Efficacy of Low-Dose Buspirone for Restricted and Repetitive Behavior in Young Children with Autism Spectrum Disorder: A Randomized Trial

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Objectives To determine safety and efficacy of the $5HT_{1A}$ serotonin partial agonist buspirone on core autism and associated features in children with autism spectrum disorder (ASD).

Study design Children 2-6 years of age with ASD (N = 166) were randomized to receive placebo or 2.5 or 5.0 mg of buspirone twice daily. The primary objective was to evaluate the effects of 24 weeks of buspirone on the Autism Diagnostic Observation Schedule (ADOS) Composite Total Score. Secondary objectives included evaluating the effects of buspirone on social competence, repetitive behaviors, language, sensory dysfunction, and anxiety and to assess side effects. Positron emission tomography measures of tryptophan metabolism and blood serotonin concentrations were assessed as predictors of buspirone efficacy.

Results There was no difference in the ADOS Composite Total Score between baseline and 24 weeks among the 3 treatment groups (P = .400); however, the ADOS Restricted and Repetitive Behavior score showed a time-by-treatment effect (P = .006); the 2.5-mg buspirone group showed significant improvement (P = .003), whereas placebo and 5.0-mg buspirone groups showed no change. Children in the 2.5-mg buspirone group were more likely to improve if they had fewer foci of increased brain tryptophan metabolism on positron emission tomography (P = .018) or if they showed normal levels of blood serotonin (P = .044). Adverse events did not differ significantly among treatment groups.

Conclusions Treatment with 2.5 mg of buspirone in young children with ASD might be a useful adjunct therapy to target restrictive and repetitive behaviors in conjunction with behavioral interventions. *(J Pediatr 2016;170:45-53)*.

Trial registration ClinicalTrials.gov: NCT00873509.

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized behaviorally by impairment in social communication and the presence of repetitive and restricted behaviors. Current evidence suggests that the risk for ASD is conferred by rare variants in hundreds of genes that converge on networks related to neuronal signaling and development.[1] Although there are hundreds of genes that place individuals at risk for autism, it is striking that 30%-50% of individuals with ASD show an elevated concentration of serotonin in the blood.[2-5] Alterations in serotonin receptors and serotonin synthesis/degradation enzymes are involved in the risk for ASD.[6] Evidence also exists for altered serotonin mechanisms in humans and in animal models in which genetic changes associated with ASD are not directly related to serotonin function,[7-10] as well as with environmental exposures linked with ASD, such as in utero exposure to the anticonvulsant sodium valproate[11,12] and prenatal viral infections.[13] Thus, there is strong evidence that serotonin mechanisms may be influenced by disparate genetic and environmental risks for ASD.

1-PP	1-pyrimidylpiperazine	ADOS-RRB	ADOS Restricted and Repetitive Behavior
ABC	Aberrant Behavior Checklist	ADOS-SA	Autism Diagnostic Observation Schedule Social Affect
ADI-R	Autism Diagnostic Interview-Revised	AMT	$\alpha[^{11}C]$methyl-L-tryptophan
ADOS	Autism Diagnostic Observation Schedule	ASD	Autism spectrum disorder
ADOS-CTS	Autism Diagnostic Observation Schedule Composite Total Score	PET	Positron emission tomography
		RBS	Repetitive Behaviors Scale-Revised
		SUV	Standard uptake value

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The present study was designed on the basis of in vivo imaging data in children with ASD that demonstrated a deviation from the normal developmental time course of changes in serotonin synthesis measured by the tryptophan analog α[^{11}C]methyl-L-tryptophan (AMT) on positron emission tomography (PET) imaging.[14,15] Because serotonin function is important in postnatal brain development,[16] we hypothesized that one approach to the treatment of core features of ASD pharmacologically would be the use of serotonin agonists in children younger than 6 years of age, when their brain serotonin synthesis capacity is lower than in children without ASD. Agonists of the $5HT_{1A}$ receptor have been shown to improve social function in disparate animal models of ASD.[17-19]

