Ethanol and Pain Sensitivity: Effects in Healthy Subjects Using an Acute Pain Paradigm

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Background: The primary objective of this study was to determine whether healthy subjects without a history of heavy alcohol use or a family history of alcoholism exhibit a concentration-dependent analgesic effect of ethanol. In a preliminary fashion, we also compared this sample to a group of subjects with a strong positive family history for alcoholism (FHP) to test the secondary hypothesis that FHP individuals will be more sensitive to the analgesic effects of alcohol compared to healthy subjects who are negative for a family history of alcoholism (FHN).

Methods: Forty-one healthy FHN subjects and 19 FHP subjects participated. Test days included an ethanol high concentration (breathalyzer = 0.100 g/dl), ethanol low concentration (breathalyzer = 0.040 g/dl) or placebo. The infusion of ethanol was via computerized pump to achieve a steady-state ("clamp") ethanol concentration. Noxious electrical stimulation and pain assessments were performed prior to start of placebo/ethanol infusion and at the 60-min infusion mark. The applied current was progressively increased until the pain was reported as 5 or higher on an 11-point Verbal Numeric Scale (VNS). Outcome variables included measures of pain threshold and tolerance and Visual Analog Scales of mood states.

Results: Among FHN subjects there was a significant ethanol concentration effect on pain tolerance ($F = 3.0$, $p = 0.05$). The average change in pain stimuli required to reach a VNS of 5 or greater were (−2.4, −1.0, and 2.2 mAmps respectively) for high concentration, low concentration, and placebo. There were no ethanol concentration related differences in pain threshold. The analgesic effect of ethanol was not correlated with changes in mood states, suggesting an independent analgesic effect of the drug. A comparison of FHP to FHN subjects produced no differences on pain responses.

Conclusion: The findings support the hypothesis that in healthy subjects intravenous ethanol administration has a concentration effect on pain tolerance but not on pain threshold. Additional studies are planned to further elucidate the mechanisms of ethanol's analgesic effects.

Key Words: Ethanol, Analgesia, Pain, Alcoholism, Vulnerability, Family History.

THE ANESTHETIC AND analgesic properties of alcohol have been recorded for centuries. Despite its long history, the medical literature contains few systematic studies examining alcohol's analgesic properties or its ability to suppress pain in a controlled laboratory setting.

Several studies provide empirical evidence that pain sensitivity decreases after ethanol consumption in an experimental paradigm (James et al., 1978; Mullin and Luckhardt, 1934; Wolff et al., 1941, 1942; Woodrow and Eltherington, 1988). Ethanol was reported to be a promising analgesic adjunct with an efficacy comparable to that of opiates (James et al., 1978; Mullin and Luckhardt, 1934; Wolff et al., 1941; Woodrow and Eltherington, 1988). In one study, 56 g of orally administered ethanol caused a decrease in cutaneous pain sensitivity and there was a dissociation between tactile and pain sensation (Mullin and Luckhardt, 1934). In separate studies, 23 and 46 g oral ethanol increased pain thresholds using experimentally induced heat pain by irradiating a small patch of skin with a 1,000 W bulb (Wolff et al., 1941, 1942). The higher dose increased the duration of the analgesic effect, but not the intensity. Intravenous (IV) ethanol producing blood alcohol levels (BAL) of 0.2 g/dl increased pain threshold of experimentally induced pressure pain in a group of healthy men (James et al., 1978). Similarly, oral ethanol at lower concentrations (BAL 0.07 g/dl) attenuated pain tolerance, but not pain threshold following noxious mechanical pressure to the Achilles tendon in a group of healthy women (Woodrow and Eltherington, 1988).

The analgesic effects of ethanol remain poorly defined as these earlier studies have a number of limitations. The lack of

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randomized, double blind, placebo controlled design suggests that other factors, such as expectation, may have confounded the results. Another limitation is the absence of strict subject selection criteria. Pain sensitivity to analgesics varies amongst individuals; several factors are implicated in influencing pain responses. Such factors include gender (Noble, 1996), history of alcoholism (Brown and Cutter, 1977; Petrie, 1978), and familial history of alcoholism (Stewart et al., 1995). A gender difference in pain response has been a consistent finding, with women exhibiting more response to the analgesic effects of morphine than men (Pud et al., 2006). With the exception of the Woodrow and Eltherington (1988) study conducted in females, the studies cited above were conducted in men only or in subjects where gender is not mentioned.

