Peer-Reviewed Letter

EFFICACY OF ONDANSETRON IN THE TREATMENT OF GENERALIZED ANXIETY DISORDER

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Ondansetron is a highly selective antagonist at the 5-HT_3 subtype of serotonin (5-HT) receptors (Butler et al., 1988). The 5-HT_3 receptors are the only receptors whose effects are mediated through the ion channels rather than the G-protein series (Moulignier, 1994). Ondansetron has no appreciable affinity for other 5-HT receptor subtypes, the 5-HT or other monoamine uptake sites, or the GABA/benzodiazepine receptor complex. Within the central nervous system, 5-HT_3 receptors are found in highest concentrations in cortical and limbic areas and may, thus, modulate higher cortical and emotional functions (Costall et al., 1990). In addition, ondansetron may have unique properties among 5-HT_3 antagonists. Toral et al. (1995) reported ondansetron's unique ability to block voltage gated potassium channels in human neuroblastoma cells compared to other 5-HT_3 antagonists, which may be independent of its 5-HT_3 properties.

Unlike benzodiazepines, ondansetron appears to be devoid of sedative effects (Costall et al., 1990; Costall and Naylor, 1992). Furthermore, in animal models, ondansetron does not demonstrate potential for abuse, tolerance, or withdrawal symptoms following abrupt discontinuation (Costall and Naylor, 1992). Ondansetron has shown potential efficacy in the treatment of generalized anxiety disorder (GAD) in unpublished open-label and controlled clinical trials in the U.S. and Europe (Evoniuk, Glaxo personal communication). Studies in humans demonstrate no driving impairments (O'Hanlon et al., 1995) and no acute reduction in cerebral blood flow or anxiety in GAD subjects when given intravenously (Matthew and Wilson, 1991), similar to other non benzodiazepine anti-anxiety agents.

An open-label pilot study (Schneier et al., 1996) and a multisite double blind clinical trial (Ballenger et al., 1997) have suggested that ondansetron might have efficacy in the treatment of panic disorder. The objective of the present study was to assess the efficacy and safety of ondansetron in a double-blind, placebo-controlled pilot study in GAD.

This study was randomized, double-blinded, and placebo-controlled with a parallel multi-center group design, with eight participating groups. Fifty-four subjects diagnosed with GAD according to DSM-III-R criteria were randomized into this site's study. Subjects continuing in the active treatment phase were randomly allocated to four treatment groups using a balanced block design. Subjects entering the study met the following inclusion criteria: 18 years older, male or surgically sterilized or post-menopausal females; outpatients suffering from GAD with symptoms of sufficient intensity to provide a HAM-A score of 22 or more at screening and present for at least 4 weeks (diagnosed by unstructured clinical interview using DSM-III-R criteria).

Subjects with any acute systemic illness, untreated hypertension (blood pressure of greater than 160/90 mm Hg), or with clinically significant abnormalities in hematology, biochemistry, and urinalysis screening tests were excluded from this study. Subjects with bipolar disorder, psychosis, mental retardation, organic brain disease, senility, partial or generalized seizure disorders, severe personality disorders, more than four panic attacks per month, with a Montgomery-Asberg Depression Rating (Montgomery and Asberg, 1979) score of above twenty, and receiving any form of psychotherapy in the last 2 weeks prior to enrollment were also excluded.

Subjects with a positive history of ethanol abuse within 6 months preceding the screening visit as indicated by the presence of any of the following characteristics, i.e., previous hospitalization for treatment of a medical complication of excessive ethanol intake, unwillingness of the subject to restrict alcoholic beverages during the study, and complaints by a family member regarding the subject's abuse of alcohol, were also excluded from the study. Exclusion criteria also eliminated subjects with a history of drug abuse within the last 6 months or who had a positive urine screen for illicit drugs.

Subjects who were using one or more of the following drugs were also excluded from the study: routine benzodiazepine use within 2 weeks prior to start of the study, psychotropics at the time of the study entry, any other investigational drug within 1 month prior to start of the study, beta-blockers (allowed if subject has been stabilized for 6 months or more), antihypertensive medications with direct CNS effects (e.g., methyldopa), and insulin therapy (oral hypoglycemics were allowed).

