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Quetiapine: A Novel Strategy of Psychopharmacological Treatment of Children with Autistic Disorder

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Abstract **Objectives:** Many autistic children have problems of eye contact and expressive language that limit the effectiveness of educational and behavioural interventions. Few controlled psychopharmacologic trials have been conducted in autistic children to determine which agents may be effective for these associated features. **Methods:** Twelve male children (7.0 +/- 3.2 years) with autistic disorder, diagnosed by ICD-10 criteria, completed a placebo-controlled, double-blind crossover trial of Quetiapine. Subjects were included in the study if their eye contact and expressive language was inadaequate for their developmental level. Subjects had not tolerated or responded to other psychopharmacologic treatments (methylphenidate, clonidine or desipramine). **Results:** Teacher ratings on the Aberrant Behavior Checklist irritability, stereotypy, and inappropriate speech factors were slightly lower during treatment with Quetiapine than during treatment with placebo. Clinician ratings (Children's Psychiatric Rating Scale Autism, Anger and Speech Deviance factors; Children's Global Assessment Scale; Clinical Global Impressions efficacy) of videotaped sessions were not significantly different between Quetiapine and placebo. **Discussion:** Quetiapine was only modestly effective in the short-term treatment of irritability in some children with autistic disorder.

Key words Autism; Psychopharmacology; Quetiapine

Introduction

Autistic disorder is a chronic pervasive developmental disorder, characterised by qualitative impairments in reciprocal social interaction, verbal and nonverbal communication, and imaginative activity with a markedly restricted repertoire of activities and interests. Additionally, hyperactivity, poor attention span, and impulsivity are often prominent associated clinical features and have been target symptoms in previous medication trials.[1] In an earlier open trial of dextroamphetamine, autistic children had an adverse response.[2] Jaselskis et al[3] and Hunt et al[4] report good efficacy of clonidine treatment of autistic children. An open trial[5] suggested that methylphenidate use in autistic hyperactive children may ameliorate hyperactivity, inattention, and impulsivity in children with autistic disorder. Neuroleptics are somewhat effective in reducing hyperactivity, impulsivity, and inattention in children with autistic disorder.[6] However, chronic use of some neuroleptics may be complicated by cognitive blunting and the often irreversible side effect of tardive dyskinesia.[7] The development of efficacious and safe therapeutic interventions remains an area of significant need in this disorder. Therapeutic effects in other disorders with similar target symptoms may guide development of treatments for children with autistic disorder.

Immune system abnormalities have been associated with autism. These have included inhibition of macrophage migration in response to human myelin basic protein,[8] reduced mitogen-induced lymphocyte blastogenesis,[9,10] decreased numbers of T-lymphocytes with altered ratios of helper to suppressor T-cells,[10] decreased helper T-cell and B-cell numbers,[11] deficiency of suppressor-inducer T-cells,[12]

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decreased natural killer cell activity,[13] and the demonstration of circulating antibodies to serotonin receptors.[14] In another study of 14 patients with autism, eight had an abnormal lymphocyte proliferative response to mitogens and to autologous lymphocytes and monocytes.[15]

Quetiapine is an atypical neuroleptic, which mainly affects the dopamine system by reducing the cerebral dopamine level.[16] It is reported also to reduce aggression.[17] Adverse side effects, especially in autistic children, such as sedation, increased appetite, weight gain, possible seizures,[18] hyperglycemia[19], restless legs[20] and a case of malignant neuroleptic syndrome[21] have been described.[18]

This placebo-controlled study was conducted to examine the effects of Quetiapine on a variety of target behaviours in young boys with autistic disorder.

Methods

Twelve outpatient male children (age range 4.2-14.9 years; mean=7.0 years; SD=3.2 years) meeting ICD-10 criteria for autistic disorder were recruited from our clinic. The study was conducted according to the European Good Clinical Practice Guidelines and the Declaration of Helsinki, after having obtained informed consent of the patients and/or their parents and the approval of the local ethic committee.

