Elevated Liver Enzyme Levels in Opioid-Dependent Patients with Hepatitis Treated with Buprenorphine

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The purpose of this study was to assess changes in liver enzyme levels among opioid-dependent patients treated with buprenorphine. Liver enzyme levels were evaluated among 120 individuals before treatment and following a minimum of 40 days of buprenorphine treatment (2, 4, or 8 mg/70 kg/day). Among patients with a history of hepatitis, AST and ALT levels significantly increased ($p < .05$) with buprenorphine treatment. The odds of observing an increase in AST were determined to be dependent upon buprenorphine dose ($p < .05$; odds ratio $= 1.23$ per 1 mg increase in dose). These results suggest that liver enzyme levels should be monitored carefully when patients with hepatitis are treated with buprenorphine. (Am J Addict 2000;9:265–269)

Buprenorphine, a partial mu opioid agonist, may soon be approved by the Food and Drug Administration for treatment of opioid dependence in the United States. Buprenorphine blocks the effects of other opioids and compares favorably to methadone in controlled trials of maintenance and detoxification of opioid-dependent individuals. Only two known published reports have suggested a possible relationship between buprenorphine treatment and hepatic dysfunction. Lange and colleagues showed a trend toward increased serum aminotransferase levels in 18 heroin addicts treated with buprenorphine. In a case report, Houdret et al. found that a patient developed severe hepatitis, acute renal failure, and anuria after consuming 112 mg of buprenorphine; hepatic and renal function normalized following discontinuation of buprenorphine and hemodialysis treatment. The purpose of this study was to evaluate liver...
enzyme aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels among buprenorphine-treated individuals.

METHODS

Liver enzyme data were examined from all admissions to an outpatient buprenorphine clinic between January 1991 and June 1996. Inclusion criteria for treatment were age ≥18 years and federal criteria for methadone maintenance (eg, significant opioid withdrawal symptoms or opioid-positive urine specimens). All subjects signed an informed consent for study participation, which was approved by the Institutional Review Board at the University of Vermont.

In total, 120 subjects received buprenorphine for a minimum of 40 days and had liver enzyme levels taken at intake (prior to buprenorphine treatment) and again between days 41 and 90 of buprenorphine treatment (median 51, interquartile [IQ] range 44–61 days). These time intervals were chosen to include the greatest number of subjects possible in the analyses and to coincide with the intervals prior to buprenorphine dose decreases for patients enrolled in detoxification studies. Subjects received sublingual buprenorphine on a daily or less than daily basis in doses of 2, 4, or 8 mg/70 kg/day (range 1.5 mg to 12.8 mg/day), depending on severity of opioid dependence.

Across the sample, 66% were male, average age was 42, and 95% were Caucasian. Subjects had an average of 12.6 years of education, a 9-year history of heroin dependence, and 86% were intravenous drug users.

A medical history was conducted at intake to treatment. Liver enzyme levels were measured prior to buprenorphine administration, and subsequent tests were scheduled every six weeks thereafter (or more often if clinically indicated). Hepatitis status was determined by laboratory screening and history. In total, 72 patients were diagnosed with hepatitis (9 with hepatitis B, 19 with hepatitis C, 38 with both B and C, and 6 reported a history of hepatitis but did not have their status verified by a blood test at this clinic). Forty-eight patients had no evidence of hepatitis at intake.

RESULTS

Figure 1 shows the median AST and ALT values at intake and following buprenorphine treatment. Due to non-normally distributed data, the nonparametric Wilcoxon signed rank test was used to test whether AST and ALT enzyme levels changed during buprenorphine treatment. Data were analysed separately for subjects with and without hepatitis.

For non-hepatitis subjects, buprenorphine treatment showed no evidence of altered liver enzyme levels. The median change in ALT values was 0 (IQ range −7 to 8). The median change in AST was 0.5 (IQ range −6 to 4.5).

In contrast, AST and ALT levels increased significantly with buprenorphine treatment among patients with a history of hepatitis. The median change in ALT values was 8.5 (IQ range: −12 to 54, n = 72, S = 323, p = .04), and the median change in AST values was 9.5 (IQ range −7.5 to 31.5, n = 72, S = 480, p = .006).

Furthermore, the odds of observing an increase in AST among patients with hepatitis was determined to be dependent upon buprenorphine dose ($X^2 = 4.7, p = .03$). Based on logistic regression, the estimated odds ratio was 1.23 per mg increase in buprenorphine dose (95% CI 1.02 to 1.50). No association was noted between buprenorphine dose and increases in ALT values ($X^2 = 0.4, p = .52$).