An individual's personal drinking history, as well as a family history of alcoholism are additional factors to consider in assessing the analgesic response to ethanol. Sober alcoholics have been found to be more sensitive to painful stimulation than nonalcoholic controls (Brown and Cutter, 1977; Petrie, 1978), and may be more sensitive to the analgesic effects of ethanol as well (Brown and Cutter, 1977; Petrie, 1978). There is evidence that individuals with a family history of alcoholism, even if they do not have a personal history of alcoholism, experience pain and the analgesic effects of ethanol differently than those without a family history (Stewart et al., 1995). Young healthy males with a family history of alcoholism rated an aversive electrical stimulation as more painful than age-matched controls without a family history. Following oral ethanol 53 g/70 kg the group differences were eliminated, suggesting subjects with a family history of alcoholism were more responsive to ethanol's analgesic effects compared to low risk controls (Stewart et al., 1995). Similarly, high-risk males, defined as those with mutigenerational history of alcoholism, were more reactive by cardiovascular parameters, to an aversive stimulus than low risk controls (Finn and Pihl, 1987, 1988). High-risk individuals' increased sensitivity to pain and discomfort, combined with ethanol's ability to attenuate these perceptions, has been hypothesized to play a role in predisposing these individuals for the development of alcoholism (Pihl et al., 1989; Stewart and Pihl, 1994). Consequently, rigorous subject screening to control for these factors is essential to advancing understanding of the analgesic properties of ethanol.

Firm conclusions on the analgesic effects of ethanol are additionally impeded by methodology related to the route of ethanol administration and the chosen experimental pain stimulus. Historically, there has been a diversity of alcohol administration paradigms as each mode of administration carries particular limitations. Oral alcohol administration is plagued by variable absorption, side-effects such as nausea, and variable BAL even when controlling for factors such as gender and weight. Oral alcohol protocols are also affected by subject expectations resulting from the smell and taste of the alcohol beverage. The administration of a fixed IV dose has similar problems in variable BAL since equivalent doses lead to different BAL. A novel way to evaluate responses to alcohol administration is to use a "clamp procedure" where a target BAL is achieved with an IV infusion that is titrated to breathalyzer readings and maintained at a steady state (O'Connor et al., 1998, 2000; Subramanian et al., 2002). This approach allows for direct comparisons of effects of a specific concentration of ethanol between groups, without the confounding factors of variable alcohol absorption and peak BAL's that have negatively affected earlier studies of ethanol analgesia.

New study designs which control for these methodological and subject related criteria are required to better elucidate the pharmacologic effects of alcohol on pain. To that end, we set out to define and expand upon the prior findings of ethanol analgesia using an IV alcohol clamping procedure and a large, well characterized sample in order to evaluate ethanol's analgesic effects in healthy individuals. We conducted a randomized, double blind, placebo controlled, cross over examination of pain response to noxious electrical stimulation. The subjects were within a narrow age range, included both male and females, and were well screened for medical, psychiatric and substance use disorders. We also report preliminary findings from a comparison with a small group of subjects who have a family history of alcoholism.

The primary hypothesis of this study is that healthy subjects without a history of heavy alcohol use or a family history of alcoholism will exhibit a concentration-dependent analgesic effect to ethanol administered by the IV "clamp" procedure. Our secondary hypothesis was that FHP individuals will be more sensitive to the analgesic effects of alcohol compared to healthy subjects who are negative for a family history of alcoholism (FHN).

METHODS

Subject Selection

Healthy individuals ($n = 41$) were recruited by advertisement and compensated for their participation in this institutional review board approved protocol. Inclusion criteria included: (i) males and females between the ages of 21 and 30; (ii) no lifetime axis I psychiatric or substance use disorder; (iii) no family history of alcoholism in any first or second-degree relatives and (iv) medically and neurologically healthy on the basis of history, physical examination, electrocardiogram, and screening laboratories. In addition a small comparison group of FHP subjects ($n = 19$) were recruited. These subjects met the above criteria except they all had a biological father and another first or second-degree biological relative with history of alcoholism.

