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Intranasal Oxytocin Blocks Alcohol Withdrawal in Human Subjects

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Abstract

Background—The neuropeptide, oxytocin, has been reported to block tolerance formation to alcohol and decrease withdrawal symptoms in alcohol-dependent rodents. Numerous recent studies in human subjects indicate that oxytocin administered by the intranasal route penetrates into and exerts effects within the brain.

Methods—In a randomized, double-blind clinical trial, intranasal oxytocin (24 IU/dose, N=7)) or placebo (N=4) was given BID for 3 days in alcohol dependent subjects admitted to a research unit for medical detoxification using Clinical Institute Withdrawal Assessment for Alcohol (CIWA) score-driven PRN administration of lorazepam. Subjects rated themselves on the Alcohol Withdrawal Symptom Checklist (AWSC) each time CIWA scores were obtained. Subjects also completed the Penn Alcohol Craving Scale (PACS), an Alcohol Craving Visual Analog Scale (ACVAS) and the Profile of Mood States (POMS) on inpatient days 2 and 3.

Results—All subjects had drunk heavily each day for at least 2 weeks prior to study and had previously experienced withdrawal upon stopping/decreasing alcohol consumption. Oxytocin was superior to placebo in reducing alcohol withdrawal as evidenced by: less total lorazepam required to complete detoxification (3.4 mg [4.7, SD] vs. 16.5 [4.4], p=.0015), lower mean CIWA scores on admission day 1 (4.3 [2.3] vs. 11.8 [0.4], p<.0001) and day 2 (3.4 [2.2] vs. 11.1 [3.6], p<.002), lower AWSC scores on days 1 and 2 (p<.02; p=.07), lower ACVAS ratings (p=.01) and lower POMS Tension/Anxiety subscale scores on day 2 (p<.01).

Conclusions—This is the first demonstration that oxytocin treatment may block alcohol withdrawal in human subjects. Our results are consistent with previous findings in rodents that oxytocin inhibits neuroadaptation to and withdrawal from alcohol. Oxytocin could have advantages over benzodiazepines in managing alcohol withdrawal because it may reverse rather than maintain sedative-hypnotic tolerance. It will be important to test whether oxytocin treatment is effective in reducing drinking in alcohol dependent outpatients.

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Keywords

Oxytocin; alcohol withdrawal; detoxification; dependence; tolerance; human subjects

Introduction

Numerous studies in rodents have found that oxytocin (OT), a neuropeptide that is widely distributed within the brain (Gimpl and Fahrenholz, 2001; Lee et al., 2009), alters neuroadaptation to addictive substances including alcohol (Kovács et al., 1998). Peripheral or central administration of OT prior to each daily dose of alcohol over multiple days has been reported to block the development of tolerance to the hypothermic, myorelaxant, akinetic and hypnotic effects of alcohol in mice (Jodogne et al., 1991; Pucilowski et al., 1985; Rigter et al., 1980; Szabó et al., 1985; 1989). OT gene knockout compared to wild type mice exhibit significantly more rapid tolerance formation to the effects of repeated doses of alcohol (Vadlamudi et al., 2004). A single injection of OT also significantly reduced picrotoxin-induced withdrawal symptoms in alcohol-dependent mice (Kovács et al., 1998; Szabó et al., 1987) suggesting that OT rapidly reverses established tolerance. While OT has been reported to reverse changes in monoamine content in some brain areas in alcohol-dependent rodents (Szabó et al., 1988), the mechanisms by which OT inhibits tolerance formation and reduces withdrawal symptoms remain largely unknown.

A rapidly increasing number of studies in human subjects have found that acute (single dose) intranasal OT treatment, which appears to result in penetration of a significant amount of the neuropeptide into the brain (Born et al., 2002; Domes et al., 2007a; 2010; Kirsch et al., 2005), increases interpersonal trust and cooperation, improves social cognition and reduces anxiety (Andari et al., 2010; Baumgartner et al., 2008; de Oliveira et al., 2011; Domes et al., 2007b; Guastella et al., 2008; Heinrichs et al., 2003; Kosfeld et al., 2005; MacDonald and MacDonald, 2010). Several small clinical trials involving multiple daily doses of intranasal OT for weeks have found beneficial effects in schizophrenia (Feifel et al., 2010; Pedersen et al., 2011) but not in obsessive-compulsive disorder (den Boer and Westenberg, 1992; Epperson et al., 1996). OT had no adverse effects in the acute treatment studies or clinical trials.

