0145-6008/01/2506-0847$03.00/0
Alcoholism: Clinical and Experimental Research

Vol. 25, No. 6
June 2001

Combining Ondansetron and Naltrexone Treats Biological Alcoholics: Corroboration of Self-Reported Drinking by Serum Carbohydrate Deficient Transferrin, A Biomarker

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Background: Recently, we showed by using self-report that combining ondansetron (4 μg/kg twice a day) and naltrexone (25 mg twice a day) was effective at reducing drinking and increasing abstinence among early-onset alcoholics (EOAs), who are characterized by a range of antisocial behaviors and high biological and familial disease predisposition. Here, we investigated whether the self-reported differences in drinking would be corroborated by measurements of serum carbohydrate-deficient transferrin (CDT) level, a sensitive, reliable, and well-validated marker of transient alcohol consumption.

Method: An 8-week double-blind clinical trial was performed in which 20 EOAs were randomized to receive ondansetron (4 μg/kg twice a day) and naltrexone (25 mg twice a day) or placebo as an adjunct to weekly standardized cognitive behavioral therapy. Serum CDT was assessed at weeks 0 (baseline), 4, and 8.

Results: Log serum CDT was significantly lower in the ondansetron and naltrexone group (group mean, 1.44 ± 0.076) compared with the placebo group (group mean, 1.82 ± 0.113), as evidenced by a main effect of group [$F(1,15) = 7.2, p = 0.017$; effect size = 0.32], visit [$F(1,16) = 11.2, p = 0.004$; effect size = 0.41], and an interaction between group and visit [$F(1,16) = 27.54, p < 0.001$; effect size = 0.63].

Conclusions: The combination of ondansetron plus naltrexone was superior to placebo at reducing serum CDT. This corroborated our self-reported drinking data and demonstrated that the medication combination is an effective treatment for EOAs.

EARLY ONSET ALCOHOLICS (EOAs) are characterized by an onset of problem drinking before the age of 25 years, increased propensity toward a broad range of antisocial behaviors, and high biological disease predisposition, with increased familial loading among first-degree relatives (Johnson et al., 2000b). Recently, we showed by using self-report that combining ondansetron (4 μg/kg twice a day) and naltrexone (25 mg twice a day) effectively reduced drinking and increased abstinence among EOAs, presumably by ameliorating neurochemical abnormalities in central opioid and serotonergic systems (Johnson et al., 2000a). Although those efficacy data were limited to self-report, we now present biochemical evidence to corroborate these results by using serum carbohydrate-deficient transferrin (CDT) level, a sensitive, reliable, and well-validated marker of transient alcohol consumption (Anton et al., 1996; Schmidt et al., 1997; Stibler, 1991).

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Received for publication January 16, 2001; accepted March 7, 2001.

Supported by NIAAA Grant R01 AA10522.

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MATERIALS AND METHODS

Subjects and General Procedures

Subjects and procedures were identical to those detailed previously (Johnson et al., 2000a). Briefly, we enrolled 20 DSM-IV–diagnosed alcoholics, all with an age of onset of problem drinking less than 25 years, derived from item B 28 of the Comprehensive Drinking Profile (Miller and Marlatt, 1984). We confirmed that subjects were in good physical health by conducting hematological and biochemical screens, a 12-lead electrocardiogram, and physical examination. Women were not pregnant or lactating.

Enrolled subjects at baseline (week 0) attended weekly for a further 8 weeks, during which they received their randomized, double-blind medication assignment. Of the 20 alcohol-dependent subjects randomized, 10 received ondansetron 4 μg/kg twice a day plus naltrexone 25 mg twice a day, and the other 10 had placebo. At each weekly visit, subjects received manual-guided group cognitive behavioral therapy (US Department of Health and Human Services, 1992), timeline follow-back (Sobell and Sobell, 1992) assessments of self-reported drinking, and other standardized measures, including evaluations of withdrawal, compliance, concomitant medications, and adverse events. Physical health checks were repeated at weeks 4 and 8.

Blood draws for assessment of serum CDT levels were conducted at weeks 0, 4, and 8. CDT was determined as %CDT by using the %CDT Turbidometric Immunoassay kit™ supplied by BioRad (Hercules, CA). CDT was expressed as a percentage of total transferrin.

The institutional review board at the University of Texas–Health Science Center at San Antonio provided ethical approval for the study.

Statistics

Database validation was conducted by rechecking all entries on each subject's responses and data to the experimental measures. Verified data were analyzed with the Statistical Package for the Social Sciences (SPSS™, SPSS Inc., Chicago, IL) version 10.0 (SPSS, 1999).