Exclusion criteria included: (i) for women: positive pregnancy test at screening or intention to engage in unprotected sex during the study; (ii) alcohol naïve; (iii) adoptees with no contact with family members; and (v) a history of alcoholism in mothers, to exclude the potential for effect of fetal alcohol exposure.

After signing informed consent, subjects underwent baseline screening. As part of the baseline screening, subjects participated in an orientation session where the pain procedures and pain rating scale were explained and electrical stimulation was applied and rated as described in detail below. Ninety-six subjects signed informed consent and underwent an intake assessment. Of those, 30 did not meet the inclusion criteria while 66 did and were enrolled in the study. Sixty individuals (FHN = 41, FHP = 19) participated in all 3 test days and were included in the analysis. Subjects who did not

complete the entire study included 2 subjects who completed 2 test days (1 became ill during infusion on the high concentration day and the other did not finish because the subject started a full time job), and 4 subjects who completed 1 test day (1 stopped infusion on high-dose day and 3 withdrew from the study as a result of time commitments).

After screening, subjects were scheduled for three *separate* test days at least 3-d apart in a randomized order under double-blind conditions. Test days included an ethanol high concentration (targeted breathalyzer = 0.100 g/dl), ethanol low concentration (targeted breathalyzer = 0.040 g/dl) or placebo. Prior to each test session, participants fasted overnight. They presented to the Biological Studies Unit at VA Connecticut Healthcare System, West Haven campus, at approximately 8:30 AM. Prior to testing, subjects underwent urine drug screening for toxicology and breathalyzer screening, and after all tests were negative, an IV line was placed. They then received a light breakfast (individual serving of cereal with milk, and a cup of either cranberry juice or orange juice).

Ethanol Infusion

Infusion of ethanol was a solution of ethanol 6% (v/v) in 0.9% normal saline solution via computerized pump (Braun Horizon NXT) to achieve a predetermined steady-state ("clamp") breath alcohol concentration (BrAc). The infusion rate was designed to achieve the target concentration at approximately 20 min and then to maintain steady state concentration using a clamp procedure for 60 min. This method is well documented and validated in the literature (O'Connor et al., 1998, 2000; Ramchandani et al., 1999; Subramanian et al., 2002). The loading phase rate is determined using a MATLAB (MATLAB 1987) calculation package that includes patient age, gender, height and weight to generate a linear ascension to target BrAc in 20 min. Thereafter the infusion pump rate is adjusted so that the subjects are maintained within ±5 mg% of target BrAc for 1 h. BrAc is measured every 2 min during the ascension phase and every 2 to 8 min during steady-state by Alcotest 7410-plus device (Dräger Safety AG & Co. KGaA, Lübeck, Germany) and adjustments in infusion rates are made to maintain the clamped BrAc. The placebo infusion used identically marked IV bottles as that for ethanol infusion and BrAC testing and pump alterations mimicked the procedures followed on the ethanol test days. The concentrations were chosen to represent a low concentration, in the range of 1 to 2 drinks over an hour, while the high concentration was selected to achieve the legal limit for intoxication in the State of Connecticut at the time of study initiation.

Pain Testing

At the beginning of each test day, a standardized explanation was read to subjects explaining the pain testing procedure. Noxious electrical stimulation and pain assessments were performed at 2 time points, 60 min prior to start of placebo/alcohol infusion ("baseline") and at the 60-min infusion mark (Fig. 1). A constant current device (Innervator Model NS252, Fisher Paykel) provided square wave stimulation in a 830 ms double-burst pattern (two short burst of three stimuli at a frequency of 50 Hz separated by 750 ms) to the volar surface of the distal forearm via conductive gel electrodes (distance between adjacent margins 20 mm). Starting at 0 mAmps, the applied current was progressively increased at 10 mAmp intervals until the pain was reported as 5 or higher on a an 11 point Verbal Numeric Scale (VNS) anchored at 0 representing no pain and 10 the worst pain imaginable. A-β low threshold mechanoreceptors are the most sensitive to electrical stimulation and are the only fibers activated at detection-threshold levels of stimulation. As stimulation intensity is increases further, A-δ fibers and ultimately C-fibers are activated resulting in pain sensations. The lowest current which produced pain was noted as the pain threshold and the current achieving a score of 5 was noted as the pain tolerance. A score of 5 was chosen for 2 purposes: (i) it reflects significant pain but avoids extreme