Benzodiazepines are the current drugs of choice for alcohol detoxification (Daeppen et al., 2002; Mayo-Smith, 1997; Saitz and O'Malley, 1997). However, benzodiazepines, like alcohol, are sedative-hypnotics. Therefore, benzodiazepine treatment of alcohol withdrawal may maintain sedative-hypnotic tolerance that could exacerbate post-detoxification symptoms such as anxiety, sleep difficulties and alcohol craving that increase risk for relapse. Furthermore, benzodiazepines have the potential to become addictive and can enhance the depressant actions of alcohol, including respiratory depression, and lead to increased morbidity and mortality—these actions limit their use in outpatient settings. Treatment of alcohol withdrawal with anticonvulsants such as gabapentin, a non-sedative-hypnotic drug, has been reported to be efficacious for treatment of mild alcohol withdrawal and to decrease post-detoxification anxiety, craving and drinking (Myrick et al., 2009). These agents are of interest for the treatment of alcohol withdrawal as alternatives to benzodiazepines and continue to undergo investigation. OT treatment could be even more advantageous in managing withdrawal symptoms because it may reverse tolerance and, therefore, could further decrease post-detoxification symptoms that increase risk of relapse.

The goal of the current study was to test whether twice daily intranasal OT treatment is superior to intranasal placebo in reducing withdrawal symptoms and the total amount of

benzodiazepine administered in alcohol dependent inpatients undergoing medical detoxification using symptom-driven PRN administration of lorazepam.

Materials and Methods

With FDA approval (IND 104,540), we conducted a randomized, double-blind pilot study of 3 days of BID intranasal OT (24 IU/dose) vs. placebo in 11 alcohol-dependent inpatient subjects undergoing detoxification with symptom-driven PRN lorazepam. The study was approved by the University of North Carolina Biomedical Institutional Review Board and conducted in accordance with The Code of Ethics of the World Medical Association. Written informed consent was obtained from all subjects.

Subjects

Inclusion criteria: 1) At least one prior episode 2 days or longer in duration during which the subject experienced withdrawal symptoms that caused significant incapacitation (e.g., inability to work or do normal activities) OR at least one prior inpatient or outpatient medical detoxification during which the subject exhibited withdrawal symptoms of sufficient magnitude that sedative-hypnotic or anticonvulsant medication was required at least once on 2 consecutive days after cessation of or reduction in the use of alcohol following 2 weeks or more of heavy daily consumption; 2) average consumption of 8-30 standard drinks per day for at least 2 weeks prior to enrollment in the study; 3) age 18-65.

Exclusion criteria: 1) history of alcohol withdrawal-related seizures, delirium tremens or hallucinations; 2) current or past alcohol-related medical complications such as cirrhosis of the liver, esophageal varices, pancreatitis, severe gastritis, hemoptysis, hematochezia or melena; 3) blood alcohol level at screening or upon admission > 300 mg/dl; 4) treatment/ingestion during the previous week of benzodiazepines or other sedative-hypnotic medications or history of recent chronic treatment with sedative-hypnotic medications; 5) dependence on substances other than alcohol, nicotine or caffeine (abuse of other substances other than sedative-hypnotics was not exclusionary); 6) inadequately treated, unstable and/or compromising medical or psychiatric conditions; 7) low body weight (BMI < 17); 8) history of anorexia nervosa or bulimia in the past 2 years; 9) significant trauma or surgery in the previous 2 months; 10) pregnancy; parturition or breast-feeding in the past 6 months; 11) very elevated vital signs (SBP > 180, DBP > 120 or P > 120) during screening or upon admission; 12) any of the following laboratory values during screening or upon admission: AST > 165 U/L (normal range 19-55), ALT > 216 U/L (normal range 19-72), alkaline phosphatase > 378 U/L (normal range 38-126) , non-fasting glucose > 250 mg/ml (normal range 65-179); hematocrit < 38 % (normal range 41-53); hemoglobin < 12 g/dl (normal range 13.5-17.5) or any other laboratory value significantly outside the normal range; 12) ECG evidence of cardiac ischemia or conduction abnormalities; 13) inability to read well enough to complete study questionnaires determined by whether the prospective subject can read the consent form without help and correctly answer basic questions about information in the consent form; 12) participation in other clinical trials within the past 60 days; 13) court-mandated participation in alcohol treatment or pending incarceration.