All subjects who met initial inclusion/exclusion criteria were provided with two bottles of placebo medication and were instructed to take one tablet from each bottle in the morning and in the evening for at least 7 consecutive days and not more than 14 days. The subject's anxiety symptoms was evaluated again at visit 2 following placebo treatment using the HAM-A rating scale. All subjects who exhibited a reduction of 10 or more points or a score of less than 22 on the HAM-A, or a score of over 20 on the MADRS did not qualify for entry into the double-blind treatment phase of the study.

After the placebo run-in phase, subjects were randomized to a double-blind bid dosing of ondansetron 1.0 mg, ondansetron 0.25 mg, diazepam 5.0 mg, or placebo for an 8-week period. There were no significant differences between the placebo and treatment groups in sex, age, or MADRS scores. The double-blind phase was followed by a 2-week placebo washout.

The HAM-A (Hamilton, 1959) in the 15-item version and the CGI (Guy, 1976) assessments were performed weekly, biweekly, or on the day of termination if the subject terminated the study prematurely. Change from baseline was analyzed at week 8 for all assessments. "Last Observation Carry Forward" (LOCF) analyses were performed. If a subject withdrew from the trial prematurely, the last response was "carried forward" to week 8 for LOCF analysis. One subject was eliminated as that subject had no observation in the double-blind period. Comparison of baseline efficacy scores indicated no statistically sig-

nificant differences among the treatment groups at the end of the initial single-blind.

The mean ages for the subjects in the four treatment groups were as follows: placebo, 37 years, n = 13; ondansetron .25 mg, 44 years, n = 13; ondansetron 1.0 mg, 38 years, n = 13; diazepam 5 mg, 44 years, n = 14. The following were the percentages of females in each group: placebo, 54%; ondansetron .25 mg, 77%; ondansetron 1.0 mg, 54%; diazepam 5 mg, 86%.

The following mean decreases from baseline for HAM-A for the LOCF week 8 analysis. Placebo, –8.2; ondansetron 0.25 mg, –9.3; ondansetron 1.0 mg, –14.3; and diazepam 5.0 mg, –10.8. A multiple comparison technique was used to compare the group means. The only statistically significant difference achieved was for ondansetron 1.0 mg vs. placebo ($P = 0.0429$) (see Table 1).

The following are the mean decreases from baseline for CGI Severity for the LOCF week-8 analysis: Placebo, –0.8; ondansetron 0.25, –1.2; = 1.0 mg, –1.5; and diazepam 5.0 mg, –1.1. Based on multiple comparisons, the only statistically significant difference between groups was again for ondansetron 1.0 mg vs. placebo ($P = 0.0472$) (see Table 2).

No significant adverse effects were observed in this study. No significant EKG or laboratory abnormalities were noted. The most commonly reported adverse events in this study were fairly typical of an adult population in general (e.g., cold symptoms, constipation, and headache). Ondansetron treatment was generally well tolerated. The data indicate that the only side effect associated with ondansetron treatment was constipation, which approximately 57% of subjects reported.

The results from this center possibly support the efficacy of ondansetron 1.0 mg bid in the treatment of a subgroup of generalized anxiety disorder within the limitations of this study. The positive results at this site could be due to chance alone, selection bias, or weak therapeutic effect of ondansetron at the 2 mg dosage. Ondansetron's efficacy in GAD merits further investigation and replication in other sites.

GAD is still a controversial diagnostic category with significant overlap with affective disorder and panic (Robins and Regier, 1991). In the ECA study 54% of subjects with GAD had comorbid panic or depressive diagnoses (Brown et al., 1994). Since this study was completed, DSM-IV reformulated the disorder with more emphasis on six core symptoms of restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance compared to the eighteen symptoms of DSM-III-R. The initial findings on efficacy of ondansetron in panic disorder and its mixed findings in this study provokes several questions of pathophysociological and pharmacological interest. Are there subgroups of GAD, possibly mixed anxiety and depression, which have evidence of $5HT_{1A}$ responsiveness (Sramek et al., 1996), and mixed panic and anxiety, which may be $5HT_3$ or ondansetron responsive?

If ondansetron treats panic disorder but not GAD, there could be pharmacological and pathophysiological implications for $5HT_3$ and/or ion channel system involvement in panic disorder. These questions could be further elevated by a larger double-blind RCT utilizing DSM-IV criteria and better description of affective and panic disorder comorbidity especially the temporal sequencing of symptoms.

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