The mechanism remains unclear, as does the incidence of subclinical hepatic injury. Because of this uncertainty, a tendency exists to use abnormal liver function test results as a contraindication to disulfiram use, depriving some patients of a possibly effective treatment.[4,5] Further clouding the issue, most investigations of the hepatic effects of disulfiram took place prior to the availability of assays for hepatitis C virus (HCV), which can independently cause periodic fluctuations in hepatic enzyme levels.[6] Thus, consensus does not exist about safe use of disulfiram in alcohol-dependent patients with liver disease. This study examines whether baseline elevations in liver function test results and/or serologic evidence of HCV infection is associated with subsequent increases in serum transaminase levels.

METHOD

Male veterans (N = 57) in treatment for substance dependence at the Seattle Veterans Affairs Medical Center who met DSM-IV criteria for current alcohol dependence and were planning to have disulfiram prescribed by their medical provider were eligible to enroll in the study. Exclusionary criteria were clinical jaundice; enlarged, tender liver; total bilirubin above 2.0 mg/dL; or alkaline phosphatase, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels above 200 U/L. Of referred subjects, only 2 were excluded—1 with a baseline alkaline phosphatase of 361 U/L and the other with a baseline ALT level of 294 U/L. Both did receive disulfiram off protocol and both experienced marked transaminase elevations.

Prior to starting treatment with disulfiram, all patients underwent a complete history, physical examination, and laboratory measurements including serum bilirubin, alkaline phosphatase, AST, and ALT levels and assays for HCV antibody and hepatitis B virus (HBV) surface antigen, surface antibody, and core antibody. Study personnel saw patients who were interested in participating within 7 days of starting disulfiram and obtained written, informed consent from them. Enrolled subjects completed the Addiction Severity Index[7] and were scheduled for repeat liver function tests at weeks 1, 2, 4, 8, and 12 while they remained on disulfiram treatment.

Elevations in transaminase levels after starting disulfiram therapy were the outcome measures of interest. However, nearly half of the subjects started treatment with elevated transaminase levels. We therefore needed a clinically meaningful definition of “elevated” that exam-

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Table 1. Hepatitis Serologies, Medical Status, Alcohol Use, and Transaminase Levels for Subjects Receiving Disulfiram*

	Full Sample (N = 57)		Elevation in Liver Function Test Results: No or Minimal (N = 40)		Moderate (N = 12)		Marked (N = 5)		χ^2	
Variable	N	%	N	%	N	%	N	%	(df = 2)	p Value
HBV antibody–positive	18	31.6	11	27.5	4	33.3	3	60.0	3.61	NS
HCV antibody–positive	18	31.6	8	20.0	6	50.0	4	80.0	9.42	< .01
History of iv drug use	11	19.3	4	10.0	3	25.0	4	80.0	14.30	< .002
Chronic medical problems present	27	47.4	20	50.0	2	16.7	5	100.0	10.20	< .007
	Median	Range	Median	Range	Median	Range	Median	Range	H[a] (df = 2)	p Value
Times medically hospitalized, lifetime	2	0–25	3	0–12	1	0–4	2	0–25	4.772	NS
Lifetime alcohol use, y	22	3–43	20.5	3–43	26.0	5–40	22.0	14–31	2.500	NS
Days alcohol use in prior 30	4	0–25	2.0	0–22	8.5	0–25	6.0	4–14	7.100	< .03
AST baseline, U/L	27	13–103	24	13–103	27	15–56	51	29–80	6.830	.033
ALT baseline, U/L	30	9–131	28.5	9–131	27	20–52	77	51–117	9.587	.008

*Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, HBV = hepatitis B virus, HCV = hepatitis C virus.
[a]Kruskal-Wallis H statistic.

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ined both absolute value as well as change from baseline of transaminase levels. We conceptualized 3 categories of changes in transaminase levels after initiation of disulfiram that would evoke 3 distinct clinical responses. "Marked elevation" would prompt very strong consideration to discontinue disulfiram immediately. "Moderate elevation" would raise concern but would permit further observation in trends of transaminase levels. "No or minimal elevation" would indicate no current reason to suspect any hepatotoxicity.