Full-scale IQs ranged from 35 to 84 (65±16), and were obtained from several tests, including parts of the Wechsler Intelligence Scale for Children Revised, Leiter International Performance Scale, or the Cattell Infant Intelligence Scale. A thirteenth subject entered the study but was dropped because of noncompliance with medication beginning during the first week of the study. Agreement of the independent diagnosis of autistic disorder using the Autism Diagnostic Inventory was obtained. Parents provided written informed consent for their children after the procedures and possible side effects were explained to them. Assent was obtained from the two children who appeared to be capable of expressing it.

The subjects had no history of identified medical or neurologic illnesses and had been off medications for at least 1 month before the study. All of these children had been treated with either methylphenidate, neuroleptics, or desipramine before entry into the study. In each case, these medications had either not been effective or caused intolerable side effects.

All subjects lived at home with either both parents (8 subjects) or their mothers (4 subjects). Sociooeonomic status for the subjects' families was class I (6 subjects), class II (4 subjects), and class IV (2 subjects).[22] Two children's languages consisted of monosyllabic utterances, another two children's languages consisted of single words (10-word vocabulary), and the other children spoke in sentences. However, all children had social and pragmatic language deficits consistent with autistic disorder.

All raters (parents, teachers, and clinicians) were blind to drug order until ratings were completed.

Parent and teacher-rated instruments included weekly ratings. Side effects monitored included increased thirst, drowsiness, sleep disturbance, sadness, dizziness, irritability, appetite change, and decreased activity. Parents and teachers responded with "yes" (coded as 0) or "no" (coded as 1) for each item each week. These Symptom Checklist responses were summed over each 6-week treatment period.

Weekly teacher ratings included the Aberrant Behavior (ABC) and Symptom Checklist.[23]

A 15-minute videotape paradigm was constructed to determine clinician ratings of the effects of Quetiapine on inadaequate eye contact and expressive language deficits. There were sessions that were done at baseline and at the end of each treatment period. The videotaping was done in a small office with the equipment visible in the room. The first 5 minutes of taping were free play. The second 5 minutes consisted of tasks with the parent, including Copying a square and a circle and drawing a picture; the parent asking child to name an object; verbalising the name of a "Cup"; standing in front of the mother while she straightened the child's clothes; and having the parent leave the room and return after a few minutes. The last 5 minutes consisted of parent reunion, asking for assistance with clean-up, and leaving the room with the child. Clinician ratings (average of both raters) consisted of videotaped observations at baseline, 6 weeks, and 13 weeks using the Children's Global Assessment Scale,[24] modified Children's Psychiatric Rating Scale (CPRS),[25] and Clinical Global Impressions.[26]

This was a double-blind and placbo-controlled crossover study. Quetiapine and identical placebo tablets were administered for 4 weeks (dosage: 150 mg daily). The subjects were randomly assigned by a nonrating clinician to begin Quetiapine or placebo. Patients were free of medication for at least 4 weeks (12 weeks for a single subject who bad been taking fenfluramine) before beginning the study but there was no placebo washout phase. Blood pressure and clinical symptoms were monitored via telephone conversations and scheduled visits. School nurses

or the family physician measured blood pressure on a weekly basis.

Subjects continued to receive educational and behavioural interventions in school during the course of the study that were not substantially altered for any of the children during their participation in the study.

Parent and teacher ratings were averaged over each 6-week treatment period. Clinician ratings were only made at the end of each treatment period. The outcome measure, i.e. the ratings after a 6 week placebo and drug treatment was compared using paired, two-tailed t-tests. We expected to see less Autism-related symptoms at Quetiapine-treated patients compared to the placebo group. Statistics were computed using SPSS V9.O.

