

Risperidone Monotherapy in Children and Adolescents with Autism Spectrum Disorders : A Naturalistic Study

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Objectives : We retrospectively investigated the efficacy and tolerability of risperidone monotherapy in subjects with autism spectrum disorder (ASD). In addition, we did mixed effect model analysis of the effects of risperidone in patients with ASDs naturalistically treated in a routine clinical setting to determine whether the clinical effects were maintained and the side effects were tolerable.

Methods : This retrospective study assessed children and adolescents with ASD, who were on risperidone monotherapy from July 2010 to July 2011 at the Child and Adolescent ASD Clinic at Seoul National Hospital. Outcome measures included the Clinical Global Impression-Severity of Illness (CGI-S) and the CGI-Improvement (CGI-I) scales along with other clinical indices: dosage, target symptoms, and side effects.

Results : The mean dose of risperidone in 47 children and adolescents with ASD (40 males, 7 females; age range 5–19 years) who were on risperidone monotherapy was 1.6 ± 0.8 mg/day, and the mean duration of the treatment period was 20.2 ± 17.3 months. Aggressive behavior, stereotypic behavior, irritability, and self-injurious behavior were the most frequent target symptoms of risperidone. The most common side effects were weight gain followed by somnolence and extrapyramidal symptoms. In a mixed effects model analysis of CGI-I scores, the mean CGI-I score at the 1 month follow-up was significantly different from the mean CGI-I score of the 3-month follow-up ($p=.046$), and the CGI-I scores were equally maintained over 3 to 48 months [$F(6, 28.9)=4.393, p=.003$]. Of the 47 patients, 33 patients (70.2%) were identified as the response group, showing an end point CGI-I rating of 3 or under and having continued risperidone treatment for at least 6 months. The baseline CGI-S score showed significant association with clinical response to risperidone ($p=.005$), the mean baseline CGI-S was higher in the response group compared to the non-response group.

Conclusion : In this study, clinical improvement of risperidone stabilized around 3 months and was equally maintained up to 48 months with tolerable side effects, supporting maintenance of risperidone treatment in children and adolescents with ASDs.

KEY WORDS : Adolescents · Autism Spectrum Disorder · Children · Clinical Global Impression · Maintenance · Risperidone.

Introduction

Autism spectrum disorders (ASDs) are characterized by impaired development of social interactions, communication difficulties, repetitive patterns of movements and behaviors

that include restricted interests and activities.¹⁾ Recent estimates of the prevalence of ASDs are in the range of 6.5–6.6 per 1000 individuals, with a male to female ratio of 4:1.^{2,3)} The primary treatments for ASDs, including educational interventions, behavioral strategies, and social skills instruction, are used to relieve the core features of ASDs. Despite positive results, several limitations and feasibility issues remain when considering the cost, amount of time required, and practitioner availability required for behavior interventions. Although pharmacotherapy has not been proven to correct the core deficits, it has been used in patients with ASDs.⁴⁾ Behavioral problems, such as aggression, impulsivity, self-injurious behavior, irritability and hyperactivity, are common

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in individuals with ASDs and are associated with caregiver stress.

The appropriate use of medications in patients with ASDs can improve some maladaptive behaviors and increase patients' abilities to benefit from psychosocial interventions.⁴ The pharmacological approach is primarily aimed at reducing problematic behaviors, such as aggression, self-injurious behavior, stereotypic behavior, and tantrums.⁵ Low dose antipsychotics have been shown to reduce repetitive behaviors and social withdrawal as well as a number of related symptoms, such as hyperactivity, aggression, self-injurious behavior, labile mood and irritability.⁶ In October 2006, the Food and Drug Administration approved risperidone for the treatment of maladaptive behaviors in autistic children and adolescents.⁶ Risperidone is the most extensively studied antipsychotic for use in children with ASDs. Most studies were conducted on children and adolescents with maladaptive behaviors.⁷

In many studies, the efficacy and safety of risperidone treatment has been evaluated. These previous studies showed that risperidone was superior to a placebo in controlling behavioral disturbances in more than half of the participants.^{8,9} Risperidone has also been associated with adjuvant agents with the aim of treating maladaptive behaviors in autism.¹⁰ Pharmacotherapy with a low dose of risperidone in addition to parental training resulted in a greater reduction in maladaptive behaviors.¹¹ Although there is increased use of antipsychotics in child and adolescent group, the randomized controlled trials on the long-term efficacy of antipsychotics on these populations are inherently difficult due to ethical, logistical, economical and epidemiological reasons. The efficacy of risperidone in ASDs has been reported in long-term studies,^{9,12,13} which divided outcomes into short-term (less than three months) and long term (over three months). But there were several limitations in these studies. The data collection period was a maximum of 8 months and the study group was comparatively small.

