Buspirone in the Management of Anxiety and Irritability in Children With Pervasive Developmental Disorders: Results of an Open-Label Study

Jan K. Buitelaar, M.D., Rutger Jan van der Gaag, M.D., and Joost van der Hoeven, M.D.

Background: We evaluated the efficacy and safety of buspirone in the management of anxiety and irritability in children with pervasive developmental disorders (PDD).

Method: Twenty-two subjects, 6 to 17 years old, with DSM-III-R diagnosed PDD-NOS (N = 20) or autistic disorder (N = 2), were included. They were treated with buspirone in dosages ranging from 15 to 45 mg/day in an open-label trial lasting 6 to 8 weeks. Responders continued buspirone treatment and were followed up for up to 12 months.

Results: Nine subjects had a marked therapeutic response and 7 subjects a moderate response on the Clinical Global Impressions (CGI) scale after 6 to 8 weeks of treatment. Side effects were minimal, except for 1 patient who developed abnormal involuntary movements.

Conclusion: These results suggest that buspirone may be useful for treating symptoms of anxiety and irritability in children with PDD.

(J Clin Psychiatry 1998;59:56–59)

Received March 4, 1997; accepted Aug. 20, 1997. *From the Rudolf Magnus Institute for Neurosciences and the Department of Child Psychiatry, Utrecht (all authors), the Veldwijk Research Institute, Ermelo (Dr. van der Gaag), and the Zonnehuizen Veldheim Stenia, Zeist, the Netherlands (Dr. van der Hoeven).*

Reprint requests to: Jan K. Buitelaar, M.D., Department of Child Psychiatry, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.

Medication can be an important component of a comprehensive treatment program for children with pervasive developmental disorders (PDD). Drugs are commonly prescribed for the symptomatic treatment of troublesome or disruptive targets such as hyperactivity, aggression, anxiety, excitement, and stereotyped or self-injurious behaviors.[1] A number of children with PDD are particularly characterized by increased anxiety and an impaired regulation of affective state.[2–4] The affective symptoms of these children may include intense generalized anxiety, unusual and primitive fears and phobias (e.g., fear of annihilation or fear of bodily disintegration), recurrent panic episodes and terror, and marked idiosyncratic anxiety reactions with inappropriate affect.[5] These children may also show chronic irritability with frequent temper tantrums or impulsive aggression.

It has been shown that neuroleptics, such as haloperidol and pimozide, improve hyperactivity, aggression, and stereotypies in children with autism[6–8] and PDD-NOS.[9,10] The risk for drug-related dyskinesias,[11] excessive sedation and cognitive side effects, and serious impact on motivation, however, limits the long-term use of the classic neuroleptics in this population. Moreover, neuroleptic drugs have not emerged as very effective in the treatment of anxieties and affective dysregulation in these children.

Buspirone is a serotonin (5-HT) receptor type 1A agonist that has antianxiety and possible antidepressant effects. It also has affinity for dopamine receptors. Buspirone and chemically related compounds appear to be of particular interest for the developmentally disabled populations because of their generally benign side effect profiles, including the absence of significant sedative properties and problematic interactions with other CNS agents. Buspirone in dosages from 15 to 45 mg/day was found to decrease anxiety, temper tantrums, aggression, and self-injury in developmentally disabled adults, including several subjects with autism.[12–14] One small case series reported that two of four autistic children aged 9 to 10 years showed a beneficial response to treatment with buspirone 5 mg t.i.d. for 4 weeks.[15]

The aim of this report is to add to the still limited database on buspirone in the pediatric population. Results are presented from a systematic evaluation of the efficacy and safety of buspirone in children with PDD. We examined treatment effects on two domains of symptoms (anxieties and irritability) using the Clinical Global Impressions scale (CGI)[16] (CGI-anxiety and CGI-irritability).