Medical or psychiatric disorders that were not unstable, incapacitating and were currently adequately-controlled for at least 1 month on stable doses of standing or PRN medication (other than sedative-hypnotics) and/or other management regimens were not exclusionary.

Our inclusion and exclusion criteria selected subjects who were likely to experience withdrawal symptoms but were at low risk of developing dangerous withdrawal problems such as seizures, delirium tremens, Wernicke’s encephalopathy or hallucinations and had no serious or unstable comorbidities. This is a population of alcohol dependent patients in

whom symptom-triggered benzodiazepine treatment has been shown to be as safe and requires less total medication administration compared to fixed regimen benzodiazepine tapers (Daeppen et al 2002; Mayo-Smith 1997).

Ninety-six individuals who responded to advertisements (see recruitment procedures below) were screened by telephone. Fifteen who appeared to meet study criteria based on the telephone screen were evaluated in greater depth during a visit to a research unit. Two were excluded based on history and/or laboratory results obtained during the evaluation. The remaining 13 whose history and laboratory studies indicated that they met criteria were admitted to a research unit where they began the treatment trial. Further history obtained from 2 of these subjects after they began the treatment trial revealed that they actually had no history of significant withdrawal after previous bouts of drinking, which contradicted history obtained during their screening evaluations. Withdrawal symptoms in another subject could not be adequately controlled with PRN lorazepam. Upon further questioning, he admitted that his daily alcohol consumption had been far greater than reported during his screening evaluation and exceeded the upper limit specified in our inclusion criteria. This information would have made these subjects ineligible for participation in the study so data from these subjects were not included in our analyses. We also attempted to recruit 5 individuals admitted to inpatient services at the University of North Carolina Hospitals for medical detoxification, but only one met criteria and completed the protocol. Therefore, our total sample consisted of 11 subjects.

Procedures

Recruitment: Radio and print advertisements including a contact telephone number were used to attract prospective subjects. Individuals who responded were initially screened during telephone conversations with research assistants who followed an IRB-approved script. Those who were not excluded were then interviewed over the telephone by the Principal Investigator (Dr. Pedersen). For individuals who appeared to meet criteria based on the phone screens, informed consent was obtained prior to admission to the research unit and the evaluation described below was conducted either immediately after admission to the unit or during an outpatient appointment preceding admission to the research unit. An additional 5 individuals admitted to inpatient units at the University of North Carolina Hospitals for medical detoxification were approached about the study and gave informed consent but only one met criteria for inclusion and completed the protocol.

Evaluation of all prospective subjects included a physical examination, medical history, administration of the Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998), review of their past drinking history as well as their recent consumption of alcohol using the Timeline Followback interview (Sobell et al., 1988), an ECG, and blood and urine collection for laboratory studies (including CBC, electrolytes, BUN, creatinine, glucose, albumin, ALT, AST, alkaline phosphatase, total bilirubin, LDH, GGT, TSH, B12, folate, blood alcohol concentration, urinalysis, urine toxicology screen and pregnancy test).

As soon as possible on the first day of admission, subjects' vital signs were measured and their withdrawal symptoms quantified using a version of the Clinical Institute Withdrawal Assessment for Alcohol scale (hereafter referred to as the CIWA scale, Sullivan et al., 1989) modified to include vital sign measures in the total score (see Supplement 1). Subjects also rated their symptoms using the Alcohol Withdrawal Symptom Checklist (AWSC, Pittman et al., 2007). Immediately after obtaining these baseline objective and subjective measures of withdrawal symptoms, subjects took their first intranasal dose of the test substance to which they had been randomized. Research nurses instructed subjects in proper intranasal self-administration technique during their first dose. A second intranasal test dose was taken at

approximately 1700h on admission day 1. On admission days 2 and 3, intranasal test doses were taken at approximately 0900 and 1700h. All test doses were supervised by research staff. Each test dose consisted of 6 insufflations of Syntocinon Spray (Novartis, containing approximately 24 IU of OT) or placebo (containing the same ingredients as Syntocinon Spray except for OT), with each insufflation given 30 seconds apart and alternating between nostrils. OT and placebo test doses were self-administered from blind-labeled vials designed to deliver 0.1 ml metered volume per insufflation. Randomization of treatment assignment was done in blocks of 4 within each gender.