For purposes of data analysis in this study, we then defined these 3 groups as follows: "marked elevation" as a peak transaminase of twice the baseline *and* 3 times the upper limit of normal; "moderate elevation" as a peak transaminase between 1.5 and 2 times baseline *and* above the upper limit of normal; and "no or minimal elevation" as a peak transaminase less than 1.5 times baseline *or* within normal limits. We then categorized our subjects according to these definitions. Since the clinical response to the "moderate" and "no or minimal groups" would not differ vastly, we wondered if these groups could be combined into a single category for analysis. Preliminary analyses revealed significant differences in baseline characteristics of the "no or minimal" and the "moderate" elevation groups on chronic medical problems ($\chi^2 = 4.20$, df = 1, p = .04), number of times medically hospitalized (Mann-Whitney U = 141.5, p = .03), and days of alcohol use in the prior 30 days (Mann-Whitney U = 133.0, p = .018), so we elected to maintain the 3 distinct categories of transaminase elevation for further analysis.

RESULTS

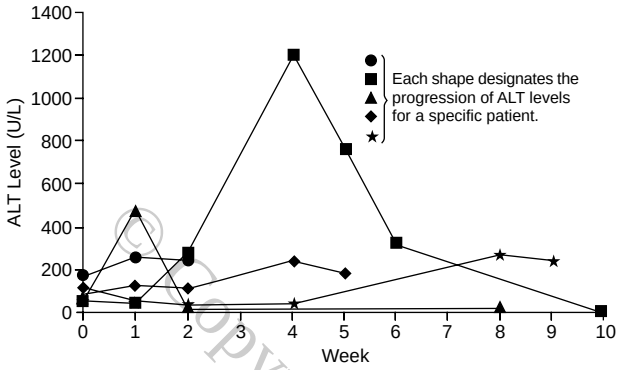
Sixty-two percent of subjects were white, 22% black, and 16% of other ethnic origin. Mean ± SD age was 42.6 ± 7.6 years. Thirty-two (56.1%) were in a controlled environment, typically substance abuse treatment, at the time of enrollment, and thus had some enforced abstinence from alcohol. Nevertheless, at baseline, 13 (22.8%) of 57 had elevations of AST levels, and 18 (31.6%) of 57 had elevations of ALT levels. Eleven had elevations of both AST and ALT levels.

Follow-up liver function test results were obtained at weeks 1, 2, 4, 8, and 12 for 48, 49, 38, 32, and 23 subjects, respectively. Only 1 subject had no follow-up testing done in the first 8 weeks, and 50 of 57 had at least 2 follow-up test batteries over that period.

Table 1 contrasts hepatitis serologies, medical problems, alcohol use, and transaminase levels for the 3 groups. Elevated baseline ALT and AST levels both were associated with subsequent marked elevations in liver function test results. Although 13 (72.2%) of 18 subjects with elevated baseline ALT levels took disulfiram without incident, no subject without an elevated baseline ALT level experienced subsequent marked elevations in liver function test results. Likewise, although 9 (69.2%) of 13 subjects with elevated baseline AST levels took disulfiram without incident, 1 subject had a baseline AST level within normal limits and then progressed to marked elevations in liver function test results. Baseline elevations of neither alkaline phosphatase nor bilirubin levels were associated with subsequent transaminase elevations.

Figure 1 conveys sequential ALT data for the 5 subjects with marked elevations. One subject had exceedingly rapid, high ALT elevations up to 1200 U/L (paralleled by elevations in AST, data not shown) with subsequent rapid declines after stopping disulfiram treatment. This HCV-negative subject remained entirely asymptomatic. Three subjects, all HCV-positive, had more gradual, less severe elevations that appeared to plateau while they remained on disulfiram treatment. One HCV-positive subject had a rapid increase in ALT level to 478 U/L with a subsequent

Figure 1. ALT Levels (U/L) for Subjects With Marked Elevations of Transaminase Levels While Taking Disulfiram (N = 5)*



*Data provided for each subject until subject was lost to follow-up.

rapid decline. He admitted to consuming alcohol while taking disulfiram during this interval.

