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A prospective, open-label trial of ondansetron in adolescents with alcohol dependence

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Abstract

Ondansetron has been shown to be effective in the treatment of early-onset adult alcohol dependence. To date, no studies have been conducted in adolescents with alcohol dependence to assess the feasibility, safety, tolerability, and potential utility of ondansetron treatment. We conducted an 8-week, prospective, open-label study of ondansetron (4 μg/kg b.i.d.) in 12 adolescents who had alcohol dependence. Oral ondansetron was safe and well tolerated in our sample. Adverse events were mild and resolved quickly without intervention. No subjects discontinued due to adverse events. Intent-to-treat analyses showed a significant within-group decrease (improvement) for drinks/drinking day (t=−3.10, df=11, p=0.01), as well as decreases in drinks/day (t=−2.01, df=11, p=0.06) and percentage of days abstinent (t=1.45, df=11, p=0.18). These preliminary data suggest that ondansetron is safe and well tolerated in adolescents with alcohol dependence. Findings of decreased drinking underscore the need for future double-blind, placebo-controlled studies in this adolescent population.

Keywords: Adolescents; Alcohol dependence; Open-label trial; Ondansetron

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1. Introduction

In the United States, the prevalence of adolescent alcohol use remains a major public health concern. While alcohol and illicit drug use by adolescents declined slightly from the early 1990s, drug use remains common in this population (National Institute on Drug Abuse News Release, 2002). In addition to the high rates of drug use, the prevalence of alcohol abuse, other substance abuse, and related problems remains high in youths 12–20 years of age (Substance Abuse and Mental Health Services Administration, 2003). Despite small decreases in prevalence, alcohol problems remain a major public health concern due to the illegality of alcohol use during adolescence, and to the socioeconomic, psychological, and physical consequences that occur (Grunbaum et al., 2002). Consequences of adolescent alcohol use include death, injury, assault, sexual abuse, sexually transmitted diseases, academic problems, suicide, vandalism, and property damage (National Institute on Alcohol Abuse and Alcoholism, 2004).

Findings from prospective studies show that when left untreated, adolescent alcohol problems often lead to alcohol and other drug dependencies by young adulthood (Fleming, Kellam, & Brown, 1982; Tubman, Vicary, von Eye, & Lerner, 1990). Effective treatment of adolescent alcohol dependence may prevent progression to adult alcohol dependence and other substance use disorders.

Unfortunately, current treatments for adolescent alcohol dependence have been limited mostly to psychosocial therapies (Deas & Thomas, 2001). Many adolescents with alcohol dependence do not benefit from psychosocial treatment alone (Brown & D'Amico, 2003). Even among those adolescent addicts who benefit from psychosocial treatment, relapse rates and continued alcohol and other drug use remain high (Brown, D'Amico, McCarthy, & Tapert, 2001). In contrast to adult alcohol dependence treatment research, few open-label or placebo-controlled medication trials have been conducted to determine the safety, tolerability, and efficacy of medications for the treatment of adolescent alcohol dependence (Dawes & Johnson, 2004). The lack of treatment research using medications as adjuncts to psychosocial treatment is unfortunate, in that the use of medications with psychosocial treatment holds the promise of improved efficacy over psychosocial treatments alone (Dawes & Johnson, 2004).

Of particular interest in the treatment of early-onset alcohol dependence (EOA; i.e., alcohol dependence that develops by age 25 years) is ondansetron, a serotonin-3 antagonist. Ondansetron has been shown to be efficacious only in the treatment of EOA adults who had developed alcohol dependence more than 15 years prior to study enrollment (Johnson et al., 2000; Kranzler, Pierucci-Lagha, Feinn, & Hernandez-Avila, 2003). Johnson et al. (2000) showed that in a sample of EOA adults (N=161), but not in late-onset alcohol-dependent (LOA) adults (N=160), ondansetron was superior to placebo at improving drinking outcomes. Although the 1-, 4-, and 16-μg/kg doses of ondansetron twice per day all decreased alcohol consumption significantly in EOA adults, the 4-μg/kg dose appeared to result in the best drinking outcomes. In a recent prospective, open-label study of ondansetron for EOA adults compared with LOA adults (N=40; 20 EOA, 20 LOA), EOA adults had significantly greater decreases in drinks/day, drinks/drinking day, and alcohol-related

problems (Kranzler et al., 2003). In both of these EOA adult samples, ondansetron was safe and well tolerated.