Vital sign measurements and CIWA scores were obtained every 4 hours while subjects were awake (0600h, 1000h, 1400h, 1600h, 2000h) or whenever subjects reported or nurses observed worsening of withdrawal symptoms. If a CIWA score was > 12, the subject was given a 2 mg dose of lorazepam. CIWA scores were repeated 1 hour after each lorazepam dose. If the CIWA score remained > 10, another 2 mg dose of lorazepam was administered.

Subjects completed the AWSC immediately after each CIWA score was obtained. Shortly after the morning test dose on admission days 2 and 3, subjects also rated themselves on the Penn Alcohol Craving Scale (Flannery et al., 1999), an Alcohol Craving Visual Analog Scales (ACVAS) on which they marked on a 100 mm line how much they craved alcohol between Not At All on the left end to Extremely on the right end of the line, and the Profile of Mood States (McNair et al, 1971). After the morning test dose on admission day 2, another ECG was run and additional blood was drawn for laboratory tests (magnesium, electrolytes, BUN, creatinine, and GGT).

Statistical Analyses: All comparisons between OT and placebo groups were done using t tests. Given that these groups did not differ on age and mean daily drinks, we did not control for these variables in data analyses comparing the groups. Given the small sample size and skewness in some outcome variables, we ran nonparametric analyses on all comparisons in Table 1, and found virtually identical results. We also examined the effects of treatment group on CIWA scores on admission days 1 and 2 using analysis of covariance controlling for CIWA scores obtained before initiation of intranasal test doses on admission day 1 because there was a trend for the OT group to have lower baseline scores.

Results

Data included in the analyses were collected from 9 men and 2 women. Mean age (41.27 ±14.67) did not differ between treatment groups (p=.82). Mean number of standard drinks per day prior to enrollment did not differ significantly (p=.33) between the OT and placebo groups (17.7±6.0 vs.14.5±1.7). The OT group was composed of 6 men and 1 woman and the placebo group was composed of 3 men and 1 woman. Several factors contributed to the small sample and the disparity in the number of subjects in the treatment groups. As stated above in the description of subjects, data from 3 participants (all men) who completed the protocol were not included in the analyses because additional history obtained during their stay on the research unit indicated that, contrary to history obtained during the screening process, they did not meet criteria for inclusion in the study. Two of those subjects had been randomized to placebo and one to OT. We originally planned to study more subjects but unexpectedly high costs (radio advertisements, research unit per diem charges) exhausted our limited funds after studying less than half the original target sample. Our randomization scheme (blocks of 4 within each gender) may have also contributed to uneven treatment group numbers in the small number of subjects who completed the protocol.

Outcome measures are summarized in Table 1. The OT compared to the placebo group required almost 5 times less total lorazepam to complete detoxification. Mean CIWA scores

and AWSC self-ratings on admission days 1 and 2 were approximately 3 times lower in the OT group. The CIWA differences were significant on both days and the AWSC differences were significant on admission day 1 and trended toward significance on admission day 2. Alcohol craving scores trended toward being lower (PACS) or were significantly lower (ACVAS) in the OT group on admission day 2 but not admission day 3. POMS Tension/Anxiety subscores were also significantly lower in the OT compared to the placebo group on admission day 2 but not admission day 3.