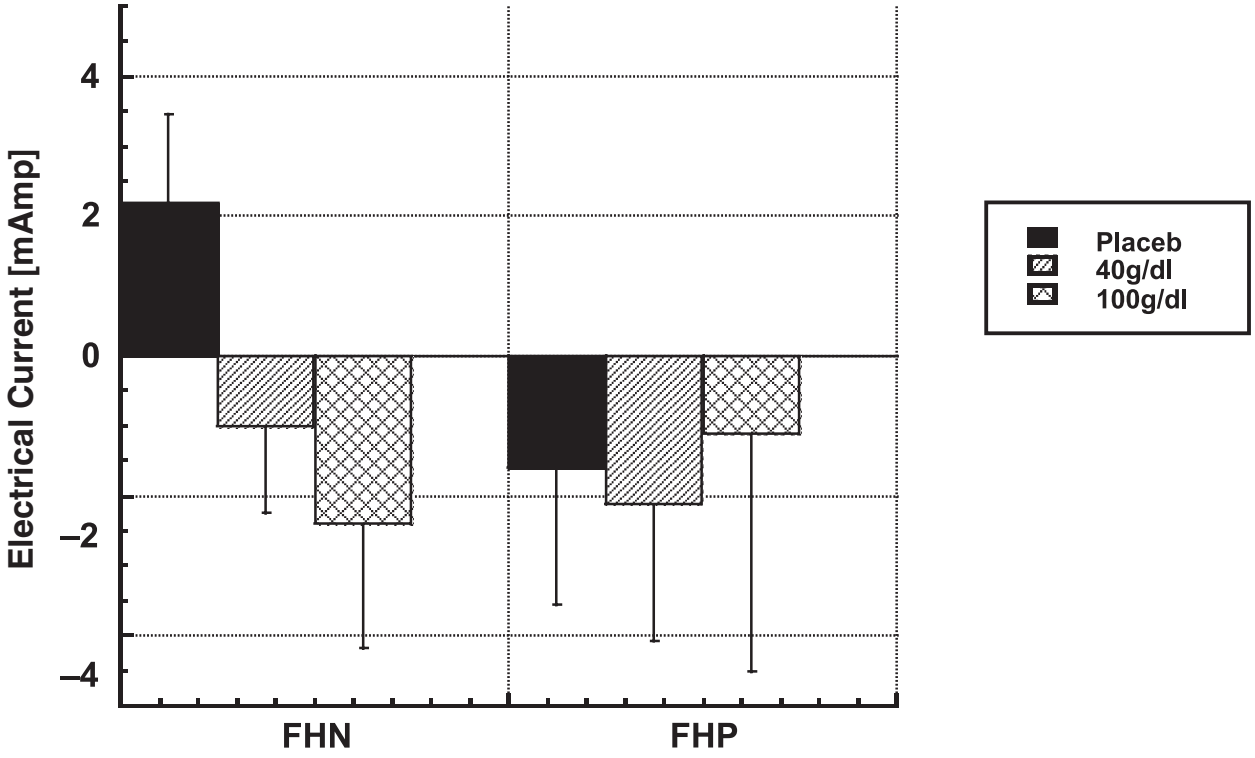

Fig. 1. Infusion begins at 0:00, and target BrAc achieved at 0:30 and the clamp technique maintains targeted BrAc for 60 min, at which time the infusion is terminated. First stimulation is 60 min before the alcohol infusion starts. The second stimulation is at 60 min after the alcohol infusion starts.

discomfort to the subjects, and (ii) it avoids the nonlinearity in grading pain intensity that can occur with higher degrees of pain (Hartmannsgruber et al., 1999). The inter-stimulus interval was 15 s. Two ramps of electrical stimulation were performed at each time point (baseline and infusion) and the data from the two ramps from each time point was averaged.

