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Effects of Buprenorphine and Hepatitis C on Liver Enzymes in Adolescents and Young Adults

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Abstract

Objective—The purpose of this study was to explore changes in transaminase values associated with buprenorphine treatment and hepatitis C status among opioid dependent subjects aged 15–21.

Methods—152 subjects seeking treatment for opioid dependence were randomized to 2-week detoxification with buprenorphine/naloxone (DETOX) or 12 weeks buprenorphine/naloxone (BUP). Liver chemistries including transaminases were obtained baseline and at 4, 8, and 12 weeks. 111 patients had at least one set of transaminases during treatment and were included in analyses of treatment effects.

Results—Overall, 8/60 BUP participants vs. 12/51 DETOX participants had at least one elevated ALT value during follow-up (Chi-square n.s.). 5/60 BUP participants vs. 11/51 DETOX participants had at least one elevated AST value (Chi-square = 3.194, $p = .048$). Twenty-eight out of 152 participants were hepatitis C (HCV) positive at baseline, and 4 seroconverted within 12 weeks, 2 in each group. HCV status was significantly associated with transaminase abnormalities ($p = .009$ and $p = .006$ for ALT and AST, respectively). HCV status had a strong effect on transaminase abnormalities among participants assigned to DETOX, but not among those assigned to BUP.

Conclusions—No evidence was found for hepatotoxicity of buprenorphine in this exploratory analysis. HCV was present in a significant minority of participants and was a significant predictor of transaminase elevation. Results suggest that stabilization on buprenorphine may decrease the frequency of transaminase abnormalities associated with HCV in opioid dependent young people. The high rate of seroconversion underscores the importance of effective treatment and prevention.

Keywords

buprenorphine; opioid dependence; adolescent; heroin; hepatitis C

Introduction

Buprenorphine is increasingly used as a first-line medication for opioid dependence due to evidence of efficacy and safety as well as greater convenience relative to methadone (Mattick et al., 2004). The potential of buprenorphine to cause liver toxicity has not been fully evaluated. Hepatotoxicity in overdose (Houdret et al., 1999) or intravenous use (Berson et al., 2001) has been reported, and cases of acute cytolytic hepatitis have been seen with therapeutic sublingual dosing (Herve et al., 2004; Zuin et al., 2008). Elevated transaminases have also been observed in patients with a history of liver disease who were treated with therapeutic doses of sublingual buprenorphine (Petry et al., 2000). A multi-site study was designed specifically to address the question of buprenorphine hepatotoxicity and is currently underway in the NIDA Clinical Trials Network (CTN-0027: Starting Treatment with Agonist Replacement Therapies (START)). Liver safety is of particular concern in opioid addicts due to the high prevalence of Hepatitis C (HCV). Seroprevalence in various cohorts of adult injection drug users range from 64% to almost 100%, with higher rates in older cohorts (Diaz et al., 2001; Murrill et al., 2002; Patrick et al., 2001).

Since the beginning of the 21st century, rates of heroin and prescription opioid use among adolescents, including injection use, have plateaued at levels 2–3 times those seen in the early 1990s. According to Monitoring the Future data from 2007, current past year heroin use among 12th graders is about 1%, and past year use of other opioids including prescription analgesics is over 9% (Johnston et al., 2008). There is evidence that younger heroin users (< 25 years old) progress more rapidly from first use of heroin to regular use and treatment for opioid dependence (Mills et al., 2004). Although buprenorphine is an attractive treatment option for this population, there are few efficacy or safety data for buprenorphine in adolescents, and limited clinical experience. A small randomized trial by Marsch et al. found significantly improved treatment retention and abstinence in adolescents undergoing 28-day detoxification with buprenorphine relative to detoxification with clonidine (Marsch et al., 2005). Woody et al. (2008) reported a robust improvement in outcomes in adolescents and young adults treated with buprenorphine/naloxone for 12 weeks relative to 2-week detoxification. The prevalence of HCV and HIV among adolescent opioid addicts is not well characterized, but incidence appears to be particularly high for those who initiate injection at an early age (Miller et al., 2006).

Given the significant numbers of adolescents now using opioids and the increase in those presenting for treatment of prescription opioid addiction (2008), it would be useful to know more about the incidence and prevalence of hepatitis C and liver function abnormalities in this population, and to know whether buprenorphine has any effect on liver function in young patients with or without HCV. It is not safe to assume that results of studies in adult populations transfer to younger populations, as is illustrated by recent data showing age-related effects of antidepressants on suicidal behavior (Hammad et al., 2006). Here we report on liver safety and Hepatitis C data from a trial of buprenorphine/naloxone treatment of adolescents and young adults recently completed through the NIDA Clinical Trials Network (Woody et al., 2008). The aims of the study reported here are to 1) describe the liver chemistry results and HCV status of this sample, and 2) explore the effects of treatment assignment and HCV status on rates of transaminase abnormalities.

