Risperidone in the Treatment of Autistic Thai Children Under 4 Years of Age

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Abstract

The authors report five cases of very young children with autistic disorder, aged 2.1-3.7 years, treated with risperidone, as part of the comprehensive intervention. Treatment with risperidone 0.25-0.5 mg per day was associated with clinically meaningful decreases in problem behaviors including hyperactivity, irritability, and aggressiveness. There were also improvements in social relatedness and cooperation with developmental treatment. All of the children tolerated the medication well and experienced no untoward effects. The efficacy of risperidone in the treatment of very young children with autistic disorder reported here is consistent with findings in the limited number of cases previously reported in the literature. Controlled studies are needed to confirm the efficacy and safety of risperidone in the treatment of these children.

Key word : Risperidone, Autistic, Pervasive Developmental Disorders

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Autistic disorder and other pervasive developmental disorders (PDDs) are chronic and disabling disorders characterized by impairments in social interaction and communicative competence, and restricted patterns of interest. Treatment for these disorders consists mainly of early developmental stimulation and behavioral interventions to improve communication and socialization. Medication is not the primary treatment and no medication has been proven to be effective in treating social and relationship pro-

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blems in autism[1]. However, when there are persisting behavioral disturbances such as hyperactivity, irritability, or aggressiveness, which often worsen the child's communication and socialization, medication trials might be warranted. Several medications including corticosteroids, fenfluramine, naltrexone, secretin, and vitamin B_6 plus magnesium have been studied in this population. Although originally proposed as helpful, these medications were proven not effective in more recent and well-designed studies [1]. Recently, more attention has been paid to drugs targeting dopamine and serotonin for the treatment of disturbing symptoms associated with autistic disorder, as these two neurotransmitter systems have been shown to be dysfunctional in these individuals[2,3].

A potent dopamine D_2 antagonist, haloperidol, has been extensively studied, and shown to be effective in improving hyperactivity and aggressiveness in autistic children[4]. The use of haloperidol, however, is limited by the extrapyramidal side effects, such as acute dystonia and akathisia, and the risk of developing permanent neurological sequale, tardive dyskinesia[5]. Moreover, haloperidol is less effective in treating core symptoms of autism, namely impaired communication and socialization[6]. Risperidone, a new generation antipsychotic medication, which has antagonistic activities on dopamine D_2, serotonin 2A, and other serotonin receptors, has been shown to be effective in improving negative symptoms such as social withdrawal in schizophrenic patients[7]. It is thought that some core symptoms of autism are similar to schizophrenic negative symptoms and risperidone might also be helpful in autistic patients[2,8]. Positive results of risperidone in the treatment of adults with autistic disorder and other PDDs were reported in a number of open-label studies[9,10] and one controlled study[11]. While there have not been reports of controlled studies in children, a number of open-label studies showed risperidone to be effective in improving problem behaviors and socialization in children and adolescents with autistic disorder and other PDDs[12-15]. In these studies, the age range of the subjects was 5-18 years old and the dose range of risperidone was 0.75-6 mg daily, with weight gain being the most common side effect.

In preschool children, there are only a few case reports and a limited number of open-label studies on the use of risperidone. Schwam et al (1998)[16] reported successful treatment of food refusal with risperidone in a 3-year-old autistic boy. Posey et al (1999)[17] reported the use of risperidone in the treatment of two young autistic children aged 23 and 29 months, who had persistent symptoms of aggression and irritability not responding to non-pharmacological interventions. In both cases, risperidone was shown to significantly reduce aggression and improve social relatedness. Masi et al (2001)[18] reported a 16-week open-label trial of risperidone in 10 preschool children with PDDs, aged 3.9 to 6.6 years. Risperidone was shown to be safe and moderately effective in these children. The same group of investigators reported a larger open-label study in 24 children with PDDs, aged 3.6-6.6 years[19]. In this study, two subjects dropped out due to side effects of sedation in one child, and tachycardia in the other. With the mean risperidone dosage of 0.49 mg/day, 8 of 22 were rated as much or very much improved on the Clinical Global Impression-Improvement (CGI-I) Scale and were considered responders. However, data regarding the efficacy of risperidone in very young children from this study is still limited, as the number of children younger than 4 years old was only 4 from the 22 children there were no children younger than 3 years old.