Mood Assessments

Mood ratings were assessed at baseline (−140 min before the start of the infusion) and 60 min after the alcohol was clamped and target was reached (+60) (and always preceded the pain stimulation procedure) using Visual Analog Scales (VAS). These scales are 0 to 7 VAS marked proportionately to the perceived intensity of the subjective experience (0 = not at all, 7 = extremely) for the following mood states: buzzed, depressed, anxious, and irritable. These mood ratings have shown convergent validity with other measures of mood states during similar challenge studies (Buck, 1996; Harris et al., 1998; Kumar et al., 2004). Subjects were also asked to report on the number of drinks they felt they had consumed using the Number of Drinks Scale (NDS), which has also been used in several previous challenge studies conducted by this group (Buck, 1996). The NDS scale was administered at baseline (−140) and once the target was reached (0).

Data Analysis

The main outcome variables included measures of pain threshold and pain tolerance. The effect of the infusion on pain threshold and tolerance was calculated as the difference in recorded current between infusion and baseline. All analyses were performed using SPSS version 12.0. All variables were tested using the Kolgomorrov–Smirnov test for normality. The pain data were analyzed using ANOVA and a model that included the effects of infusion as a within subject factor (placebo, BrAC.040 g/dl alcohol and BrAC 0.100 g/dl alcohol), gender as a between subject factor, and their interaction. In the secondary analysis family history (FHP and FHN) was added as a between subject factor. We also examined the relationship between pain sensitivity and mood by performing Pearson's correlations between pain tolerance, pain threshold scores and VAS "buzzed" scores.

Other analysis included variables of alcohol effects and included breath alcohol levels during infusion, number of drinks, and the VAS mood scores. In order to confirm that the amount of alcohol remained constant during the pain assessment, we calculated the average breath alcohol level over the period of 60-min infusion for 0.040 and 0.100 g/dl alcohol. We used the NDS as another test of alcohol effects. In order to examine the affective changes often attributed to alcohol we analyzed differences between placebo, 0.040 and 0.100 g/dl alcohol using the VAS scale (feeling "buzzed", "depressed", "anxious", and "irritable"). Bonferroni procedure was used where appropriate to adjust the α level for multiple comparisons (VAS scale).

RESULTS

Demographic Characteristics

Forty-one subjects without a family history of alcoholism (FHN) participated in 3 test days. The average age was 23.4 (SD = 2.3) years, 21 were male, and 30 (73%) were white. The average age at which subjects began drinking was 17.5 (SD = 1.7) years. The average number of drinking days within the past 30 d before infusion was 6.7 (SD = 5.1, range: 1–25) and the average number of standard drinks within the past 30 d before infusion was 20.0 (SD = 18.4, range: 1–69). Since we found no significant time effect (differences between day 1, 2, or 3) for baseline pain threshold or pain tolerance ($F = 1.2$, $p = 0.28$; $F = 1.1$, $p = 0.33$ for pain threshold and tolerance respectively), we averaged the baseline scores over time and present baseline pain threshold and tolerance as an average score (see Table 1). The average threshold sensitivity at baseline was 15.5 mAmps (SD = 1.18), and the average pain tolerance at baseline was 48.3 mAmps (SD = 2.3).

The comparison group included 19 FHP subjects. The average age among these subjects was 23.7 (SD = 3.3), 11 were male, and 10 (53%) were white. The average age at which subjects started drinking was 17.4 (SD = 2.7) years.

Table 1. Demographic Characteristics

Variable	FHPn = 19 Mean, SD	FHNn = 41 Mean, SD	Family History$F$, p-value	Statistics Gender$F$, p-value	Interaction$F$, p-value
Age					
Male	24.0, 3.38	24.01, 2.46	0.09, 0.72	1.46, 0.232	0.13, 0.723
Female	23.4, 3.34	22.9, 1.94			
Age at first drink					
Male	18.3, 1.35	17.7, 1.68	0.23, 0.64	5.65, **0.021**	2.17, 0.146
Female	16.1, 3.60	17.2, 1.69			
Total drinking days (last 30 d)					
Male	6.9, 4.66	22.6, 21.12	1.67, 0.20	2.93, 0.093	0.70, 0.408
Female	3.5, 2.33	18.79, 16.40			
Total number of drinks (last 30 d)					
Male	18.6, 19.54	22.6, 21.12	1.88, 0.18	1.81, 0.185	0.36, 0.551
Female	8.8, 7.80	18.8, 16.40			
Years of education					
Male	16.3, 2.37	16.29, 1.31	0.27, 0.61	3.84, **0.055**	0.25, 0.623
Female	15.0, 2.78	15.53, 1.54			
Average baseline pain threshold					
Male	10.9, 3.02	14.8, 6.80	0.36, 0.55	1.99, 0.164	0.04, 0.837
Female	15.0, 10.69	16.0, 11.42			
Average baseline pain response					
Male	47.2, 14.8	47.4, 12.9	0.26, 0.61	0.004, 0.94	0.21, 0.64
Female	45.0, 17.6	49.2, 16.5			