Methods

Baseline data were available for 152 subjects at 6 sites who sought treatment for opioid dependence. Details of the study have been published elsewhere (Woody et al., 2008). Participants were aged 14–21, met DSM-IV criteria for opioid dependence with physiologic features, and were seeking outpatient treatment. Exclusion criteria included serious medical

or psychiatric conditions, frequent use of benzodiazepines or sedatives, pregnancy or lactation, and psychotropic medication other than SSRIs. Participants were randomized to 2 week detoxification with buprenorphine/naloxone (DETOX) or 12 weeks buprenorphine/naloxone (BUP). In the BUP group, buprenorphine/naloxone was tapered during the last 3 weeks of treatment. Participants in both groups were offered weekly individual and group drug counseling.

Liver chemistries were evaluated prior to treatment and at 4, 8, and 12 weeks, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, lactate dehydrogenase, total bilirubin, and alkaline phosphatase. HCV antibody was determined at baseline and at 12 weeks. We were primarily interested in the transaminases (ALT and AST) because past reports of hepatotoxicity in buprenorphine-treated patients with and without HCV have focused on these enzymes (Berson et al., 2001; Herve et al., 2004; Petry et al., 2000). One hundred and eleven participants had at least one set of transaminases during treatment and were included in analyses of treatment effects.

The liver chemistry data collected for the study included the numerical value for each test, whether this value was normal, and whether the value of any test was greater than five times normal. Therefore, we were able to compare both the distribution of values and the frequency of abnormal values between groups. 95% confidence intervals for proportions were computed according to the method of Wilson with continuity correction (Newcombe, 1998). Labs were processed locally rather than at a central lab, so methodologies and normal ranges were not identical across the sites, and the upper limit of normal was not recorded. Bivariate associations between treatment assignment and HCV status and frequency of transaminase abnormalities were examined using Pearson Chi-Square or Fisher's Exact Test. Because transaminase values showed extremely skewed distributions that did not respond to standard techniques to normalize them, we used non-parametric tests (Mann-Whitney U) to compare them. Logistic regression was used to explore the independent contribution of treatment group, HCV status, and their interaction on the presence of any transaminase elevation during treatment. The size of the available sample was sufficient to detect medium to large effects with adequate power. For example, with the sample of 111 participants, alpha set at .05, and desired power of .80, the study was able to detect an effect of $w = .265$. No corrections were made for multiple comparisons due to the exploratory nature of the study.

Results

Sample characteristics and summary of main study results

Table 1 summarizes demographic and clinical features of the 152 participants included in the study, by treatment group. Mean age was 19.1 years, and mean duration of opioid dependence was 1.5 years. 76% used heroin, 56% used prescription opioids, and 50% injected drugs. Maximum doses for DETOX patients were as follows: 24 (31%) received 2 to 8 mg and 53 (68%) received 9 to 14 mg. For BUP patients, 20 (27%) received 2 to 8 mg, 43 (59%) received 9 to 16 mg, and 10 (14%) received 17 to 24 mg. As reported previously (Woody et al., 2008), during-treatment substance use outcomes were much more favorable in the BUP group. At 4 and 8 weeks, 61% and 54% of DETOX patients had urines positive for opioids, vs. 26% and 23% of BUP patients, respectively. Self-reported opioid, cocaine, marijuana, and injection drug use were also significantly lower in BUP patients (Odds ratios (95% CI) = 4.30 (2.25–8.22), 16.39 (3.07–87.47), 6.15 (2.10–18.01), 3.54 (1.27–9.87), respectively).

Rates of transaminase abnormalities at baseline and during treatment

Overall, 8/60 BUP participants (13.3%, 95% CI 6.3–25.1%) vs. 12/51 DETOX participants (23.5%, 95% CI 13.3–37.8%) had at least one elevated ALT value during follow-up (Chi-square n.s.). 5/60 BUP participants (8.3%, 95% CI 3.1–19.1%) vs. 11/51 DETOX participants (21.6%, 95% CI 11.8–35.7%) had at least one elevated AST value (Chi-square = 3.194, $p = .048$). Figure 1a illustrates rates of abnormal transaminase values for each time point in BUP and DETOX participants. Elevated AST values were significantly more common in the DETOX group than in the BUP group at 4 and 8 weeks. Two individuals in the DETOX group and 2 in the BUP group developed markedly elevated transaminases (greater than 5 times the upper limit of the normal range).