As early diagnosis and timely treatment are crucial prognostic factors for autistic children[20], early effective pharmacotherapy targeting symptoms that interfere with the child's development might improve the treatment outcomes. Therefore, more knowledge on the efficacy and safety of medications for these very young children is needed. Given the limited number of case reports and studies in very young children reported in the above-cited articles, the authors would like to report their experience with five autistic Thai children younger than 4 years old.

CASE REPORTS

The following are reports of five cases that received risperidone as part of the comprehensive treatment. All cases met the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)* [21] for autistic disorder.

Case 1

A 3.6-year-old boy was evaluated for delayed speech and abnormal social behavior at the

age of 3 years. He usually was not responsive when his parents called and not interested in playing with other children. His birth and early developmental history were unremarkable. At the age of 1.1 years, his parents first noticed that he was not making eye contact and seemed to pay little attention to people. His physical exam and hearing test were normal.

After six months of weekly developmental therapy along with social stimulation by the parents, the child gained only minimal improvement. Problem behaviors included hyperactivity, frequent temper tantrums and physical aggression towards his mother. The child was still not communicating, not responding when his name was being called, and not cooperative with developmental therapy.

A trial of risperidone was started at 0.25 mg, which was later increased to 0.5 mg at bedtime. After 6 weeks of trial, the child demonstrated an improvement in eye contact and social interaction with his parents. His temper tantrums and aggressive behavior lessened. Although he was still hyperactive, his attention span improved and he was more cooperative with developmental therapy. He continued to have this improvement till the most recent follow-up at the 22nd week visit. No side effects have occurred. His complete blood count and liver function test were normal.

Case 2

A 3.7-year-old boy, diagnosed with autistic disorder at the age of 3, presented with failure to develop meaningful words, lack of interest in playing with other children, and hyperactivity. He would use his own non-comprehensible language and pull his parents' hands when he wanted them to do things for him without making eye contact. After 3 months of weekly developmental and speech therapies, his eye contact improved but he continued to be hyperactive and aggressive toward his mother. A trial of methylphenidate at 5 mg twice daily resulted in a slight decrease in hyperactivity but no changes in aggressiveness. After he had been on methylphenidate for three months, the child continued to be distracted and was not cooperative with developmental treatment. Methylphenidate was then discontinued and risperidone at 0.5 mg at bedtime was started.

After six weeks on risperidone, the child's mood improved and he was more cooperative with developmental and speech therapies. His repetitive behavior decreased and he started to imitate words taught by the speech therapist. The child tolerated the trial well and has not experienced any side effects. His electrocardiogram (ECG) and liver function test at the 6-week follow-up were normal.

Case 3

A 2.10-year-old boy was evaluated and diagnosed with autistic disorder on the basis of delayed speech, impaired social development, and restricted interest. He had an uneventful prenatal and birth history. At the age of 11 months he started to say "ma" and used this word for a month before it disappeared. He was then not using meaningful words but was able to sing the last part of the Thai National Anthem which he heard from the television. He did not make eye contact and did not respond when his parents called him. He was preoccupied with the examiner's necktie, while paying minimal attention to people during the play interview. He was markedly hyperactive, not responsive to redirection, and not cooperative with developmental therapy.

Risperidone was started at 0.25 mg at bedtime and was later increased to 0.25 mg twice daily. Two weeks after the start, he demonstrated significant improvements in his hyperactivity and responsiveness. These improvements have been maintained until the most current follow-up visit at 16 weeks. He was making more sustained eye contact, less hyperactive, and responding more to developmental interventions. The child has not experienced side effects. His ECG and liver function test were normal.

Case 4

A 2.9 year-old boy, who has been receiving weekly speech therapy for 9 months for delayed receptive and expressive language, continued to have significant impairment in communication and socialization. He was born by caesarian section due to twin pregnancy and weighed 2,490 g at birth. He had an uneventful neonatal period and normal developmental milestones during the first year. He was the first twin and his female second twin has been developing normally. At the age of 2 years, there was little response to his parents and he was not able to wave bye-bye despite being taught repeatedly by his parents. At the age of 2.3 years, he was seen by a child psychiatrist who diagnosed him with autistic disorder and recommended continued speech therapy

and stimulation by the parents. At the age of 2.9 years, the child showed minimal improvement in communication. He occasionally used single words such as "want" when he wanted something, and continued to pull adults' hands as a way of communication. His eye contact was still poor and he continued to have repetitive behavior such as playing and watching his own hands in a mirror.