In this study, we retrospectively investigated the clinical improvement with risperidone in patients with ASDs naturally treated in a routine clinical setting using mixed-effect analysis to determine whether the clinical improvement were maintained and the side effects tolerable.

Methods

1. Subjects

This retrospective study assessed children and adolescents with ASD, who were on risperidone monotherapy from July 2010 to July 2011 in the Child and Adolescent ASD Clinic

at Seoul National Hospital. Patients with ages ranging from 5 to 19 years old were included, and total follow-up periods ranged from 1 month to 48 months. All participants were diagnosed with autistic disorder, pervasive developmental disorder not otherwise specified (PDD NOS), or Asperger's disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised.¹¹ Diagnoses were based on a clinical interview of the parent and the child by a child and adolescent psychiatrist. The diagnosis was confirmed by another psychiatrist through review of psychiatric records. The clinical variables including medication history, intelligence quotient (IQ), Social Maturity Scale (SMS) and Childhood Autism Rating Scale (CARS)¹⁴ scores, were obtained from medical records. The study protocol was approved by the Institutional Review Board at Seoul National Hospital (IRB No. 2011-7).

2. Measurements

Previously, it was shown that the Clinical Global Impression (CGI) scale has good psychometric properties for children and adolescents¹⁵ and it is one of the most economic tools in assessing clinical change in autism.¹⁶ Most clinical drug trials in children with autism have used clinician report of improvement based on the CGI scale.¹⁷ We also utilized CGI to evaluate global symptom severity and symptom improvement.

Changes in illness severity were measured using the Clinical Global Impression-Severity of Illness (CGI-S) scale (1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill). CGI-Improvement (CGI-I) scales were used to evaluate target symptom improvement at 1 month, 3 months, 6 months, 12 months, 24 months, 36 months, and 48 months of risperidone treatment (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6= much worse; and 7=very much worse). A psychiatrist (Jin-Park Park) conducted the rating of CGIs on all subjects.

The response group was defined by CGI-I scores and treatment duration based on outcome measures used in previous studies.¹⁸ The responders were defined by an end point CGI-I rating of 3 or under, and treatment continuation for at least 6 months.

3. Statistical analysis

Descriptive analyses were used as appropriate. Independent-sample t-tests and chi-square tests were used to compare demographic and clinical characteristics between response

and non-response groups. Fisher exact test was used for non-parametric data. A mixed-effects model of repeated measurement was used to compare changes of mean CGI-I scores according to follow-up intervals. We considered $p < .05$ to be statistically significant. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Clinical characteristics of participants

Forty seven patients (40 male; 13.6 ± 3.5 years) were included in the analysis; the patients ranged in age from 5 to 19 years old. The dosage of risperidone ranged from 1–4 mg/day (1.6 ± 0.8 mg/day). The mean duration of the risperidone treatment period was 20.2 ± 17.3 months. Forty three (91.5%) patients had IQ of below 70, and the mean IQ of the subjects was 37.7 ± 11.7 . The mean SMS was 34.3 ± 19.7 , and the mean CARS was 33.9 ± 7.0 . Twenty four patients (51.1%) were diagnosed with autistic disorder, 23 patients (48.9%) were diagnosed with PDD NOS. Aggressive behavior, irritability, impulsivity, and stereotypic behavior were most frequent target symptoms of risperidone. The most common adverse effect of risperidone was weight gain (10.6%) followed by somnolence (6.4%) (Table 1).

2. Clinical improvement of risperidone

In assessing the clinical efficacy of risperidone in 47 children and adolescents with ASD, the mean CGI-I score at the 1-month follow-up was significantly different from the 3-month follow-up ($p = .046$), 6-month follow-up ($p = .001$), 12-month follow-up ($p = .015$), 24-month follow-up ($p < .001$), 36-month follow-up ($p < .001$), and the 48-month follow-up ($p = .003$) scores. The mean CGI-I score at the 3-month follow-up was significantly different from the 36-month follow-up ($p < .039$) score (Fig. 1).