The precise mechanism of ondansetron treatment response among EOA adults is unknown. Ondansetron decreases alcohol-induced reward and preference for alcohol (Johnson & Ait-Daoud, 2000). Low-dose ondansetron pretreatment also attenuates ethanol-induced positive subjective effects associated with its abuse liability (Johnson & Cowen, 1993). For EOA adults, ondansetron appears to block ethanol-induced activation of mesocorticolimbic dopamine (DA) receptors in the midbrain and cortex (Johnson & Cowen, 1993; Barnes & Sharp, 1999). Serotonin-3 antagonism is thought to decrease DA activity, thereby diminishing the rewarding effects of alcohol and other drugs (Bradbury, Costall, Domeney, & Naylor, 1985; Hagan, Jones, Jordan, & Tyers, 1990; McBride et al., 2004). Blockade of serotonin-3 receptors may also decrease DA release and subsequent alcohol consumption and craving (Johnson, 2000). We hypothesize that the mechanism of ondansetron treatment response in EOA adults should be similar in adolescents with alcohol dependence as they are by definition early-onset alcoholics. Indeed, we considered testing ondansetron treatment response in EOA adolescents as a logical extension of our study in adults. Without the deleterious effects that can be caused by lengthy periods of heavy alcohol consumption, it is even possible that EOA adolescents would be the most responsive to ondansetron treatment.

To our knowledge, this is the first prospective, open-label treatment study to report on the use of ondansetron in treating EOA adolescents.

2. Methods

2.1. Subjects

We conducted this study at the South Texas Addiction Research and Technology (START) Center in San Antonio, TX. Treatment-seeking adolescent patients were recruited primarily by health practitioners working in the community. Before study entry, the potential risks and benefits of participation were explained to potential subjects and, when applicable, to their parents. For 18–20-year-olds, written informed consent was obtained from the participant. For 14–17-year-olds, parents gave informed consent and their child his or her assent prior to study entry. The study was approved by the University of Texas Health Science Center Institutional Review Board.

We enrolled 12 treatment-seeking subjects (7 males and 5 females) between the ages of 14 and 20 years. All subjects had a DSM-IV diagnosis of alcohol dependence. Subjects were currently drinking greater than 12 alcohol-containing drinks in the last 30 days prior to enrollment and reported impairment due to drinking. One standard drink was defined as 0.35 l of beer, 0.15 l of wine, or 0.04 l of 80-proof liquor. Subjects were required to be in good physical health as determined by a complete physical examination, an EKG within normal limits, and laboratory screening tests within acceptable parameters. All participants

were willing to participate in behavioral and pharmacological treatment for alcohol problems.

We excluded subjects if they had substance abuse or dependence other than for alcohol, marijuana, or nicotine within 4 weeks prior to screening or other psychiatric co-morbidity of sufficient severity to preclude participation in the trial. Our critieria excluded subjects treated with medication for attention deficit hyperactivity disorder. We also excluded subjects with clinically significant elevation of liver enzymes or serious medical co-morbidity that required medical intervention, including severe withdrawal symptoms; female subjects who were pregnant, lactating or breastfeeding, or not adhering to an acceptable form of contraception at any time during the study; subjects with histories of severe or life-threatening adverse reactions to medications; subjects who had undergone inpatient or outpatient treatment for alcohol abuse or dependence within the last 30 days; subjects forced to participate in an alcohol treatment program to maintain their liberty; members of the same household; and subjects taking concurrent medications having a potential effect on alcohol consumption and related behaviors, or mood.

2.2. Design

We used a prospective, 8-week, open-label study design.