Risperidone was started at 0.25 mg at bedtime. Six weeks after the start, the child demonstrated an improvement in communication and socialization. His parents reported that he was more responsive and was playing more with his twin sister. His eye contact improved and repetitive behaviors decreased. In speech therapy sessions, he was more cooperative, better able to follow directions and imitated more words. The child has not experienced side effects. His liver function test and ECG at the 8-week follow-up were normal.

Case 5

A 2.1 year-old boy was diagnosed with autistic disorder at age 1.9 years, at which time he was seen for not making eye contact and not having language. He was described as not being attached to his parents, nanny, or grandmother who was helping with his care. He was not responsive when his name was called and would pull his parents' hands as a way of communication without making eye contact. He has been having weekly developmental, occupational, and speech therapies after the diagnosis was made.

After 4 months of intensive developmental intervention, the child demonstrated some improvement in his communication, being able to imitate words and responding when his name was called. However, he continued to avoid eye contact and would close his eyes or look away when attempts to make eye contact were made by adults. He was also irritable and not cooperative with the developmental interventions. Risperidone 0.25 mg was started at bedtime. Improvements in eye contact and mood were noted at the 4 week follow-up visit. These improvements were maintained for another 6 weeks, at which point his parents discontinued the medication due to the child's refusal. This resulted in a decrease in eye contact and an increase in irritability, which improved again after risperidone was resumed at the same dosage 2 weeks later. No side effects have been reported. The child's liver function test and ECG results were normal.

DISSCUSION

This is a report of successful short-term treatment with risperidone as part of the comprehensive intervention in 5 very young children with autistic disorder. Treatment with risperidone was associated with clinically meaningful improvement in problem behaviors and socialization in all of the five children. After treatment with risperidone, there were decreases in irritability, hyperactive and aggressive behaviors in case 1, 2 and 3, and in repetitive behaviors in case 4. Improvements in eye contact and responsiveness were seen in all cases. In case 4 and 5, despite not having much disturbing hyperactivity or irritability, risperidone was used on a basis of the lack of satisfying improvement after a period of nonpharmacological intervention, and was found to be effective in improving the child's socialization. The positive response to risperidone found in this report is similar to results reported by other authors[17-19].

All of the five cases tolerated the relatively low dosage (0.25-0.5 mg) of risperidone used in this report well. Side effects of risperidone reported in the literature, which include sedation, weight gain, extrapyramidal symptoms, galactorhea, hepatotoxicity and cardiovascular effects[2], were not found in these children. As recommended by several authors [2,14,19], the authors attempted to monitor liver function test and ECG in the cases. The results of liver function test obtained in all and the ECG findings obtained in 4 cases were normal. The tolerability of risperidone in this report is similar to findings from other studies[17-19]. However, longer-term studies are needed to assess the safety of risperidone in these children.

Autistic disorder is a severe and disabling illness, in which early intervention is critical and might influence the outcome[20]. It has generally been accepted that important interventions for these children include developmental, educational, occupational and speech therapies, while medication is not a primary intervention. However, when there are severe or persisting behavioral problems that are not responsive to or interfering with nonpharmacological interventions, medication treatment might be indicated. Effective medication treatment at an early age might enable the child to benefit better from nonpharmacological interventions.

As there is a limited number of young children with autistic disorder or other PDDs treated with risperidone reported in the literature, the authors

report more cases of very young autistic children who benefited from short-term treatment with this medication. All five children demonstrated improvements in problem behaviors and socialization and tolerated the trial well. Controlled studies with larger samples are needed before a conclusion about the efficacy and safety of risperidone in the treatment of young children with autistic disorder can be drawn.