Of the 47 subjects, 33 children (70.2%) were identified as the responders to risperidone, showing an end point CGI-I rating of 3 or under, and having continued treatment for at least 6 months. When we explored the moderators of risperidone response, we found that subjects in the response and non-response groups had comparable demographics and clinical characteristics, e.g., sex, the age at start of medication, target symptom, level of mental retardation, mean CARS score, mean SMS score and dosage of risperidone (Table 2). However, the baseline CGI-S score was significantly associated with clinical response to risperidone ($p = .005$). There was no significant difference between the percentage of patients reporting side effects in both response and non-re-

Table 1. Clinical characteristics of children and adolescents treated with risperidone

	Participants (N=47)
Sex, N (%)	
Male	40 (85.1)
Female	7 (14.9)
Age, years, mean (SD), range	13.6 (3.5), 5–19
Diagnosis, N (%)	
Autism	24 (51.1)
PDD NOS	23 (48.9)
Mental retardation	43 (91.5)
Comorbidity, N (%)	
ADHD	4 (8.5)
Tic disorder	3 (6.4)
Epilepsy	1 (2.1)
Baseline CGI-S score, mean (SD)	5.2 (0.7)
Age at start of any medication, years, mean (SD), range	7.1 (4.9), 1–18
Dosage of risperidone, mg/day, mean (SD), range	1.6 (0.8), 1–4
Duration of risperidone, months, mean (SD), range	20.2 (17.3), 1–48
1–3 months, N (%)	4 (8.5)
3–6 months, N (%)	7 (14.9)
6–12 months, N (%)	4 (8.5)
12–24 months, N (%)	13 (26.7)
24–36 months, N (%)	4 (8.5)
36–48 months, N (%)	15 (31.9)
Adverse effect of risperidone, N (%)	
Weight gain	5 (10.6)
Somnolence	3 (6.4)
Extrapyramidal symptoms	3 (6.4)
Galactorrhea	1 (2.1)
Amenorrhea	1 (14.3)*

* : amenorrhea was observed in one subject out of seven female subjects resulting in 14.3%. CGI-S : Clinical Global Impression-Severity, PDD NOS : pervasive developmental disorder not otherwise specified, SD : standard deviation, ADHD : attention-deficit hyperactivity disorder

sponse groups.

Discussion

In this study, we observed the clinical improvement of risperidone monotherapy in 47 children and adolescents with ASD (40 males, 7 females; age range 5–19 years). We found that the mean CGI-I score at 3 months was significantly different compared to the 1 month follow up, and the CGI-I score was equally maintained over 3 to 48 months, supporting the long-term use of risperidone beyond 6 months. Moreover, the mean duration of the treatment period for total subjects was 20 months and for response group was 27 months. Our

findings suggest that the continued use of risperidone brings about significant improvement in the disruptive behavioral symptoms of ASDs and that the clinical improvement after risperidone stabilizes around 3 months and is maintained till 48 months supporting the long-term use of risperidone be-

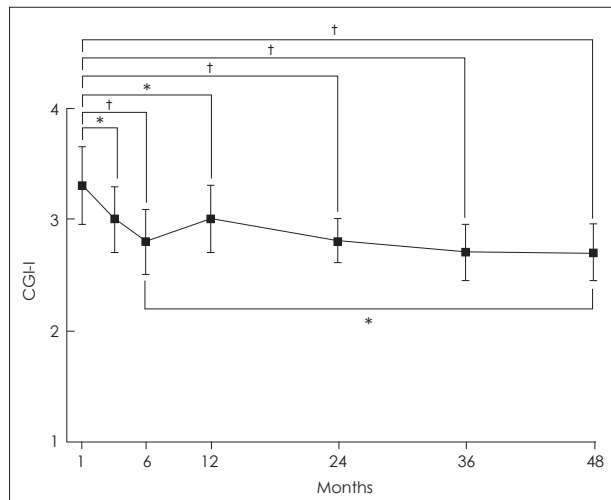


Fig. 1. The clinical improvement of the patients on risperidone stabilizes at 3 months follow-up and is maintained up to 48 month follow-up. The mean CGI-I score at the 1 month follow-up was significantly different from the mean CGI-I scores of the 3 month follow-up ($p=.046$), 6 month follow-up ($p=.001$), 12 month follow-up ($p=.015$), 24 month follow-up ($p<.001$), 36 month follow-up ($p<.001$), and the 48 month follow-up [$F(6, 28.9)=4.393, p=.003$]. The mean CGI-I score at the 3 month follow-up was significantly different from those of the 36 month follow-up ($p=.039$). * : $p<.05$, † : $p<.005$. CGI-I : Global Impression-Severity-Improvement

yond 6 months. In a similar note, a previous multisite study of risperidone in children aged 5 to 17 years, the discontinuation after 6 months was associated with a rapid return of disruptive behavior in most subjects.¹³

Our exploration of moderators of risperidone response in children with ASDs showed that the baseline CGI-S score was significantly associated with clinical response to risperidone ($p=.005$) and that the mean baseline CGI-S being higher in the response group compared to the non-response group. These results are similar to previous findings, which showed that a high score in the initial Aberrant Behavior Checklist Irritability subscale was a significant moderator of response rate for risperidone.¹⁹