METHOD

Subjects

Twenty-two children between 6 and 17 years old with PDD-NOS (N = 20) or with autistic disorder (N = 2) were included in the study. The diagnosis was established on

the basis of the DSM-III-R criteria after extensive diagnostic evaluations, which included a review of prior records, a developmental history, interviews with the parents and child, and review of school and psychological testing information. Clinical features of the subjects, including comorbid disorders, are presented in Table 1. Fourteen subjects had a target symptom in the domain of anxieties, 1 subject had a target in the domain of irritability, and 7 subjects had targets in both domains of symptoms. At the time of the study, the subjects were inpatients of the Child Psychiatric Unit at the Utrecht University Hospital in Utrecht (N = 16), and of the Residential Treatment Center De Beele in Voorst (N = 3), or outpatients of the Clinic Zonnehuizen in Zeist (N = 3) in the Netherlands.

Procedure

Subjects were offered an open-label buspirone trial if they presented with a chronic pattern of manifest pervasive anxiety, irritability, and/or affective dysregulation that had failed to improve with behavioral treatment approaches and persisted at least 4 weeks after the start of the hospitalization or of the outpatient consultation. Informed consent was obtained from the parents and the children. A number of subjects had been previously treated with psychotropics, all of which had been found to be ineffective (see Table 1). Four children continued taking concomitant drugs (pimozide N = 2, haloperidol N = 1, and methylphenidate N = 1) that had yielded therapeutic gains short of complete remission. The starting dosage of buspirone was 5 mg t.i.d. in all cases, and dosages were adjusted depending on response and side effects. The maximum dosage of 45 mg/day could be reached within 3 weeks. Treatment response was based on reports by nurses on the ward, parents, teachers, and the attending psychiatrist and was coded on the CGI. The CGI includes subscales for global severity (CGI-S: 1 indicates not at all ill; 2, borderline mentally ill; 3, mildy ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, extremely ill) and global improvement (CGI-I: 1 indicates very much improved; 2, markedly improved; 3, moderately improved; 4, no change; 5, moderately worse; 6, markedly worse; 7, very much worse). Drug efficacy as reported below was evaluated within 6 to 8 weeks after the start of treatment with buspirone. Thereafter, subjects responding to buspirone were followed up regularly for several months to monitor for possible placebo effects, development of tolerance, and treatment-emergent side effects.

RESULTS

Twenty-two subjects were found eligible for the study, and all of them agreed to participate. Twenty-one subjects completed the study through the assessment of drug efficacy at 6 to 8 weeks. One subject dropped out of the study at the end of Week 4 because of absence of therapeutic effects. Buspirone was administered in a mean dosage of 29.3 mg/day (range, 15–45) during the 6 to 8 weeks of evaluation. Behavioral changes associated with buspirone became apparent after 2 or 3 weeks of treatment. The benefits included foremost a reduction of overwhelming anxiety and of irritability and temper outbursts. On the basis of the CGI-I, 9 subjects showed a marked drug response, and 7 subjects a moderate response. Six subjects failed to show any therapeutic effect. Sixteen of 21 subjects with anxiety targets showed a positive treatment response (9 subjects a marked and 7 a moderate response). Beneficial changes were noted in 5 of 8 subjects with irritability symptoms (2 subjects had marked response and 3 subjects had moderate response). On an individual level, improvements in the domains of anxiety and irritability appeared to be tightly coupled (Table 1). Responders (N = 16) continued treatment with buspirone and were followed up for a mean period of 5.4 months (range, 2–12). In all cases, therapeutic benefits were sustained.

One child developed abnormal involuntary movements of the mouth, cheeks, and tongue after having been treated with buspirone at a dosage of 20 mg/day for 10 months. No concurrent medication was prescribed. Neurologic examination including computed tomography scanning of the head revealed no focal abnormalities. Results of other evaluations, such as serum ceruloplasmin and a fresh peripheral blood smear for acanthocytes, were also normal. His family history did not point to any loading with movement disorders, particularly with Tourette's disorder. Because we concluded that he most likely had a buspirone-associated orofacial-lingual dyskinesia, we discontinued the administration of buspirone. Thereafter, the abnormal movements disappeared completely within 2 weeks. Other side effects in our subjects were minimal and included initial sedation (N = 2), slight agitation (N = 2), and initial nausea (N = 1).