Boldface values indicate statistical significance.

The average number of drinking days within the past 30 d before infusion was 5.5 (SD = 4.1, Range: 0–14), and the average number of standard drinks within the past 30 d before infusion was 14.5 (SD = 16.1, range: 0–71) (See Table 1). The average threshold sensitivity at baseline was 14.1 mAmps (SD = 1.75), and the average pain tolerance at baseline was 46.1 mAmps (SD = 3.53).

There were no differences in demographic characteristics between the FHP and FHN. However, significant gender differences were found in the overall sample for two variables: age when drinking was first reported and years of education.

Pain Tolerance and Threshold

As shown in Fig. 2, among those subjects with a negative family history for alcoholism there was a significant ethanol concentration effect on pain tolerance ($F = 3.0$, $p = 0.05$). The average change in pain stimuli required to reach a VNS of 5 or greater were (−2.4, −1.0, and 2.2 mAmps respectively) for high concentration, low concentration and placebo. In contrast, there were no ethanol concentration related differences in pain threshold. There was no significant concentration by gender interaction ($F = 0.05$, $p = 0.94$). Similarly there was no effect of gender on pain threshold.

In the secondary analysis comparing FHN and FHP subjects, the average change scores for pain tolerance were (FHN = −2.4, −1.0, and 2.2 mAmps, FHP = −1.83, −1.21, and 0.3 mAmps respectively) for high concentration, low concentration, and placebo. There was no significant ethanol concentration effect on pain tolerance ($F = 0.75$, $p = 0.475$), gender effect on pain, ($F = 1.8$, $p = 0.18$), family history effects on pain ($F = 0.465$, $p = 0.498$) or any interaction between concentration, family history, and gender on pain tolerance. Similarly, there were no significant differences in pain threshold for concentration, gender, family history, and their interactions.

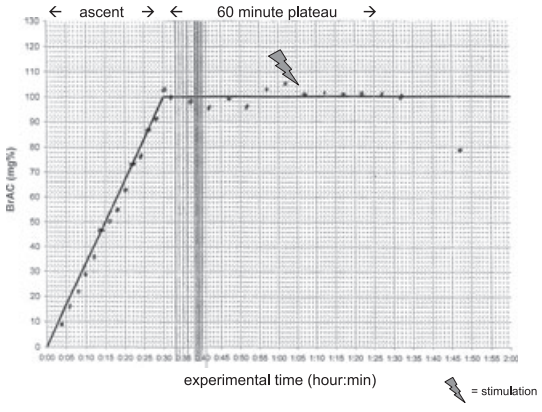

Fig. 2. Change in pain tolerance (post–pre) for healthy subjects without a family history of alcoholism (FHN) ($n = 41$): a comparison group of subjects with a strong family history of alcoholism (FHP) ($n = 19$) is also included.

Ethanol Effects

In order to confirm that the ethanol clamp procedure administered the predicted amount of ethanol, the BrAc data was analyzed. After reaching the desired ethanol concentration, and during the clamped hour of infusion, an average BrAc reading for each subject was calculated. For the low concentration of ethanol (0.040 g/dl alcohol) the mean BrAc reading was 0.0437 g/dl (SD = 0.011), and for the high concentration of ethanol (0.100 g/dl alcohol) it was 0.100 g/dl (SD = 0.018). In order to test whether the procedure produced the expected mood effects the VAS and the NDS scales were also analyzed using the model specified earlier. The analysis of the 4 VAS scales produces significant differences in "buzzed" and "irritable" only. For "buzzed" gender ($F = 6.6$, $p = 0.01$), and concentration were both significant ($F = 39.5$, $p = 0.000$), but there was no significant interaction. This indicated that overall the females reported feeling more "buzzed" than males and the increase in "buzzed" was concentration dependent. For "irritable", concentration was the only significant finding ($F = 4.3$, $p = 0.01$) showing that an increase in irritability was concentration dependent.