2.3. Clinical assessment

At baseline, the Children's Interview for Psychiatric Syndromes (ChIPS) (Rooney, Fristad, Weller, & Weller, 1999), Adolescent Diagnostic Interview (ADI) (Winters & Henly, 1993; Winters, Stinchfield, Fulkerson, & Henly, 1993), and Timeline Follow-Back (TLFB) (Sobell & Sobell, 1992) were administered. The TLFB was measured weekly after baseline assessment.

Trained therapists who were post-doctoral candidates from clinical psychology programs performed the ChIPS to provide psychiatric profiles for the following DSM-IV psychiatric disorders: attention deficit hyperactivity disorder (inattentive, hyperactive-impulsive, or combined types), oppositional defiant disorder; conduct disorder (onset: childhood or adolescent; severity: mild, moderate, or severe), substance abuse, specific phobias, social phobias, separation anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder (type: acute or chronic; onset: regular or delayed), acute stress disorder, anorexia, bulimia, major depressive disorder, dysthymic disorder, mania, hypomania, schizophrenia, and psychosis. Inter-rater reliability after training has been reported by Rooney et al. (1999) to be at least 0.90. The parent (P-ChIPS) and child (ChIPS) versions were used. Both measures have been shown to provide accurate and valid diagnosis of psychiatric disorders (Rooney et al., 1999).

The ADI, a structured interview, was used to assess symptoms for psychoactive substance use disorder as described in the DSM-IV. The ADI also measured sociodemographic information, substance use consumption history, and psychosocial

functioning. The ADI has reasonable inter-rater agreement (κ=0.66–0.96), test–retest reliability (κ=0.53–0.79), and concurrent and criterion validity (Winters & Henly, 1993; Winters et al., 1993).

The TLFB (Sobell & Sobell, 1992) procedure was used to capture the extent of the participants' alcohol and drug use over the past 90 days prior to screening for participation in the study and during the study.

2.4. Treatment

Participants were given 4 μg/kg p.o. b.i.d. of ondansetron, administered in opaque gelatin capsules. All subjects received weekly cognitive behavioral therapy (CBT), with motivational enhancement, after an initial functional analysis. CBT was adapted to the needs of adolescents, to help them decrease and stop alcohol and other drug use by increasing their skills for coping in general and in high-risk situations such as drinking with friends. Therapy was conducted by post-doctoral therapists who were in training in our clinical psychology programs. All ratings for the study, including baseline assessments and subsequent outcome ratings, were conducted by trained research assistants.

2.5. Outcome variables

Safety and tolerability of ondansetron were assessed at each weekly visit. Criteria for evaluating safety included the incidence and perseverance of adverse events and physical examination findings. Pill counts were conducted weekly to assess compliance. Primary drinking outcome was self-reported alcohol consumption (frequency: drinks/day, severity: drinks/drinking day, and abstinence: percentage of days abstinent).

2.6. Statistical analyses

Safety and tolerability outcomes were reported as the percentage of subjects who reported each adverse event.

Continuous drinking outcomes such as drinks/day, drinks/drinking day, and percentage of days abstinent were reported as their mean (standard deviation). Categorical data for adverse events were reported as percentages. Statistical analyses were performed using paired *t*-tests for continuous measures and chi-square tests for categorical measures. All tests were two-tailed. Intention-to-treat analyses were employed for outcome measures.

The weekly average drinks/day, drinks/drinking day, and percentage of days abstinent were calculated for the baseline period and each follow-up week, as well as for the entire study period. We used the paired *t*-tests for the intent-to-treat analyses to test whether there were significant declines in drinks/day, drinks/drinking day, and percentage of days abstinent at last follow-up week from baseline for all 12 subjects.

3. Results

3.1. Sample characteristics

The mean age was 18.0 years (range: 14–20 years). As can be seen in Table 1, the majority of adolescents had disruptive behavior disorders and three had mood disorders. In addition to alcohol dependence, 10 of 12 subjects also met DSM-IV-R criteria for cannabis dependence.

3.2. Dropouts

Nine of 12 subjects completed at least 3 weeks of the study and 6 of 12 subjects completed the 8-week study. Of those participants who dropped out, three moved out of town, two obtained jobs that reportedly had hours that precluded further participation, and one decided that he was no longer interested in treatment. None of the dropouts reported that adverse events related to the medication were reasons for their termination.