In this study, 33 out of 47 patients (70.2%) were identified as the response group, showing end point CGI-I rating of 3 or under and having continued risperidone treatment for at least 6 months. The 70.2% response rate of risperidone in this study, was similar to previous clinical trials of risperidone in children and adolescents with autism which reported 64–69% response rate to risperidone in ASDs.^{9,17} A multisite, double-blind, placebo-controlled trials in children and adolescents with autism revealed a 69% response rate with a 57% decrease in irritability as measured by the Aberrant Behavior Checklist (ABC) irritability subscale.²⁰ In another randomized study of 79 children with PDD, risperidone-treated subjects exhibited a 64% improvement in irritability as measured by the ABC irritability subscale.⁹

Table 2. Clinical characteristics of the responders and non-responders according to CGI-I scores

	Response (N=33)	Non-response (N=14)	p*
Gender, N (%)			.658
Male	28 (84.8)	12 (85.7)	
Female	5 (15.2)	2 (14.3)	
Age, years, mean (SD)	13.2 (3.7)	14.7 (2.7)	.115
Target symptom, N (%)			.616
Aggression	12 (36.4)	4 (28.6)	
Irritability	9 (27.3)	2 (14.3)	
Impulsivity	6 (18.2)	4 (28.6)	
Stereotypies	6 (18.2)	4 (28.6)	
Level of mental retardation, N (%)			.658
Mild to moderate	3 (9.1)	1 (7.1)	
Severe to profound	30 (90.9)	13 (92.9)	
SMS, mean (SD)	34.0 (19.1)	35.1 (22.7)	.909
CARS, mean (SD)	33.2 (5.1)	35.8 (10.6)	.519
Baseline CGI-S, mean (SD)	5.0 (0.7)	5.6 (0.5)	.005
Dosage of risperidone, mg/day, mean (SD)	1.7 (0.9)	1.5 (0.6)	.316
Duration of risperidone, months, mean (SD)	27.1 (16.1)	3.9 (3.7)	<.001
Side effects, N (%)	9 (27.3)	4 (28.6)	.596

* : comparisons were performed using t-tests and the Fisher exact test. CARS : Childhood Autism Rating Scale, CGI-I : Clinical Global Impression-Improvement, CGI-S : Clinical Global Impression-Severity, SD : standard deviation, SMS : Social Maturity Scale

In this study, the mean dose of risperidone was 1.6 ± 0.8 mg/day. Dosages in the previous controlled studies of risperidone ranged from 0.5 to 3.5 mg/day, with the combination of risperidone and parent management training group requiring a lower mean dose compared with the risperidone monotherapy group (1.98 mg/day versus 2.26 mg/day, respectively).²¹⁾ The mean dosage of risperidone in our study, 1.6 mg/day is consistent with previous results.

The most common side effects were weight gain followed by somnolence and extrapyramidal symptoms in this study. But, there was no significant difference in the percentage of subjects reporting side effects in both the response and non-response groups of risperidone. As with previous findings, weight gain was the most commonly reported adverse effect in our study.¹³⁾ According to a naturalistic study of 23 subjects with pervasive developmental disorders, some improvement in the safety and tolerability issues, such as weight gain and somnolence, occurred after switching to aripiprazole.¹⁶⁾ Our finding is also consistent with the results from a 6-month prospective study examining 63 children and adolescents with ASD, which reported weight gain in excess of developmentally expected norms.²²⁾

There are several limitations in this study, including the fact that it is a naturalistic study without placebo control group. A retrospective chart review was conducted without systematic clinical data collection; thus, there was no randomization, and the duration of treatment was highly variable. Furthermore, more than 85% of patients were male, making the findings potentially less generalizable to females. When we assessed the tolerability of risperidone in this study, there was no information on heights and weights at the initiation of risperidone in some subjects. Thus, we could not evaluate the mean weight gain and body mass index score from this study.

Despite the limitations discussed above, a total of 47 patients in Korean population were included in the study, and the mean duration of risperidone monotherapy was long enough to assess the clinical improvement of risperidone for as long as 48 months. Future treatment studies in ASDs need to focus on the frequency and titration of prescribing risperidone and the discontinuation rate due to side effects. Studies are also needed to compare risperidone with other antipsychotics e.g., aripiprazole, which is one of the first agents for the treatment of severe irritability associated with ASD.

Conclusion

In this study, clinical improvement of risperidone stabi-

lized around 3 months and was equally maintained up to 48 months with tolerable side effects, supporting maintenance of risperidone treatment in children and adolescents with ASDs.

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