Table 2 shows the mean transaminase values at each time point for participants assigned to BUP vs. DETOX. When means were compared, the only significant difference between BUP and DETOX was the 8-week AST value (24.3 ± 10.3 vs. 40.6 ± 45.7 , $U = 649.5$, $Z = 2.49$, $p = .013$). No significant differences were found for any of the other liver chemistries at any time point.

Relationship of HCV status and treatment assignment to transaminase abnormalities

28/152 (18.4%) of participants were HCV positive at baseline. Highly significant differences were found between sites in rates of HCV, with 3/3, 12/51, 0/28, 11/39, and 2/30 participants HCV positive at baseline at each of the participating nodes (Excluding the node that had only 3 subjects, Chi Square = 11.93, $p = .008$). Four participants seroconverted within 12 weeks, 2 in each group. A fifth participant had newly elevated liver chemistries at 4 weeks but was lost to follow-up until 12 months, at which time he had seroconverted.

Combining across time points, 9/24 participants (37.5%, 95% CI 19.6–59.2%) who were HCV seropositive at baseline or at 12 weeks had at least one elevated ALT value, vs. 11/87 (12.6%, 95% CI 6.78–21.9%) of those who were HCV-negative ($p = .009$, Fisher's Exact Test). 8/24 HCV-positive participants (33.3%, 95% CI 16.4–55.3%) had an elevated AST value during follow-up, vs. 8/87 (9.2%, 95% CI 4.3–17.8%) of those who were seronegative ($p = .006$, Fisher's Exact Test). Figure 1b illustrates the corresponding rates of transaminase abnormalities by HCV status at each time point. Again, significant differences were found for both transaminases at each time point with the exception of week 8, where the differences were not statistically significant. Table 2 shows mean transaminase values of HCV+ and HCV- participants at each time point. Values for both transaminases were significantly higher in the HCV+ group for all time points except week 8.

Logistic Regression models

Logistic regression was used to assess the independent contributions of treatment assignment, HCV status, and their interaction to the presence of any abnormal AST or ALT value during treatment ($n = 111$). The baseline transaminase value was entered first as a covariate. In these models (Table 3), treatment assignment was a significant predictor of both ALT and AST elevation. In addition, the interaction between treatment assignment and HCV status was significantly related to ALT abnormalities, and was related to AST abnormalities at the level of a trend. After accounting for these effects, HCV status was a significant predictor of neither ALT nor AST elevations. This interaction may be interpreted by noting that among DETOX patients, 8/12 (66.7%, 95% CI 35.4–88.7%) who were HCV+ had at least one abnormal ALT value, compared to 4/39 HCV- participants (10.3%, 95% CI 3.3–25.2%) (Chi-Square = 16.229, $p = .0001$). Among BUP patients, 1/12 HCV+ participants (8.3%, 95% CI 0.4–40.2%) had an abnormal ALT value, not significantly different from 7/48 (14.6% 95% CI 6.5–28.4%) of the HCV- participants. Similarly, for AST, 7/12 DETOX patients (58.3% 95% CI 28.6–83.5%) who were HCV+ had at least one

abnormal AST value, compared to 4/39 (10.3% 95% CI 3.3–25.2%) of HCV- participants (Chi-Square = 12.538, $p = .0004$). Among BUP patients, 1/12 (8.3% 95% CI 0.4–40.2) of HCV+ participants had an abnormal AST value, equivalent to 4/48 (8.3% 95% CI 2.7–20.9%) of the HCV- participants.

Relationship of transaminase abnormalities to use of hepatotoxic substances

It is plausible that the relationship between treatment assignment and transaminase abnormalities could be mediated by greater use of alcohol, acetaminophen or prescription opioid use in the DETOX group. Prescription opioids are of interest in this regard because they are frequently compounded with acetaminophen. 19/51 DETOX vs. 27/60 BUP participants reported acetaminophen use during the trial (n.s.). There were no significant relationships between reported acetaminophen use and transaminase elevations, neither for the entire sample nor the HCV-positive sub-group. Alcohol use was more frequent at 4 weeks in DETOX than in BUP participants (1.04 days per week vs. .34 days per week, $p = .008$), and opioid use (excluding heroin and methadone) was higher at 4 and 8 weeks (respectively .93 vs. .16 days per week, $p = .010$; .62 vs. .10 days per week, $p = .012$). However, neither was significantly correlated with transaminase abnormalities or values at any time point. Again, this was true for both the entire sample and those who were HCV-positive. Thus we found no evidence that toxicity due to these substances mediated the observed treatment effect.

