Ondansetron Treatment in Tourette's Disorder: A 3-Week, Randomized, Double-Blind, Placebo-Controlled Study

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Objective: The aim of the present study was to evaluate the efficacy of ondansetron, a selective 5-HT_3 antagonist, in the treatment of Tourette's disorder.

Method: Participants (N = 30) aged 12 to 46 years, diagnosed with DSM-IV Tourette's disorder and resistant to previous haloperidol treatment, were enrolled in a 3-week, randomized, double-blind, placebo-controlled outpatient study. Assessments were conducted at baseline and once a week during the study period. Scales used included the Tourette's Syndrome Global Scale (TSGS), the Yale Global Tic Severity Scale (YGTSS), and the Yale-Brown Obsessive Compulsive Scale. Ondansetron dose was 8, 16, and 24 mg/day in the first, second, and third weeks, respectively.

Results: A significant positive effect of ondansetron on tic severity, as assessed by the TSGS, was noted (baseline vs. endpoint: mean ± SD = 29.62 ± 20.33 vs. 20.58 ± 12.82, p = .002 vs. placebo). However, no significant effect was detected upon assessing ondansetron/placebo effect on tic severity with the YGTSS (baseline vs. endpoint: mean ± SD = 24.04 ± 9.44 vs. 17.50 ± 9.48, p = .15 vs. placebo). No change in obsessive-compulsive symptoms was noted in either group. Adverse effects included mild and transient abdominal pain.

Conclusions: Ondansetron may have anti-tic effects in patients with Tourette's disorder. Large-scale, double-blind studies should further assess the anti-tic efficacy of ondansetron.

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Tourette's disorder is defined by multiple motor and vocal tics.[1] The noradrenergic, serotonergic, and mainly the dopaminergic systems have been suggested to play a role in the pathophysiology of Tourette's disorder.[2] The most commonly prescribed anti-tic agents in Tourette's disorder are dopamine D_2 antagonists (antipsychotic agents),[3] especially haloperidol, pimozide, and risperidone.[4–7] However, the typical antipsychotics (e.g., haloperidol) can cause parkinsonism and tardive dyskinesia. Risperidone, an atypical agent, is not devoid of extrapyramidal symptoms[8,9] and is also associated with significant weight gain.[10] Further, treatment with haloperidol and especially pimozide requires electrocardiographic monitoring for prolonged QTc.[11,12] Other drugs, such as the α_2 agonists clonidine and guanfacine, as well as the mixed D_1, D_2, and D_3 agonist pergolide, have also been suggested as anti-tic agents.[13]

Some of the anti-tic/antipsychotic agents, but not risperidone, also possess antagonistic activity at the 5-HT_3 receptor.[14] Ondansetron, a selective 5-HT_3 receptor antagonist usually prescribed as an antinausea/antiemesis (postoperational and chemotherapy-induced) agent,[15] has already been suggested as a possible anti-tic agent.[16] In an open-label pilot study, we evaluated the efficacy of ondansetron in 6 patients (aged 14–48 years) with Tourette's disorder resistant to haloperidol. Ondansetron treatment was associated with a significant decrease in tic severity. Two patients showed a definite response (score improvement of 40% or more), 2 showed a probable response (> 25% improvement), and 2 did not improve. Ondansetron was well tolerated with minimal and transient side effects of abdominal pain and constipation and no extrapyramidal symptoms.[16]

The aim of the present double-blind, placebo-controlled study was to assess the efficacy of ondansetron versus placebo in alleviating tic severity in patients with Tourette's disorder.

METHOD

Subjects

Thirty patients admitted to the Tourette's disorder outpatient clinic of Tel-Aviv Community Mental Health Cen-

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ter (Tel-Aviv, Israel) who agreed to participate in the study and met the inclusion criteria as follows were recruited. Inclusion criteria were age ≥ 12 years, DSM-IV diagnosis of Tourette's disorder, resistance to prior treatment with haloperidol (patients who did not benefit clinically from an adequate dose of haloperidol for a minimal period of 8 weeks or reported adverse effects that necessitated drug discontinuation or caused noncompliance; a history of haloperidol nonresponse was a sufficient criterion), and lack of drug treatment for at least 3 weeks. Tic severity was not an inclusion criterion. Exclusion criteria included the presence of a chronic medical illness or clinically significant abnormal baseline laboratory values, alcohol or drug dependence, and mood or psychotic disorders. Diagnoses were established according to the DSM-IV-TR criteria[1] by senior child and adolescent psychiatrists following a comprehensive psychiatric interview. The study was approved by the Institutional and the Ministry of Health Review Boards. Written informed consent was obtained from all adult participants and from the parents of participants under the age of 18 years. All participants < 18 years gave their assent to participate in the study.