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REFERENCES

1. Tanguay P. Pervasive developmental disorders: A 10-year review. J Am Acad Child Adolesc Psychiatry 2000; 39: 1079-95.
2. McDougle CJ, Lawrence S, McCracken JT, et al. Research Units on Pediatric Psychopharmacology (RUPP)-Autism Network: Background and rationale for an initial controlled study of risperidone. Child Adolesc Psychiatr Clin N Am 2000; 9: 201-24.
3. Cook E. Review of neurochemical investigation. Synapse 1990; 6: 293-308.
4. Anderson L, Campbell M. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989; 19: 227-39.
5. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: A prospective, longitudinal study. J Am Acad Child Adolesc Psychiatry 1997; 36: 835-43.
6. Locascio J, Malone R, Small A, et al. Factors related to haloperidol response and dyskinesias in autistic children. Psychopharmacol Bull 1991; 27: 119-26.
7. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo- controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13: 25-40.
8. Fisman S, Steele M. Use of risperidone in pervasive developmental disorders: A case series. J Child Adolesc Psychopharmacol 1996; 6: 177-90.
9. McDougle CJ, Brodkin ES, Yeung PP, et al. Risperidone in adults with autism or pervasive developmental disorder. J Child Adolesc Psychopharmacol 1995; 5: 273-82.
10. Purdon SE, Lit W, Labelle A, et al. Risperidone in the treatment of pervasive developmental disorder. Can J Psychiatry 1994; 39: 400-5.
11. McDougle CJ, Holmes JP, Carlson DC, et al. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998; 55: 633-41.
12. Findling RL, Maxwell K, Wiznicker M. An open clinical trial of risperidone monotherapy in young autistic children. Psychopharmacol Bull 1997; 33: 155-9.
13. McDougle CJ, Holmes JP, Bronson MR, et al. Risperidone treatment of children and adolescents with pervasive developmental disorder: A prospective, open-label study. J Am Acad Child Adolesc Psychiatry 1997; 36: 685-93.
14. Perry R, Pataki C, Munoz-Silva DM, Armenteros J, Silva RR. Risperidone in children and adolescents with pervasive developmental disorder: Pilot trial and follow-up. J Child Adolesc Psychopharmacol 1997; 7: 167-79.
15. Zuddas A, Di Martino A, Muglia P Cianchetti C. Long-term risperidone for pervasive developmental disorder: efficacy, tolerability and discontinuation. J Child Adolesc Psychopharmacol 2000; 10: 79-90.
16. Schwam JS, Klass E, Alonso C, Perry R. Risperidone and refusal to eat. J Am Acad Child Adolesc Psychiatry 1998; 37: 572-3.
17. Posey DJ, Walsh KH, Wilson GA, McDougle CJ. Risperidone in the treatment of two very young children with autism. J Child Adolesc Psychopharmacol 1999; 9: 273-6.
18. Masi G, Cosenza A, Mucci, M, De Vito G. Risperidone monotherapy in preschool children with young children autistic disorder. J Child Neurol 2001; 16: 395-400.
19. Masi G, Cosenza A, Mucci M, Brovedani P. Open trial of risperidone in 24 young children with pervasive developmental disorder. J Am Acad Child Adolesc Psychiatry 2001; 40: 1206-14.
20. Volkmar FR, Klin A, Marans W, Cohen DJ. The pervasive developmental disorders: diagnosis and assessment. Child Adolesc Psychiatr Clin N Am 1996; 5: 963-78.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Press, 1994.

การใช้ริสเพริโดนในการรักษาเด็กออทิสติกที่มีอายุน้อยกว่า 4 ปี

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ได้รายงานการใช้ริสเพริโดนในการร่วมรักษาผู้ป่วยเด็กเล็กที่มีภาวะออทิสติกจำนวน 5 ราย อายุตั้งแต่ 2.1 ถึง 3.7 ปี พบว่าการใช้ริสเพริโดนในขนาด 0.25–0.5 มิลลิกรัมต่อวันสามารถลดพฤติกรรมอยู่ไม่นิ่ง หงุดหงิด ก้าวร้าวและช่วยให้ปฏิสัมพันธ์ทางสังคมของผู้ป่วยดีขึ้นได้ ผู้ป่วยทุกรายทนการให้ยาได้ดีและไม่เกิดผลข้างเคียง รายงานนี้เป็นการแสดงถึงการรักษาด้วยริสเพริโดนที่ได้ผลในผู้ป่วยออทิสติกที่มีอายุน้อย และมีปัญหาพฤติกรรมที่ไม่ตอบสนองต่อการช่วยเหลือด้วยการกระตุ้นพัฒนาการและการปรับพฤติกรรม อย่างไรก็ตาม ยังมีความจำเป็นที่จะต้องมีการศึกษาเพิ่มเติมด้วยวิธีเปรียบเทียบกับกลุ่มควบคุมเพื่อประเมินประสิทธิภาพและความปลอดภัยของ risperidone ในผู้ป่วยเด็กเหล่านี้

คำสำคัญ : ริสเพริโดน, ออทิสติก

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