Results

Parent's and Teacher's ratings on the ABC factors irritability (placebo, 14.5±5.4; Quetiapine, 11.3±7.6; p=0.040), hyperactivity, i.e. excessive agitation (placebo, 22.3±11.5; Quetiapine, 18.7±12.4; p=0.038), inadaequate eye contact, i.e. watching the other person during conversation (placebo, 8.4±5.1; Quetiapine, 7.6±3.9; p=0.045), and inappropriate speech (placebo, 6.0±+2.5; Quetiapine, 4.3±3.8; p=0.040) were significantly improved on Quetiapine. The symptom checklist scores combining both parent and teacher scores revealed a significant increase in drowsiness (placebo, 1.7±2.3; Quetiapine, 3.9±3.2; p=0.03) and decreased activity (placebo, 2.2±3.4; Quetiapine, 4.0±3.1; p=0.029). None of the clinician ratings showed significant differences between placebo and Quetiapine.

None of the subjects appeared to have headaches or stomachaches, although report of such side effects was limited by the expressive language and social skills of these subjects.

Discussion

This double-blind, placebo-controlled study examined the effects of Quetiapine in male autistic children between the ages of 5 and 11 with inadaequate eye contact and expressive language deficits. Teacher and parent ratings showed a modest symptom improvement while the child was taking Quetiapine. Parents rated significant behavioral changes while their son was on Quetiapine. Clinician rating scales were insensitive to Quetiapine effects. Although inadaequate eye contact and expressive language deficits were the primary target symptoms of this study, the treatment effect of greatest size was a 33% decrease of symptomatology. Interestingly, in a recent trial of clomipramine in autistic disorder, an improvement in the anger scale of the CPRS was the stronge, but unexpected, effect.[27]

There are very few specific clinical instruments that target the response of inadaequate eye contact and expressive language deficits to drug treatment in autistic persons. Both parents and teachers remarked that several of the items of the questionnaire were irrelevant for evaluating their autistic child.

The failure of the clinician ratings to be sensitive to changes may have been influenced by several factors. Although clinician-rated effects at 1 month were equivalent to ratings at 2 months in a study of Quetiapine treatment of nonautistic children with attention deficit disorder and hyperactivity,[4] 6 weeks may have been an inadequate duration to determine full Quetiapine effect in the current study. The environment in which clinician ratings were performed was not optimal to serve as a sensitive indicator of the modest effects of Quetiapine during the 6-week trial. The videotape equipment was a focus of curiosity and attention. Several of the subjects associated their visits with blood draws done after the videotaping. Some of the children verbalised their anxiety about the blood-drawing procedure during the taping sessions. In addition, the videotaping was done in a small office, which may have limited the subjects' movement. This highly structured and defined space was not the same as that in which the teachers and parents observed the children. It would have been preferable to make clinician ratings in each child's home and school setting. Because this may he impractical for most outpatient clinicians, ratings by teachers and parents arc invaluable in the assessment of children with autistic disorder during psychopharmacologic treatment. Possible "unblinding" of parents and teachers because of side effects is another limitation of the study. Videotapes were rated by the clinicians several months after each patient's treatment period ended, and clinicians were unable to make accurate assessments of which drug phase during review of the videotapes. Another methodologic issue of concern was possible carryover, which was minimised by a 1-week taper during the crossover period. In addition, a small number of subjects was involved in this study.

Clinical implications: 8 of the 12 subjects were treated with Quetiapine in an open manner after the study. All of these 8 subjects continued to respond with a symptom

improvement within 6 weeks. Quetiapine' modest effects in the treatment of a subgroup of children with autistic disorder may be related to noradrenergic dysregulation as indicated by findings such as increased plasma norepinephrine in children with autistic disorder.[28,29]

Limitations: Although this study revealed a modest therapeutic effect of Quetiapine in the acute management of autistic children in some subjects make it clear that its role in the management of these symptoms in children with autistic disorder may be limited. Its role in acute and chronic treatment of these symptoms requires further investigation. Controlled, chronic pharmacologic trials with clinical observations in the school and home settings will be necessary to delineate further the role of Quetiapine in treating this specific population. Such trials should be designed to minimise the development of tolerance.

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