Procedure

The patients were assessed at baseline and once a week for 3 consecutive weeks of treatment (week 1–week 3). Baseline assessment included a physical examination, an electrocardiogram, a routine blood screen (including liver and kidney function), a clinical evaluation by a child and adolescent psychiatrist, and completion of baseline rating scales. The psychiatric diagnoses were established according to DSM-IV criteria.

After baseline assessment, participants were randomly assigned to 2 groups (ondansetron or placebo), each containing 15 subjects. Week 1 through week 3 assessments included completion of rating scales.

Study Medication

Ondansetron was started at a dose of 8 mg once a day for the first week (1 placebo tablet in the placebo group), was increased to 8 mg b.i.d. during the second week of treatment (or 2 placebo tablets), and was further increased to 8 mg t.i.d. (or 3 placebo tablets) during the third week. The maximum dose of ondansetron was 24 mg/day. The dose schedule was determined according to our previous study[16] and a study in bulimia nervosa patients.[17] The 3-week study duration is consistent with other studies in neuropsychiatric disorders demonstrating a beneficial clinical effect of ondansetron treatment within 1 to 4 weeks.[17–19] Compliance was monitored by pill counting as well as by participants' and parents' reports.

Rating Scales

Tourette's Syndrome Global Scale (TSGS).[20,21] This multidimensional scale of Tourette's disorder symptomatology (motor and phonic tics) and social functioning comprises 8 individually rated dimensions summed into an overall global score. The scale ranges from no symptoms (0) to worst possible Tourette's symptoms, social behavior, and inability to function in school/working environment (100). Tics are scored according to their complexity, frequency, and degree of disruption. The social functioning domain consists of behavioral problems, motor restlessness, and level of school/occupational functioning. Estimates of interrater reliability are very good (r = 0.89), as are estimates of validity of the TSGS in the context of pharmacologic studies.[20]

Yale Global Tic Severity Scale (YGTSS). This scale consists of ratings for motor and vocal tics, each for number, frequency, intensity, complexity, and interference.[22] The YGTSS has excellent interrater reliability.[22]

Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The Y-BOCS is a 10-item rating scale ranging from 0 to 40 and divided into 2 subscales: obsessions and compulsions[23]; the children's version (Children's Yale-Brown Obsessive Compulsive Scale[24]) was used for individuals under the age of 18 years.

Clinical Global Impressions-Improvement scale (CGI-I).[25] The CGI-I was used for rater's judgment of clinical improvement (1 = very much improved to 7 = very much worse). Items 1 to 3 and items 4 to 7 were grouped as "improved" versus "non-improved," respectively. The CGI-I was completed at week 3.

Adverse effects were monitored by spontaneous self-reports as well as by specific questions concerning a list of possible ondansetron-related side effects, including headache, malaise, constipation, diarrhea, dizziness, abdominal pain, xerostomia, weakness, and extrapyramidal symptoms.

Statistical Analysis

The 2 groups (study and control) were compared at baseline using the t test (for age and symptom severity) and χ^2 test (for gender). Analysis of variance (ANOVA) with repeated measures with group as between-subject factor was used to compare symptom severity at the various assessment points. Analysis of covariance (ANCOVA) with repeated measures was used for the parameters found to be significantly different at baseline between the 2 groups.

RESULTS

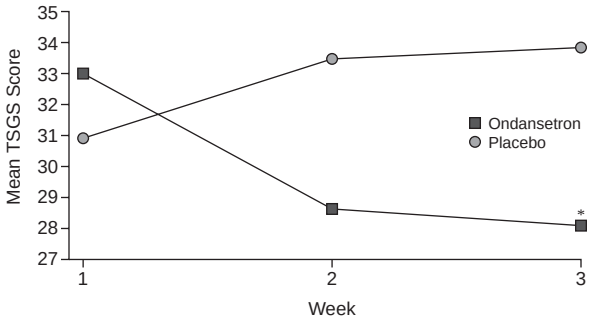
Thirty subjects (mean ± SD age = 21.7 ± 9.14 years; age range, 12–46 years; 15 subjects ≤ 18 years) participated in the study. Fifteen patients participated in the ondansetron group (mean ± SD age = 22.46 ± 7.97 years; 8 males, 7 females) and 15 in the placebo group (mean ± SD age = 20.86 ± 10.39 years; 12 males, 3 females). The ondansetron and placebo groups did not differ significantly