Finally, because of the possibility that buprenorphine itself could be hepatotoxic, we examined the distribution of buprenorphine doses among the participants who had elevated transaminases. Among the 9 such individuals in the BUP group, maximum dose was 8 or lower for $n=3$, between 9 and 16 for $n=4$, and between 17 and 24 for $n=2$, a distribution very similar to that of the entire bup-treated sample. For the DETOX participants (who received buprenorphine only for the first two weeks of treatment) 3 of the 15 participants with an abnormal transaminase had a maximum dose of 8 or less, and 12/15 had a dose between 9 and 14. This is a somewhat lower proportion of low-dose participants in the group with abnormal transaminases ($3/15 = 20\%$, vs. 31% in the whole sample), but the difference is not statistically significant ($p = .366$, Fisher's exact).

Discussion

No evidence was found for any hepatotoxic effects of buprenorphine in this sample. The vast majority of the abnormalities seen were mild elevations (less than 5 times the upper limit of normal), and AST values were less likely to be abnormal among patients in the BUP condition. Hepatitis C was present in a significant minority of participants (19% at baseline) and was much more robustly associated with transaminase elevation. The high degree of variability among sites in rates of HCV differs from the uniformly high rates seen among opioid-dependent adults in various cities. This suggests that there may have been differences in the user networks or methods of administration among the sites that affect risk of contracting HCV. The high rate of seroconversion (4 of 83 who were tested at baseline and 12 weeks) underscores the importance of effective treatment and prevention in this population, which could include longer-term agonist treatment.

The most intriguing finding of this study is that the rates of elevated transaminases associated with HCV infection were much lower in those treated with buprenorphine for 12 weeks than in those who received detoxification. Since there are no known mechanisms that could account for a direct protective effect of buprenorphine, the most parsimonious explanation is that this effect is mediated by the robust decreases in illicit drug use found in the BUP group relative to DETOX: Opioid, cocaine, marijuana and injecting drug use were significantly lower in BUP than DETOX patients during treatment (Woody et al., 2008).

Heroin use has been shown to cause abnormalities in cellular immunity which normalizes with methadone substitution (Novick et al., 1989). Decreased drug use could be associated with decreased exposure to toxins such as adulterants in illicit drugs or acetaminophen in prescription opioids. Alcohol is less likely to have played a role in this sample as alcohol use was rather low, and baseline frequency of binge drinking was not correlated with transaminase values. Positive lifestyle changes associated with decreased drug use also could enhance the immunological response to the virus. The negative effects of stress on immune function are well documented (Irwin, 2008), although the effect of stress on the course of HCV is unknown.

These differences should be interpreted cautiously due to the post hoc nature of the analyses, the relatively large number of comparisons that were made without correcting for multiple comparisons, the questionable clinical significance of most of the abnormalities, the significant number of missing follow-up data points, and the relatively small number of subjects. The most significant limitation is that the study did not have sufficient power to detect uncommon effects reliably due to relatively small sample size. Since laboratory tests were processed locally, laboratory values may not be strictly comparable across sites. While somewhat reassuring, these findings in no way rule out idiosyncratic hepatotoxic effects of buprenorphine, be they mild or severe. There were a considerable number of missing data that were handled in different ways for the various analyses. The ongoing NIDA/CTN liver study should provide additional data on the potential for buprenorphine to produce hepatotoxic effects in adults. Further adolescent studies and/or surveillance data from clinical use will be necessary to confirm the safety of buprenorphine in adolescents, and to determine if extended buprenorphine treatment has an effect on incidence and/or course of HCV in adolescents.

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Figure 1. Percent ALT and AST abnormalities at baseline, 4 weeks, 8 weeks, and 12 weeks by treatment group (BUP vs. DETOX) and HCV status (HCV+ vs. HCV-)

* $p < .05$

** $p < .01$

*** $p < .001$

p values are for Fisher's exact, two-sided.

Number of subjects is as follows. Baseline BUP = 74, DETOX = 78, HCV+ = 28, HCV- = 123; week 4 BUP = 54, DETOX = 41, HCV + = 16, HCV- = 79; week 8 BUP = 51, DETOX = 37, HCV + = 13, HCV- = 75; week 12 BUP = 46, DETOX = 37, HCV + = 14, HCV- = 68.