All subjects randomized to double-blind study medication were included in the efficacy analyses for the outcome measure, serum CDT. Outcome during double-blind treatment was measured for visits 4 and 8. Repeated-measures analysis of covariance (ANCOVA) with a split-plot design was used to examine the main effects of treatment, with the baseline measure as the covariate. The baseline covariate used for inclusion in the final model was tested for its interaction with the treatment condition. Additionally, the covariate was plotted against the residuals to determine its random normal distribution. The plot showed the covariate to be linear and resulted in valid analyses. Log transformation of the serum CDT data was necessary for normalizing the distribution of visits 0, 4, and 8 in the ANCOVA. Missing data were estimated by using the average linear group trend between visits 4 and 8. Data were estimated for one time point (week 4) in 4 subjects who had CDT assessments at baseline and week 4 but no CDT measurement at week 8. Descriptive data were distributed continuously and summarized as their mean ± SE.

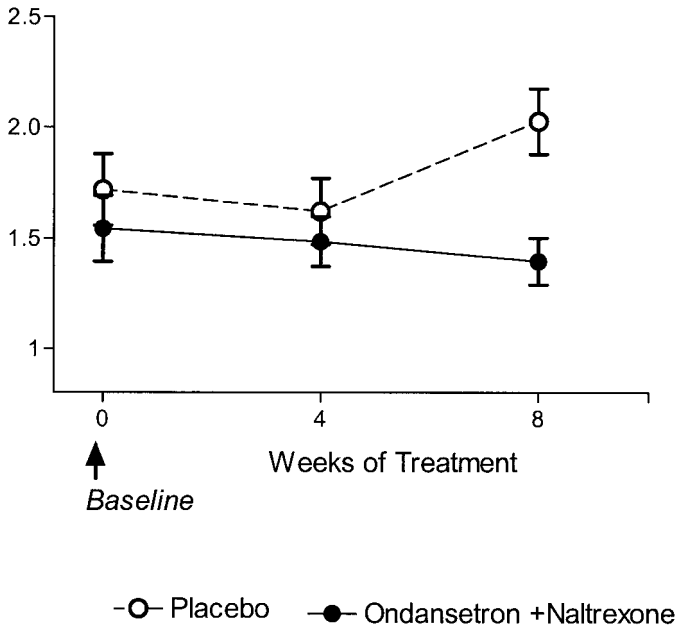

Fig. 1. Mean ± SE of serum log %CDT among EOAs who received either ondansetron and naltrexone or placebo.

RESULTS

The two treatment groups were demographically similar, with a mean age of 38.0 ± 1.78 years and a sex distribution of 5 women and 15 men. Twelve were white, and eight were Hispanic. Mean past 90-day drinking level was 7.44 ± 0.79 drinks per day, and average scores on the Michigan Alcoholism Screening Test (Selzer, 1971) were 32.94 ± 2.14. Thirty percent of subjects failed to attend all nine study visits, with no significant difference between the treatment groups. Log serum CDT was significantly lower in the ondansetron plus naltrexone group (group mean, 1.44 ± 0.076) compared with the placebo group (group mean, 1.82 ± 0.113), as evidenced by a main effect of group [$F(1,15) = 7.2, p = 0.017$; effect size = 0.32], visit [$F(1,16) = 11.2, p = 0.004$; effect size = 0.41], and an interaction between group and visit [$F(1,16) = 27.54, p < 0.001$; effect size = 0.63; Fig. 1]. Effect sizes of 0.2, 0.5, and 0.8 were defined as small, medium, and large, respectively (Cohen, 1988). Efficacy analyses of the self-reported drinking data, as well as those of other outcome measures, such as medication compliance, concomitant medications, and adverse events, have been reported elsewhere (Johnson et al., 2000a).

DISCUSSION

Previously, we demonstrated that the combination of ondansetron and naltrexone significantly reduced self-reported alcohol consumption among EOAs. This drinking reduction from baseline (i.e., visit 0) to endpoint was striking for the medication combination versus the placebo condition (85 vs. 34%; Johnson et al., 2000a). Now, we show that the significant self-reported drinking difference between the medication combination and placebo groups is corroborated by data using the biochemical marker serum CDT. These data support the use of serum CDT as a sensitive and reliable measure of transient alcohol consumption and a valid outcome measure for assessing treatment differences among alcohol-dependent individuals enrolled in clinical efficacy trials, as was shown in our previous efficacy article (Johnson et al., 2000c). Additionally, it may be even more important to corroborate alcohol consumption with serum CDT among EOAs because this type of alcoholic may less reliably self-report their drinking.

One limitation of this study is its relatively small sample size, which did not permit for meaningful correlational analyses between serum CDT and self-reported drinking. Further, it is reasonable to expect that the relationship between serum CDT and self-reported drinking is not contemporaneous and that there might be a time lag between drinking change and its quantification by serum CDT (Mundle et al., 1999); however, we did not test directly for such an effect. Finally, full characterization of the comparative absolute sensitivity of serum CDT with self-reported drinking is still ongoing.

In summary, observed serum CDT data corroborated our self-reported drinking data, showing that the combination of ondansetron and naltrexone was superior to placebo in treating EOAs. Routine use of serum CDT as a biomarker for quantifying alcohol consumption in alcohol treatment studies is recommended.

ACKNOWLEDGMENT

We are grateful to the staff of the Southwest Texas Addiction Research and Technology Center for their skilled technical assistance.

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