3.3. Adverse events

Adverse events were mild and of short duration: change in appetite, 2 (16.7%); nausea, 1 (8.3%); constipation, 1 (8.3%); abdominal pain, 1 (8.3%); dizziness, 1 (8.3%); fatigue, 1 (8.3%); somnolence, 4 (33%); and insomnia, 1 (8.3%). Somnolence was mild, lasted up to 5 days, and then resolved. There were no dropouts due to adverse events.

Table 1
Case information on the 12 alcohol-dependent subjects who received ondansetron treatment

Age (years)	Sex	Co-morbid psychiatric disorder(s)	Substance use disorder(s)
20	M	CD	Dependence: alcohol
20	F	Dysthymia	Dependence: alcohol, cannabis
20	F	CD	Dependence: alcohol, cannabis
18	M	CD, ADHD-HI	Dependence: alcohol
20	M	None diagnosed	Dependence: alcohol, cannabis
19	F	Dysthymia	Dependence: alcohol, cannabis
18	M	None diagnosed	Dependence: alcohol, cannabis
14	F	CD, ADHD-IA	Dependence: alcohol, cannabis
14	F	ODD, ADHD-IA	Dependence: alcohol, cannabis
18	M	CD	Dependence: alcohol, cannabis
18	M	CD	Dependence: alcohol, cannabis
17	M	MDD (mild), GAD, ADHD-IA, CD	Dependence: alcohol, cannabis

Sex: M=male, F=female.
DSM-IV diagnoses: CD=conduct disorder; ADHD-HI=attention deficit hyperactivity disorder, hyperactive-impulsive type; ADHD-IA=attention deficit hyperactivity disorder, inattentive type; MDD (mild)=major depressive disorder, mild; GAD=generalized anxiety disorder.

No adverse events required medical attention or intervention, and all resolved spontaneously.

3.4. Medication adherence

We estimated medication compliance (number of medication doses missed) at each study visit by subtracting the number of returned gel capsules from the amount dispensed ("pill count"). The overall compliance rate was 89%.

3.5. Drinking outcomes

Self-reported drinking outcomes were weighted by the number of study visits completed. Drinking outcome results at study end versus baseline were: drinks/day, 1.30 (1.52) vs. 3.06 (2.66); drinks/drinking day, 3.00 (3.54) vs. 7.57 (4.37); and percentage of days abstinent, 73.54 (27.25) vs. 61.31 (27.09).

Intent-to-treat analyses showed significant within-group decreases (improvement) for drinks/drinking day (t=−3.10, df=11, p=0.01). During the course of the study, drinks/day (t=−2.01, df=11, p=0.06) and percentage of days abstinent (t=1.45, df=11, p=0.18) also decreased.

4. Discussion

To our knowledge, this is the first prospective, open-label treatment study to report on the use of ondansetron in adolescent alcohol-dependent outpatients. The results indicate that the use of ondansetron in this population is safe and well tolerated. The drinking outcomes suggest that ondansetron is worthy of further consideration in double-blind, randomized, controlled clinical trials for the treatment of EOA adolescents.

Caution must be used when interpreting the results from this study. Only 12 subjects were enrolled and half completed the 8-week study. However, of those adolescents who dropped out, none reported AEs due to medication as a reason for stopping. Also, the study design was not double-blind, and the lack of a placebo group renders it impossible to make any claims pertaining to efficacy. Other factors, including placebo effects, observer bias, and the effects of CBT, may have accounted for some of the drinking improvements.

Despite the methodological limitations, the use of ondansetron in adolescents with alcohol dependence appears to be safe and well tolerated. There was significant improvement in self-reported drinking in the majority of adolescents who participated in this study. These drinking results are notable because all adolescents enrolled met criteria for alcohol dependence, with significant psychiatric co-morbidity: 8 of 12 subjects having a disruptive behavioral disorder and 3 of 12 having either dysthymia or mild major depression. Future studies should test formally ondansetron's treatment response among EOA adolescents in double-blind, randomized controlled trials.

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