Table 1**Baseline Sample Characteristics by Treatment Assignment***

	BUP (N =74)	DETOX (N =78)
Age	19.14 (1.4)	19.2 (1.6)
Age < 18 yrs	12 (16)	14 (18)
Male sex	42 (56.8)	48 (61.5)
Race/ethnicity		
<i>non-Hispanic White</i>	56 (75.7)	56 (71.8)
<i>African American</i>	1 (1.4)	2 (2.6)
<i>Hispanic</i>	18 (24.3)	20 (25.6)
<i>Filipino</i>	0	1 (1.3)
Primary drug problem		
<i>heroin</i>	42 (57)	41 (53)
<i>other opioids/analgesics</i>	27 (36)	25 (32)
<i>polydrug</i>	5 (7)	11 (14)
Years heroin use	1 (0/3)	1 (1/2)
Years opioid use	1 (0/3)	1 (0/2)
Injecting, past 30 days	35 (47)	36 (48)
Days alcohol intoxication, past 30 days	.85 (2.156)	.61 (2.231)
Past 30 days		
HCV positive	12 (16.2)	16 (20.5)

* For continuous measures, except for years heroin use and years opioid use, numbers represent means, with standard deviations in parentheses. For years heroin use and years opioid use numbers represent means, with first and third quartile given in parentheses. For dichotomous measures, numbers represent number of participants, with percentage of participants in parentheses.

Table 2

Mean transaminase values ($\pm$ S.D.) before and during treatment, by treatment assignment and HCV status

	Baseline		4 weeks		8 weeks		12 weeks	
	BUP N = 74	DETOX N = 78	BUP N = 54	DETOX N = 41	BUP N = 51	DETOX N = 37	BUP N = 46	DETOX N = 37
ALT	34.8 $\pm$ 51.7	32.6 $\pm$ 37.3	35.2 $\pm$ 75.6	49.8 $\pm$ 70.2	26.8 $\pm$ 19.7	49.8 $\pm$ 100.0	28.4 $\pm$ 33.8	46.8 $\pm$ 86.3
AST	30.6 $\pm$ 36.8	27.7 $\pm$ 18.4	29.7 $\pm$ 42.0	41.2 $\pm$ 53.0	24.3 $\pm$ 10.3*	40.6 $\pm$ 45.7	24.3 $\pm$ 15.5	33.1 $\pm$ 44.2
	HCV+ N = 28	HCV- N = 123	HCV+ N = 16	HCV- N = 79	HCV+ N = 13	HCV- N = 75	HCV+ N = 14	HCV- N = 68
ALT	51.89 $\pm$ 62.08*	29.7 $\pm$ 39.1	71.50 $\pm$ 75.77**	35.4 $\pm$ 71.8	77.54 $\pm$ 145.16	29.3 $\pm$ 39.0	93.14 $\pm$ 129.88**	24.9 $\pm$ 28.3
AST	37.71 $\pm$ 27.21*	27.2 $\pm$ 29.0	46.69 $\pm$ 35.40**	32.3 $\pm$ 49.0	48.15 $\pm$ 68.42	28.2 $\pm$ 18.6	53.86 $\pm$ 68.03***	22.9 $\pm$ 13.1

* Significant difference between groups, $p < .05$, Mann-Whitney U.

** Significant difference between groups, $p < .01$, Mann-Whitney U.

*** Significant difference between groups, $p < .001$, Mann-Whitney U.

Table 3

Logistic regression models of the effects of treatment assignment, HCV status, and their interaction on presence of transaminase abnormalities*

ALT abnormalities						
	B	S.E.	Wald	df	Sig.	Exp(B)
Baseline ALT	.009	.006	1.945	1	.163	1.009
Treatment	3.411	1.352	6.361	1	.012	30.302
HCV status	1.253	1.340	.874	1	.350	3.500
Treatment by HCV status	-3.859	1.525	6.403	1	.011	.021
Constant	-3.262	1.380	5.592	1	.018	.038

AST abnormalities						
	B	S.E.	Wald	df	Sig.	Exp(B)
Baseline AST	-.001	.012	.002	1	.962	.999
Treatment	2.729	1.201	5.164	1	.023	15.322
HCV status	-.019	1.227	.000	1	.988	.981
Treatment by HCV status	-2.498	1.415	3.115	1	.078	.082
Constant	-2.366	1.224	3.736	1	.053	.094

* Coding for these analyses: HCV status: HCV + = 1, HCV - = 0; Treatment: Bup = 1, Detox = 0.