DISCUSSION

In this study of 22 children and adolescents with PDD, a majority showed a beneficial response to an open trial with buspirone in dosages ranging from 15 to 45 mg/day. Therapeutic changes became visible within 2 or 3 weeks after the administration of buspirone and included a reduction both of overwhelming anxieties and of irritability and temper outbursts. The lack of a controlled design means that we cannot definitely exclude the possibility that the therapeutic responses were due to a nonspecific placebo response. This seems, however, less likely since therapeutic benefits were sustained in all cases during a follow-up of 2 to 12 months.

It has been suggested by Van Praag and colleagues[17] that signs of decreased central 5-HT metabolism are associated

Table 1. Buspirone in the Management of Anxiety and Irritability in Children and Adolescents With Pervasive Developmental Disorders*

Patient	Primary Diagnosis	Associated Diagnoses	Targets	Dosage (mg/d)[a]	Concomitant Drugs	CGI-Anxiety			CGI-Irritability			Complications
						Wk 0	CGI-S[b]	CGI-I[b]	Wk 0	CGI-S[b]	CGI-I[b]	
Boy, 12 y	PDD-NOS	ADHD, tic disorder NOS	Anxiety, temper tantrums	30 mg (10 mg tid) for 6 mo	None	6	5	2	6	5	3	Initial sedation
Boy, 8 y	PDD-NOS	CMT	Separation anxiety, temper tantrums	15 mg (5 mg tid) for 3 mo	None[c]	5	4	2	5	3	2	None
Boy, 9 y	PDD-NOS	Conduct disorder	Anxiety, aggressive outbursts	20 mg (5-5-10 mg qd) for 4 mo	Pimozide 2 mg/d	7	6	3	6	5	2	Initial sedation
Boy, 8 y	PDD-NOS	ADHD (mild)	Nightmares, sleeping problems	20 mg (10 mg bid) for 12 mo	None[d]	6	4	2	3	3	4	Abnormal movements after 10 mo
Boy, 8 y	Autistic disorder	None	Anxious preoccupations, thinking disorder	15 mg (5 mg tid) for 5 mo	Pimozide 1 mg/d	5	4	3	2	2	4	Slight initial agitation
Girl, 14 y	PDD-NOS	None	Primitive anxieties	30 mg (10 mg tid) for 4 mo	None	6	5	3	3	2	4	None
Boy, 9 y	PDD-NOS	GAD	General anxious tension, social withdrawal	45 mg (15 mg tid) for 8 wk	None	5	5	4	1	1	4	None
Boy, 14 y	PDD-NOS	None	Temper tantrum, self-injury	45 mg (15 mg tid) for 6 wk	None[c,d]	3	3	4	5	5	4	Slight agitation
Boy, 11 y	PDD-NOS	ADHD, enuresis	Primitive anxieties, disordered thinking	30 mg (10 mg tid) for 4 mo	None	5	4	3	2	2	4	None
Boy, 10 y	PDD-NOS	ADHD	Chaotic, primitive anxieties, sleeping problems	30 mg (10 mg tid) for 3 mo	None	5	3	2	3	2	3	None
Boy, 8 y	Autistic disorder	OCD	Anxious preoccupations, rituals	30 mg (10 mg tid) for 6 mo	None[c,d]	5	4	3	2	2	4	None
Girl, 11 y	PDD-NOS	ODD, eating disorder NOS	Anxious, negativistic	30 mg (10 mg tid) for 3 mo	None	5	3	2	3	2	3	None
Boy, 10 y	PDD-NOS	None	Panic attacks, bizarre preoccupations, primitive anxieties	25 mg (5-10-10 mg qd) for 6 mo	None[c,d]	6	4	2	3	3	4	None
Boy, 7 y	PDD-NOS	Dysthymia	Panic attacks, associative thinking	20 mg (10 mg bid) for 4 mo	None[c]	5	4	2	2	2	4	None
Boy, 9 y	PDD-NOS	GTS (mild)	Primitive anxieties, excitement, aggressive outbursts	30 mg (10 mg tid) for 8 wk	None	6	6	4	6	5	4	None
Boy, 14 y	PDD-NOS	Conduct disorder	Severe aggressive outbursts, anxiety	45 mg (15 mg tid) for 5 mo	Haloperidol 2 mg/d	5	4	3	6	5	3	Nausea
Boy, 16 y	PDD-NOS	GAD	Social phobia, social withdrawal	30 mg (10 mg tid) for 2 mo	None	5	5	3	3	3	4	None
Boy, 12 y	PDD-NOS	ADHD, GTS (mild)	Anxious preoccupations, fears, worrying	30 mg (10 mg tid) for 12 mo	Methylphenidate 10 mg bid	5	3	2	3	2	3	None
Boy, 14 y	PDD-NOS	None	Social withdrawal, aloofness	45 mg (15 mg tid) for 6 wk	None	5	5	4	3	3	4	None
Boy, 6 y	PDD-NOS	None	Anxious, impulsive, and unpredictable violent behavior	15 mg (5 mg tid) for 8 mo	None	6	4	2	6	4	2	None
Boy, 8 y	PDD-NOS	ADHD	Primitive anxieties, distractable	30 mg (10 mg tid) for 7 wk	None	5	5	4	3	2	4	None
Boy, 9 y	PDD-NOS	None	Anxious, impulsivity, aggression	35 mg (10 mg tid and 5 mg) for 4 wk	None	5	5[e]	4[e]	5	5[e]	4[e]	None

*Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI = Clinical Global Impressions scale, CGI-I = CGI-Improvement, CGI-S = CGI-Severity, CMT = chronic motor tic disorder, GAD = generalized anxiety disorder, GTS = Gilles de la Tourette's Syndrome, OCD = obsessive-compulsive disorder, ODD = oppositional defiant disorder.
[a]Maximum dosage for each patient.
[b]Measures taken after 6–8 weeks of buspirone treatment.
[c]Unsuccessful previous treatment with neuroleptic.
[d]Unsuccessful previous treatment with clonidine.
[e]Patient dropped out after week 4 of treatment. Scores are last observation carried forward.

with particular affective disturbances (i.e., augmented anxiety, increased aggression, and mood instability) across a variety of neuropsychiatric disorders. For example, trait anxiety, irritability, and impulsive violence appeared to cluster together in groups of nonpsychotic patients.[18] Further, levels of 5-HIAA in the cerebrospinal fluid of children with disruptive behavior disorders[19] and of adults with aggressive behavior[17,20] were significantly decreased compared with those of controls. The neuroendocrine responses to pharmacologic probes of the 5-HT system were observed to be blunted in subjects with autism compared with normal subjects,[21] suggesting that the activity of central 5-HT systems is reduced in subjects with PDD. Our data indicate that an enhancement of serotonergic function by means of a partial agonist at the 5-HT_{1A} receptor may be of clinical importance in a subgroup of children with PDD-NOS in the management of anxieties and irritability.

Generally, the side effects of buspirone were minimal, except for 1 responder who unfortunately developed an orofacial-lingual dyskinesia, which necessitated discontinuation of the drug. On drug cessation, the dyskinesia proved to be fully reversible. There are infrequent reports on persisting movement disorders induced by buspirone in adults.[22] This effect seems related to the affinity of buspirone for the dopaminergic system. Buspirone exerts partial agonist and antagonist effects with respect to striatal dopamine neurotransmission. For example, dopamine production is enhanced in rat striatum after buspirone administration, whereas apomorphine-induced stereotypy is inhibited.[23] Buspirone differs, however, from the classic dopamine-blocking agents such as the neuroleptics in that it does not alter the number of striatal dopamine receptors.[24]

In summary, the current study suggests that buspirone may have utility in the treatment of anxiety and irritability in children with PDD and that these apparent therapeutic effects of buspirone deserve further controlled studies.