Table 1. Tic Severity Ratings (TSGS and YGTSS) of Ondansetron and Placebo Groups at Each Assessment Point, Mean ± SD

	Ondansetron Group		Placebo Group	
Timepoint	TSGS	YGTSS	TSGS	YGTSS
Baseline	29.62 ± 20.33	24.04 ± 9.44	47.14 ± 17.59	31.82 ± 7.15
Week				
1	23.81 ± 19.01	19.00 ± 10.11	39.39 ± 23.96	26.32 ± 11.18
2	21.00 ± 12.79	17.42 ± 7.89	40.43 ± 23.58	27.21 ± 11.90
3	20.58 ± 12.82	17.50 ± 9.48	40.78 ± 23.72	27.28 ± 12.12

Abbreviations: TSGS = Tourette's Syndrome Global Scale, YGTSS = Yale Global Tic Severity Scale.

Figure 1. The Effect of Ondansetron and Placebo Treatments on Tourette's Syndrome Global Scale (TSGS) Scores (analysis of covariance)[a]



[a]All values are adjusted for the baseline score as a covariate.
*Group-by-time interaction was found for ondansetron vs. placebo (p = .002).

in gender distribution ($\chi^2 = 2.4$, df = 1, p > .05) or age (t = 0.47, df = 28, p > .05). Thirteen of 15 patients in the ondansetron group completed the trial. One patient discontinued ondansetron treatment after 4 days due to gastrointestinal complaints, and another patient discontinued the treatment after a week due to lack of efficacy. Fourteen of 15 patients in the placebo group completed the trial. One patient discontinued the treatment after 1 week due to lack of efficacy.

Upon blinded assessment of CGI-I score ("improved" versus "non-improved") of tic severity, i.e., before the code was broken, 7/13 patients in the ondansetron group and 3/14 in the placebo group were considered "improved" (p > .05, χ^2).

TSGS scores of the ondansetron and the placebo groups are given in Table 1. At baseline, TSGS scores differed significantly between the groups (p = .02). Therefore, ANCOVA with repeated measures, with baseline TSGS score as constant covariate, was used for comparisons among the groups. A statistically significant group × time interaction (p = .002) was detected, i.e., the behavior along the various assessment points was statistically different between the 2 groups (Figure 1). Further, a statistically significant group × time interaction was detected using the TSGS-tics (p < .05) as well as the TSGS-maladaptive behavior (p < .05) domains.

YGTSS scores of the ondansetron and the placebo groups are given in Table 1. At baseline, YGTSS scores differed significantly between the groups (p = .023). Therefore, ANCOVA with repeated measures, with baseline YGTSS score as covariate, was used for comparisons among the groups. No statistically significant differences were detected between the ondansetron and placebo groups at the various assessment points in tic severity, as measured by the YGTSS (p = .15, 2-tailed).

Further, ANCOVA with repeated measures of TSGS and YGTSS revealed no difference between participants ≤ 18 years of age and adults in response to ondansetron/placebo treatments (p > .05).

Seven of 14 patients in the placebo group and 4/13 in the ondansetron group had obsessive-compulsive disorder (OCD); 2/14 patients in the placebo group and 1/13 in the ondansetron group had attention-deficit/hyperactivity disorder. ANCOVA with repeated measures of TSGS and YGTSS revealed no difference between subjects with and without comorbid disorders in response to ondansetron/placebo treatments (p > .05). At baseline, Y-BOCS scores did not differ significantly between the groups (p > .05). ANOVA with repeated measures did not detect statistically significant differences between the ondansetron and the placebo groups along the various assessment points in the severity of obsessive-compulsive (OC) symptoms, as measured by the Y-BOCS (all p > .05).

Adverse effects included mild and transient abdominal pain and were reported by 1 patient in the ondansetron group and 1 patient in the placebo group (adverse effects also included gastrointestinal complaints leading to dropout of 1 patient in the ondansetron group, as mentioned).