Cases in which AST and ALT values were significantly elevated (above 150 for AST or above 200 for ALT) were evaluated individually. At intake, nine subjects met these criteria for significantly elevated liver enzyme levels. Three of these nine subjects showed reductions in liver enzyme values with buprenorphine treatment, but even among these three subjects, the values were still in the high-abnormal range (AST ranged from
42–133 and ALT from 36–165). The other six remained in the significantly elevated range (AST > 150 or ALT > 200) throughout the treatment period. An additional 14 subjects developed significantly elevated liver enzyme levels during buprenorphine treatment. At intake, the median AST and ALT values for these 14 subjects were 83 (IQ range: 50–114) and 100 (IQ range: 44–155), respectively. Following a minimum of 40 days of buprenorphine treatment, these values rose to a median of 173 (IQ range: 146–216) for AST and 273 (IQ range: 206–329) for ALT.

Seventeen of the 72 subjects with hepatitis were enrolled in a buprenorphine detoxification study and had subsequent liver enzyme levels taken when their dose of buprenorphine was reduced to less than 50% of their maintenance dose. For this liver function test conducted during the detoxification, the median number of days since intake was 106 (IQ range 96–171), and the average buprenorphine dose had decreased to 32 ± 11% the original dose. For these 17 subjects, the median AST value at intake was 53 (IQ range: 37–129). During full-dose buprenorphine treatment, AST values increased to a median of 79 (IQ range: 53–163.5), and then reduced slightly to a median of 74 (IQ range: 46–132) as the buprenorphine dose decreased. For ALT levels, the median values at intake, during full-dose buprenorphine treatment, and during the
detoxification were 89 (IQ range: 45–178.5), 108 (IQ range: 70.5–301.5), and 90 (IQ range: 40–216, respectively). None of these changes reached statistical significance, however.

DISCUSSION

These data demonstrate significant increases in AST and ALT among buprenorphine-treated patients with hepatitis. Moreover, increases in AST were dependent upon the dose of buprenorphine administered. Nine subjects evidenced clinically significantly elevated liver enzyme levels at intake, and 20 subjects met these criteria during treatment with buprenorphine. Finally, trends toward reduced AST and ALT levels were noted in a small sample of subjects who had liver function tests conducted during a buprenorphine detoxification. These findings may have important implications for the approval of buprenorphine in the United States as a medication for the treatment of opioid dependence. They may also influence clinical care of patients treated with this drug, especially because the majority of opioid-dependent patients have hepatitis.

Although these data suggest increases in liver enzyme levels with buprenorphine treatment, these results must be interpreted with caution. These data are from a relatively small number of individuals, and analyses were retrospective in nature. Replication of these results in a larger sample and with a longer history of buprenorphine treatment is necessary. In addition, other drug use (eg, alcohol, other opioids, cocaine) may affect liver enzyme levels, but other drug use was not systematically evaluated across all the studies in which these patients participated. Nevertheless, participation in most of our studies was contingent upon opioid abstinence, and even subjects in our detoxification studies tended to reduce illicit opioid use, especially prior to dose reductions. Other studies of buprenorphine and methadone-maintained patients likewise tend to report reductions in illicit drug use when patients are maintained on adequate doses of medication. Thus, it is unlikely that the elevations in AST and ALT values noted in our sample resulted from increased illicit drug use while these subjects were maintained on buprenorphine.

Large-scale multicenter trials examining the safety and efficacy of buprenorphine have been conducted, and systematic evaluations of liver enzyme results collected from these patients may further address the effects of buprenorphine on liver enzymes. Clinically significant increases in liver enzyme levels have been reported following high-dose opioid antagonist treatment. Therefore, clinical trials evaluating the safety of the buprenorphine-naloxone combination product should be conducted because buprenorphine and naloxone may have an additive effect on liver enzyme levels.

Despite the significant increases in liver enzymes noted in this study, acute symptomatic hepatitis developed in only three patients treated with buprenorphine at this clinic. Because hepatitis can have a vacillating course, these cases may or may not be related to buprenorphine. In addition, the increases in liver enzyme levels found in this study, while statistically significant, were small in magnitude.

Randomized controlled trials comparing buprenorphine’s effects on liver functioning to those of methadone and LAAM may be warranted to further evaluate the association between opioid substitution therapy and hepatotoxicity. Although use of methadone and LAAM does not seem to be associated with liver toxicity, many of these studies were published prior to the spread of hepatitis in intravenous drug using populations. Prospective studies assessing changes in liver enzyme levels as medication doses decrease during detoxification may be necessary as well. Until more systematic data on the safety of buprenorphine are available, careful monitoring of liver enzyme levels should be conducted in patients with hepatitis who are treated with buprenorphine.
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