Drug names: buspirone (BuSpar), clonidine (Catapres), haloperidol (Haldol and others), methylphenidate (Ritalin), pimozide (Orap).

REFERENCES

1. Buitelaar JK. Psychopharmacological approaches to childhood psychotic disorders. In: Den Boer JA, Westenberg HGM, Van Praag HM, eds. Advances in the Neurobiology of Schizophrenia. New York, NY: John Wiley & Sons; 1995:429–457
2. Cohen DJ, Paul R, Volkmar FR. Issues in the classification of pervasive and other developmental disorders: toward DSM-IV. J Am Acad Child Psychiatry 1986;25:213–220
3. Towbin KE, Dykens EM, Pearson GS, et al. Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 1993;32:775–782
4. van der Gaag RJ. Multiplex Developmental Disorder: An Exploration of Borderlines on the Autistic Spectrum. Utrecht, the Netherlands: University of Utrecht; 1993. Thesis
5. van der Gaag RJ, Buitelaar JK, Van den Ban E, et al. A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 1995;34:1096–1106
6. Campbell M, Anderson LT, Meier M, et al. A comparison of haloperidol and behavior therapy and their interaction in autistic children. J Am Acad Child Psychiatry 1978;17:640–655
7. Anderson LT, Campbell M, Graga DM, et al. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984;141:1195–1202
8. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989;19:227–239
9. Fisher W, Kerbeshian J, Burd L. A treatable language disorder: pharmacological treatment of pervasive developmental disorder. J Dev Behav Pediatr 1986;7:73–76
10. Joshi PT, Capozzoli JA, Coyle JT. Low-dose neuroleptic therapy for children with childhood-onset pervasive developmental disorder. Am J Psychiatry 1988;145:335–338
11. Campbell M, Adams P, Perry R, et al. Tardive and withdrawal dyskinesia in autistic children: a prospective study. Psychopharmacol Bull 1988;24: 251–255
12. Gedye A. Buspirone alone or with serotonergic diet reduced aggression in developmentally disabled adults. Biol Psychiatry 1991;30:88–91
13. Ratey JJ, Sovner R, Mikkelsen E, et al. Buspirone therapy for maladaptive behavior and anxiety in developmentally disabled persons. J Clin Psychiatry 1989;50:382–384
14. Ratey J, Sovner R, Parks A, et al. Buspirone treatment of aggression and anxiety in mentally retarded patients: a multiple-baseline, placebo lead-in study. J Clin Psychiatry 1991;52:159–162
15. Realmuto GM, August GJ, Garfinkel BD. Clinical effect of buspirone in autistic children. J Clin Psychopharmacol 1989;9:122–125
16. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Van Praag HM, Asnis GM, Kahn RS, et al. Monoamines and abnormal behaviour: a multi-aminergic perspective. Br J Psychiatry 1990;157: 723–734
18. Apter A, Van Praag HM, Plutchnik R. Interrelationships among anxiety, aggression, impulsivity and mood: a serotonergically linked cluster? Psychiatry Res 1990;32:191–199
19. Kruesi MJP, Rapoport JL, Hamburger S, et al. CSF monoamine metabolites, aggression and impulsivity in disruptive behavior disorders of children and adolescents. Arch Gen Psychiatry 1990;47:419–426
20. Van Praag HM. Serotonergic dysfunction and aggression control [editorial]. Psychol Med 1991;21:15–19
21. McBride PA, Anderson GM, Hertzig ME, et al. Serotonergic responsivity in male young adults with autistic disorder. Arch Gen Psychiatry 1989;46: 213–221
22. LeWitt PA, Walters A, Hening W, et al. Persistent movement disorders induced by buspirone. Mov Disord 1993;8:331–334
23. Wood PL, Nair NP, Lal S, et al. Buspirone: a potential atypical neuroleptic. Life Sci 1983;33:269–273
24. Cimino M, Ponzio F, Achilli G, et al. Dopaminergic effects of buspirone, a novel anxiolytic agent. Biochem Pharmacol 1983;32:1069–1074