DISCUSSION

The descriptive results of the present study are in accordance with those of Wright et al.[3] They found that among subjects with liver function test results within normal ranges placed on disulfiram, 25.0% developed elevations in ALT levels and 10.1% elevations in AST levels within 4 weeks compared with 25.6% and 18.1%, respectively, in the present study. Wright et al. also observed that ALT was the liver function test most sensitive to the effects of disulfiram.

Although this study supports the observation by Dilts and Dilts that the majority of patients who have abnormal baseline liver function test results can be safely treated with disulfiram, it argues strongly against their contention that "the routine monitoring of liver function test results during disulfiram therapy is not indicated and may be counterproductive."[5(p1505)] At least 1 patient in the present study developed hepatitis (as defined by elevated transaminase levels) that seemed to reflect disulfiram toxicity. Since the patient exhibited no clinical symptoms or signs of such toxicity, clinical monitoring alone might have permitted a case of fulminant hepatitis to progress to an adverse outcome. Therefore, sequential laboratory monitoring is essential during disulfiram treatment so that disulfiram can be discontinued when repeat transaminase levels show a trend toward a rapid increase. The present results also show, in support of the value of obtaining liver function test results prior to starting disulfiram, that marked elevations in transaminase levels occur most frequently in subjects with elevated baseline levels, particularly of ALT.

Subjects with HCV infection in this study were more likely than those without it to show elevations of transaminase levels while taking disulfiram. From these results, it cannot be determined if HCV predisposes to subclinical hepatic injury due to disulfiram use or if these elevations represent fluctuations related to HCV alone.

This study has a number of limitations. One is the lack of consistent follow-up information on disulfiram compliance. As a result, some transaminase elevations may be due to continued alcohol use rather than a direct consequence of disulfiram administration. Further work could utilize urine assay methods for disulfiram to determine the compliance rate more directly. Additionally, breath analysis tests for alcohol could be administered at each clinic visit. Another limitation is the lack of a placebo control for disulfiram. Without such control, elevations of transaminase levels occasionally seen early in the treatment of HCV-positive patients may be falsely attributed to the action of disulfiram. Finally, although serum γ-glutamyl transferase has been proposed as a sensitive indicator of alcohol-induced liver injury, levels were not measured in this study. Future work should address all of the above issues.

Because disulfiram does not demonstrate universal effectiveness in the treatment of alcohol dependence,[1] the wisdom of using it in a patient with abnormal liver function test results, or, for that matter, in any patient, might be questioned. In a double-blind, placebo-controlled trial, abstinence rates did not differ among alcoholic subjects receiving disulfiram, 250 mg q.d., disulfiram, 1 mg q.d., and placebo.[1] However, among subjects who consumed alcohol and completed all assessments during the year-long study, those taking disulfiram 250 mg q.d. reported significantly fewer days of drinking than did subjects on the other 2 regimens.[1] In that study, disulfiram administration was not supervised. In a subsequent study, which was not blinded for ethical reasons, alcoholic subjects randomly assigned to receive supervised disulfiram, 200 mg q.d., had significantly less alcohol consumption over 6 months than did subjects assigned to receive supervised vitamin C.[8] Thus, disulfiram clearly reduces total alcohol consumption for some patients. Alcohol-induced liver injury represents to some extent a dose-related event,[9] so reducing the amount of alcohol consumed takes on considerable importance, particularly in those patients for whom elevated liver function test results denote already existing liver disease.

In conclusion, the present findings support the cautious use of disulfiram in patients with elevated baseline liver function test results. We propose a protocol that selects those patients who have elevated ALT levels at baseline as targets for particularly close monitoring but does not exclude patients simply on the basis of liver function test results that, although elevated, lie within those used as inclusion criteria for this study. However, we cannot recommend the use of disulfiram in patients outside that range.

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Drug name: disulfiram (Antabuse).

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