As expected, ethanol produced a concentration-dependent increase in the perceived number of standard ethanol drinks administered based on the NDS scale. At the low concentration subjects reported they experienced the infusion as 1.9 standard drinks (SD = 1.2) and at the high concentration they experienced the infusion as 3.3 (SD = 1.7) ($F = 88.9$, $p = 0.000$).

In order to evaluate whether pain scores were related to feeling "buzzed", Pearson's correlation coefficients were performed. There was no significant relationship between pain sensitivity and feeling "buzzed".

DISCUSSION

The findings from this study provide support for the primary hypothesis and demonstrate that in young healthy adults without a family history of alcoholism IV ethanol administration at the 0.100 g/dl level elevated pain tolerance, though not pain threshold, in a noxious electrical stimulation pain paradigm. Ethanol administration at the lower concentration of 0.04 g/dl did not produce a significant effect on pain sensitivity. The analgesic effect of ethanol was not related to the mood alterations produced by the steady state clamped infusion suggesting an independent analgesic effect of the drug. There were no gender differences in pain tolerance or threshold. Our results did not provide support for our secondary hypothesis. A comparison of two healthy groups, one with family history of alcoholism to one without, produced no differences between groups on either pain tolerance or pain threshold and no effect of gender.

This study is consistent with previous research suggesting that ethanol has an effect on pain tolerance, but not pain threshold, in a laboratory setting. However, the magnitude of pain relieving effect by ethanol we report is appreciably less

than that of several earlier trials (James et al., 1978; Mullin and Luckhardt, 1934; Wolff et al., 1941, 1942; Woodrow and Eltherington, 1988). In our study, the increase in pain tolerance to electrical stimulation obtained with the high concentration ethanol was 10% above baseline electrical current. A comparison to prior studies examining the analgesic effect of opiates on noxious electrical stimulation provides a perspective on the efficacy of ethanol as an analgesic. The short acting synthetic opioid alfentanil administered in step-up infusions resulted in an analgesic effect of 117% above baseline electrical current at a blood concentration of 160 ng/ml while at a lower concentration of 35 ng/ml the analgesic effect was 19% above baseline current (Angst et al., 2004). Dahan et al. (2006) showed a progressive dose response with the opioid agonist-antagonist buprenorphine with analgesic effect increasing to 29% above baseline electrical current at the dose 0.2 mg/70 kg, and even greater analgesia at the dose of 0.4 mg/70 kg. These comparisons suggest that the analgesia obtained with ethanol at concentrations up to 0.100 g/dl compares to that of low-dose opioids and is less efficacious than that achievable with higher doses of opioids. Our results, therefore, contrast with some previous reports which claim the analgesic effects of ethanol to be on par with the analgesic effects of moderate to high doses of the opiates morphine (11 to 14 mg/70 kg) and codeine (0.03 to 0.06 g) in response to pressure pain (James et al., 1978; Mullin and Luckhardt, 1934; Woodrow and Eltherington, 1988) or heat pain (Wolff et al., 1941).

Apart from the different pain paradigm used in the current study (noxious electrical stimulation versus heat or pressure pain), the relatively low analgesic effect we observed may be attributable to methodological differences of the current study compared to earlier studies. In particular, this is the only study of ethanol analgesia to employ a randomized, double blinded, cross-over protocol. It is well recognized that studies influenced by investigator bias and subject expectations can produce exaggerated responses when compared to those of randomized, double blinded protocols (Brown and Cutter, 1977). Notably, the earlier ethanol analgesia studies failed to cope with expectancy bias and placebo effects. Wolff et al.'s (1941) study, in which the investigators themselves served as subjects and a placebo arm was not included, exemplify these concerns.