In the present study, the $5HT_{1A}$ serotonin partial agonist buspirone was used to target core symptoms during the developmental period of low serotonin synthesis capacity in children with ASD as measured with PET. For this study, we chose the $5HT_{1A}$ serotonin partial agonist buspirone for a number of reasons. Several small studies of buspirone in older children with autism showed efficacy in some children, with low incidence of adverse events.[20-22] Furthermore, buspirone is approved by the Food and Drug Administration for the treatment of anxiety in children, and anxiety increasingly is recognized as a comorbid condition in ASD.[23] Previously, we had assessed the disposition of buspirone in 2- to 6-year-old children to establish dosing guidelines for this population.[24] Children with a diagnosis of autism received a single, oral dose of buspirone solution (2.5 mg or 5.0 mg). We found plasma concentrations and pharmacokinetic measurements for buspirone and the metabolite 1-pyrimidylpiperazine (1-PP) with 2.5-5.0 mg doses to be similar to values observed in older children receiving 7.5-15.0 mg doses. In the present study, before drug treatment, subjects underwent PET scanning and blood studies to evaluate whether the response to buspirone can be predicted by brain tryptophan metabolism or blood serotonin levels.

Methods

The study and was conducted at 6 academic medical centers: Wayne State University School of Medicine, Children's Hospital of Michigan; Case Western Reserve University, Rainbow Babies Hospital; University of Texas Southwestern; Cleveland Clinic Foundation; University of California Davis; and New York University School of Medicine. All study-site institutional review boards approved the study, and written informed consent was obtained for each participant from at least 1 parent or legal guardian. The National Institutes of Neurological Disorders and Stroke established a Data and Safety Monitoring Board to monitor the trial.

Participants (N = 166, 2 to <6 years) with ASD were included based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision,* the Autism Diagnostic Interview-Revised (ADI-R),[25] and the Autism Diagnostic Observation Schedule (ADOS)[26] via use of the revised algorithms[27] with the following cutoff scores for the ADOS: Module 1, no words cutoff = 14; Module 1, some words cutoff = 10; Module 2, younger cutoff = 8; Module 2, older cutoff = 8; Module 3, cutoff = 7. Exclusion criteria were the presence or history of neurologic disorders, including seizure disorders, phenylketonuria, tuberous sclerosis complex, Rett syndrome, Fragile X syndrome, Down syndrome, and traumatic brain injury, and other medical or behavioral problems that required medications that are centrally active. Additional exclusion criteria were renal or hepatic disease, treatment with drugs known to alter the activity of CYP3A4, use of centrally acting drugs during the 6 weeks before or during the study, and previous treatment for periods longer than 2 weeks with buspirone or selective serotonin reuptake inhibitors. Participants who used a stable dose of melatonin for sleep before entry into the study were allowed to continue use during the study.

Treatment

Buspirone hydrochloride U.S.P. (Fermion, Espoo, Finland) or placebo dissolved in Orasweet (2.5 mg/mL or 5.0 mg/mL; Paddock Laboratories Inc, Minneapolis, Minnesota) was administered once per day in the evening for the first week of treatment and thereafter twice a day, approximately 12 hours apart, for 23 weeks during the placebo-controlled phase. Patients who received buspirone during the first phase were continued on the same dose during the second phase. Patients receiving placebo were randomized to 2.5 mg or 5.0 mg buspirone for the 24-week second phase. Within each site, participants were randomized in blocks for age groups (2 to <4 years and 4 to <6 years) to treatment groups of 2.5 mg, 5 mg, or placebo. Drug compliance, as assessed by measuring the volume of unused drug, showed that for 61% of the subjects there was 100% compliance, 27% had compliance between 90% and 100%, 7% had compliance between 80% and 90%, and 4% had less than 80% compliance. All site personnel were blinded to treatment during both phases of treatment. A medical monitor at a different site not involved in the enrollment of participants evaluated the adverse events.

Efficacy Measures

Efficacy measures assessed at baseline, 24 weeks, and 48 weeks included scores derived from several measures, including the ADOS, Vineland Adaptive Behavior Scales-Second Edition,[28] Aberrant Behavior Checklist (ABC),[29,30] Repetitive Behaviors Scale-Revised (RBS),[31] Sensory Profile Scale,[32] Leiter Parent-Report,[33] and the Children's Yale Brown Obsessive Compulsive Scale, Modified for Pervasive Developmental Disorders.[34] Global cognitive functioning was measured at baseline by the use of either the Mullen Scales of Early Learning[35] or the Differential Abilities Scales-Second Edition.[36] Clinicians who completed research training were required to demonstrate 90% reliability with a consensus-coded protocol of an ADI-R recording and 80% reliability with a consensus coded protocol of a Module 1 or 2 and