DISCUSSION

The present double-blind, placebo-controlled study showed an efficacy of ondansetron in alleviating tic severity in patients with Tourette's disorder. The efficacy of ondansetron was clearly demonstrated using the TSGS (p = .002), but not the YGTSS (p = .15) assessment tool. The results support the previous finding of our open-label trial.[16] Further support is given by the efficacy of ondansetron treatment in another movement disorder—tardive dyskinesia.[19,26] Sirota and coworkers evaluated 10[19] and 20[26] patients with schizophrenia and neuroleptic-induced tardive dyskinesia who were given 8[19] and 12[26] mg/day, respectively, of ondansetron (as add-on to the classical neuroleptics they were receiving) for 4[19] and 12[26] weeks in open-label studies. Administration of ondansetron in both studies resulted in a statistically significant improvement in tardive dyskinesia.[27] Tardive dyskinesia involves dysregulation of dopamine pathways,[28] which

might have been modulated by serotonin,[19] resembling the pathophysiology of Tourette's disorder.

Furthermore, parkinsonian psychosis, a neuropsychiatric disorder related to dopamine agonists, can be alleviated by ondansetron treatment. Melamed and coworkers[29] reported that treatment of parkinsonian psychosis with ondansetron attenuated visual hallucinosis, improved delusional ideation and confusion, and was well tolerated. Preclinical studies demonstrated that 5-HT_3 receptor antagonists, such as ondansetron, are potent in reducing mesolimbic dopamine hyperactivity caused by amphetamine or dopamine agonists.[30] Naidu and Kulkarni[31] assessed the role of 5-HT_3 receptor involvement in neuroleptic-induced vacuous chewing movements in rats (a model for tardive dyskinesia). Ondansetron reversed the haloperidol-induced vacuous chewing movements. The authors suggested that serotonin, acting through 5-HT_3 receptors, might play a significant role in the pathophysiology of tardive dyskinesia.

The issue of the discrepancy between the 2 scales (TSGS and YGTSS) used to assess the symptom severity of Tourette's disorder should also be addressed. It is of note that YGTSS is now the most commonly used outcome measure in Tourette's disorder clinical trials. Despite the close agreement between the 2 scales, the YGTSS has a relatively narrow scope of assessment. It measures only tic behaviors and their impact rather than attempting to assess a broader range of maladaptive behaviors, such as overall behavioral adjustment, motor restlessness, and academic/vocational performance,[22] all of which are assessed by the TSGS.[20,21] It should be underscored that, in the present study, both TSGS symptom domains (tics as well as general maladaptive behavior) showed a significant difference between the placebo and ondansetron groups. Further, on the background of our pilot study–driven hypothesis[16] that ondansetron is able to attenuate tic severity, it should be noted that the 2-tailed p value of .15 might turn more significant in a larger sample size with a stronger statistical power. Nevertheless, the inconsistency between the 2 scales weakens the results of the present study. We are aware that the results in relatively small samples are liable to both type I and II errors. Thus, our findings should be considered as preliminary and need replication in an independent, larger sample.

No effect of ondansetron on the severity of OC symptoms was noted in the present study. It should be underscored that only 8/14 patients in the placebo group and 4/13 patients in the ondansetron group had comorbid OCD. In our open-label study,[16] a trend toward a decrease in OC symptoms was noted in 2 of 3 patients with comorbid OCD. This trend did not reach statistical significance. On the other hand, Hewlett et al.,[32] in an open-label trial of 8 patients, suggested that low-dose (1 mg 3 times daily) ondansetron may have promise as a monotherapy for some patients suffering from OCD.

In the present study, ondansetron was well tolerated with minimal and transient gastrointestinal side effects. Ondansetron (0.1 mg/kg) is very often used in preventing emesis in children undergoing various surgical procedures or in addition to chemotherapy. Ondansetron is relatively free of adverse events, is generally well tolerated, and rarely necessitates treatment withdrawal.[33] Ramsook and coworkers,[34] in a randomized, double-blind trial, compared oral ondansetron with placebo in 145 children with vomiting from acute gastroenteritis. The patients in the ondansetron group had significantly more diarrhea than the placebo group. With the exception of diarrhea, none of the manufacturer's listed side effects (headache, malaise, constipation, diarrhea, dizziness, abdominal pain, xerostomia, and weakness) were reported. The present study revealed no difference between children and adults suffering from Tourette's disorder in response to ondansetron treatment.

The major limitations of the present study are the small sample size and the brief duration (3 weeks). Further, the use of 2 rating scales for the assessment of tic severity instead of 1 primary outcome measure may be another limitation of the study. Future studies should assess larger numbers of patients with Tourette's disorder, for longer periods, in double-blind, placebo-controlled, and relevant comparator (haloperidol/risperidone)–controlled studies.

Drug names: clonidine (Catapres, Duraclon, and others), guanfacine (Tenex and others), haloperidol (Haldol and others), ondansetron (Zofran), pergolide (Permax and others), pimozide (Orap), risperidone (Risperdal).

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