The current study also employed strict entrance criteria, which limited subjects to those with no current or prior history of heavy alcohol use. The earlier studies of ethanol analgesia lacked these restrictions and the effects of chronic alcohol use, tolerance to alcohol, and/or withdrawal may have affected their results. Brown and Cutter (Brown and Cutter, 1977) clearly demonstrated differential responses to alcohol based on customary drinking habits. In their studies, alcoholics and problem drinkers, but not nonalcoholics and social drinkers, showed marked reductions in pain with ethanol during a cold pressor test. These findings reinforce the impact of subject selection and prior experience with alcohol on studies addressing ethanol analgesia.

There is a question as to why we did not find increased sensitivity to ethanol analgesia in FHP subjects compared to FHN subjects as has been demonstrated in prior reports (Finn and Pihl, 1987; Stewart et al., 1995). In this preliminary report, we did not find subjects with a family history positive for alcoholism to have increased pain responses at baseline or differential responses during ethanol administration at either 0.040 or 0.100 g/dl. In fact, the findings suggest that the FHP individuals may have an *attenuated* analgesic response to alcohol. There was no concentration response in analgesia in the FHP group, and in the combined group of FHP and FHN. The only group to show an analgesic response to ethanol was the FHN group. These findings are consistent, however, with research suggesting that FHP individuals are less sensitive to some of the behavioral effects of ethanol (Pollock, 1992; Schuckit, 1994). Because comparison of FHP and FHN responses to ethanol analgesia has only been tested in 2 previous studies, and this study is not conclusive, further work in this area is necessary before firm conclusions can be drawn.

We are the first to examine gender as a factor in ethanol analgesia. The lack of gender effect in our study contrasts with the literature where females show greater response to opioid analgesia. One explanation for this finding is that the mechanism of ethanol analgesia is different from opioid-induced analgesia and that ethanol may not mediate pain via μ opioid receptor activation.

Study Limitations

While results from this study provide insight into ethanol analgesia at steady blood alcohol concentrations, there are some limitations. Ethanol's effects on analgesia during different stages of intoxication, such as during the ascending and descending limb of concentration changes, were not examined. We examined pain tolerance at moderate pain levels and alcohol's effects on responses to more intense stimuli may be different. Of potential importance is that acute pain stimuli protocols, such as used in the current study, may provide only a partial estimation of the analgesic properties of alcohol. Ethanol acts as a potent *N*-methyl-D-aspartate (NMDA) glutamate antagonist (Lovinger and Crabbe, 2005). NMDA antagonists, such as ketamine, have proven efficacious in preventing and moderating hyperalgesia, the heightened pain response resulting when the spinal cord dorsal horn neurons become hypersensitized following a sustained afferent barrage (Petrenko et al., 2003). Chronic pain syndromes and post-traumatic pain are two examples where modulations of glutamate transmission in spinal neuronal systems dramatically alters the pain messaging sent to the higher levels of the central nervous system. Characteristic of hyperalgesia is marked increase in pain sensitivity in the area surrounding the injury such that compared to the mild pricking sensation a von Frey filament produces on a nontraumatized limb, one perceives acute discomfort when the region surrounding the injury is stimulated. NMDA antagonists show lesser effects on reducing pain related to brief stimulation of peripheral pain afferent

neurons (Chizh, 2002; Fisher et al., 2000). Intrathecal ethanol has been shown to attenuate NMDA-mediated hyperalgesia in the rat (Meller et al., 1993) Accordingly, acute pain stimuli protocols may provide an incomplete examination of the pain relieving properties of ethanol. Consequently, we plan to pursue follow-up studies to examine ethanol's effects on moderating capsaicin induced hyperalgesia in human subjects. The hyperalgesia pain model may also prove to be a useful probe in alcoholism research as individuals with a FHP for alcoholism exhibit altered NMDA responses (Petrakis et al., 2004).

In conclusion, our findings show that ethanol produces significant analgesia during a rigorous experimental pain protocol. The mechanisms by which ethanol acts in pain attenuation are poorly understood but characterizing this mechanism implicates a number of receptor systems. This report reflects preliminary work from our laboratory. We plan to further explore ethanol's effects on pain sensitivities in both healthy subjects and those with a FHP for alcoholism using a hyperalgesia model to assess ethanol's effects on NMDA-mediated spinal cord pain responses.

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