We examined the CIWA and AWSC scores for the two treatment groups obtained on admission day 1 just before subjects received their first intranasal test doses. (Note one person in the OT group was missing pretreatment measures). Although the treatment groups were not significantly different on these measures (CIWA p=.13; AWSC p=.57), there was a trend for the OT group to score lower on CIWA scores obtained immediately before initiation of intranasal treatments (OT mean=2.5, SD=1.4; placebo mean=9.25, SD=6.6). Because of this difference, we further examined the effects of treatment on mean CIWA scores on admission days 1 and 2 using analysis of covariance to control for CIWA scores obtained prior to the first intranasal test doses. The difference between the least squared means and the p values (Day 1=7.5, p=.0024; Day 2=9.4; p=.0042) showed that the OT compared to the placebo group had considerably lower mean CIWA scores on admission day 1 after beginning test treatments as well as on admission day 2, even when controlling for baseline CIWA scores.

All subjects randomly assigned to placebo (N-4) had been drinking an average of < 16 standard drinks/day prior to entry into the study. Only 4 of the 7 subjects assigned to OT treatment had been drinking an average of < 16 drinks/day. We, therefore, compared outcome measures between the 4 OT and 4 placebo recipients who drank at this lower level (Table 2). This subset of OT recipients required no lorazepam to complete detoxification and also had significantly lower mean CIWA scores on all 3 admission days, significantly lower mean AWSC self-rating on admission days 1 and 2, significantly lower ACVAS self-ratings on admission day 2 and significantly lower POMS Tension/Anxiety subscores on admission day 2.

Laboratory measures (magnesium, electrolytes, BUN, creatinine, GGT) and ECGs obtained on the morning of admission day 2 did not differ significantly from baseline in either treatment group.

Discussion

Our results are the first evidence that OT may block alcohol withdrawal symptoms in humans. This finding confirms and extends earlier findings in rodents. Also, our results and previous animal studies suggest that OT may block alcohol withdrawal by a unique mechanism, rapid reversal of alcohol tolerance produced by chronic, heavy alcohol consumption.

The most widely used pharmacological treatments of alcohol withdrawal are tapered PRN or standing doses of benzodiazepines (Daeppen et al., 2002; Mayo-Smith, 1997; Saitz and O'Malley, 1997). While medical detoxification is safely achieved with benzodiazepines, these medications are, like alcohol, sedative hypnotics. Therefore detoxification with benzodiazepines may maintain sedative-hypnotic tolerance that could result in post-detoxification symptoms that increase vulnerability to relapse: high anxiety; sleep difficulties; persistent craving for alcohol; and decreased ability to cope with stress. Furthermore, should patients relapse, higher sedative-hypnotic tolerance may result in patients having to drink large quantities of alcohol to achieve inebriation and relieve post-

detoxification symptoms. These hypothetical drawbacks of maintaining sedative-hypnotic tolerance by treating alcohol withdrawal with benzodiazepines are supported by the recent report by Myrick et al. (2009) that alcohol detoxification with gabapentin, which is not a sedative-hypnotic drug, resulted in significantly less post-detoxification drinking, craving and anxiety. OT treatment of alcohol withdrawal could be even more effective in diminishing dysphoria, craving and drinking after detoxification because, in addition to not being a sedative-hypnotic, OT may reverse tolerance to alcohol.

Of course, it is important to note that benzodiazepines have been shown to reduce risk for alcohol withdrawal seizures and delirium tremens in addition to other withdrawal symptoms (Mayo-Smith, 1997). This is a very important point as other agents including anticonvulsants, baclofen, and now OT have not been shown to prevent these serious consequences and accordingly would not be recommended for the treatment of severe alcohol withdrawal (Saitz, 2007).

The small number of subjects enrolled in this study requires that our results be considered as very preliminary. Future studies of considerably larger cohorts will be necessary to adequately test the validity of our findings. If our results are confirmed, however, CNS OT will become an exciting new front for research on the pathophysiology of alcohol dependence. Of particular interest will be determining whether OT reversal of established tolerance is, indeed, how OT blocks withdrawal. This may provide new insights into the still poorly understood mechanisms of tolerance formation.

Also of great importance is testing whether OT treatment decreases drinking in alcohol dependent outpatients. Animal and human studies have found that OT decreases stress responses including anxiety (Amico et al., 2004; Bale et al., 2001; de Oliveira et al., 2011; Domes et al., 2007a; Heinrichs et al., 2003; Kirsch et al., 2005; Mantella et al., 2003; McCarthy et al., 1996; Ring et al., 2006; Windle et al., 1997). It has been hypothesized that abstinence in alcohol dependent individuals produces anxiety and that relapse often occurs because alcohol relieves that anxiety (Kushner et al., 2000). OT treatment blocked anxiety and increased alcohol intake in P (alcohol-preferring) rats subjected to repeated alcohol deprivation combined with restraint stress, an animal model of craving and relapse (Breese et al., 2004; Knapp et al., 2010; Overstreet et al., 2007). By reducing anxiety, increasing the ability to cope with stress, and possibly reversing established alcohol tolerance, OT treatment may diminish craving and facilitate sobriety in the outpatient setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparison of oxytocin and placebo treatment groups on total amount of lorazepam required to complete detoxification, mean admission days 1-3 CIWA and AWSC scores, and admission days 2-3 PACS, ACVAS, and POMS Tension/Anxiety ratings.

SD = standard deviation; t = t value; p = significance level (values < .05 [in bold] of differences between treatment groups). ACVAS = Alcohol Craving Visual Analog Scale; AWSC = Alcohol Withdrawal Symptom Checklist; CIWA = Clinical Institute Withdrawal Assessment for Alcohol scale; PACS = Penn Alcohol Craving Scale; POMS = Profile of Mood States

Measure	Oxytocin (N=7)		Placebo (N=4)			
	Mean	SD	Mean	SD	T	p
Total lorazepam (mg)	3.4	4.7	16.5	4.4	4.5	**.0015**
CIWA Day 1	4.3	2.3	11.8	0.4	8.4	**<.0001**
CIWA Day 2	3.4	2.2	11.1	3.6	4.5	**.0015**
CIWA Day 3	3.1	2.1	5.4	1.9	1.7	.1193
AWSC Day 1	6.6	1.6	16.3	4.5	4.2	**.0191**
AWSC Day 2	6.5	3.8	20.6	10.2	2.7	.0654
AWSC Day 3	4.6	3.0	9.6	5.2	2.1	.0704
PACS Day 2	14.6	5.8	21.0	4.6	1.9	.0900
PACS Day 3	10.1	7.8	12.8	3.0	0.6	.5440
ACVAS Day 2	34.9	20.9	86.1	14.5	4.3	**.0020**
ACVAS Day 3	16.7	18.8	38.9	39.3	1.3	.2283
POMS Tension/Anxiety Day 2	10.3	6.0	23.8	6.7	3.5	**.0071**
POMS Tension/Anxiety Day 3	5.3	5.9	8.3	6.1	0.8	.4482

Table 2

Comparison of oxytocin and placebo treatment groups composed of subjects drinking ≤ 16 standard drinks/ day on total amount of lorazepam required to complete detoxification, mean admission days 1-3 CIWA and AWSC scores, and admission days 2-3 PACS, ACVAS, and POMS Tension/Anxiety ratings.

See Table 1 for explanations of statistical terms and acronyms.

Measure	Oxytocin (N=4)		Placebo (N=4)			
	Mean	SD	Mean	SD	t	P
Total lorazepam (mg)	0.0	0.0	16.5	4.4	7.4	**.005**
CIWA Day 1	3.5	1.2	11.8	0.4	13.6	**<.0001**
CIWA Day 2	2.5	1.5	11.1	3.6	4.5	**.0044**
CIWA Day 3	2.8	0.6	5.4	1.9	2.6	**.0415**
AWSC Day 1	5.9	1.1	16.3	4.5	4.5	**.0163**
AWSC Day 2	5.3	3.1	20.6	10.2	2.9	**.0283**
AWSC Day 3	5.0	1.4	9.6	5.2	1.7	.1387
PACS Day 2	14.8	6.0	21.0	4.6	1.7	.1466
PACS Day 3	13.0	7.6	12.8	3.0	-0.1	.9532
ACVAS Day 2	34.1	25.7	86.1	14.5	3.5	**.0125**
ACVAS Day 3	16.0	14.1	38.9	39.3	1.1	.3150
POMS Tension/Anxiety Day 2	7.3	2.5	23.8	6.7	4.6	**.0035**
POMS Tension/Anxiety Day 3	4.8	4.3	8.3	6.1	0.9	.3823