International Journal of Pharmacy and Pharmacology ISSN: 2326-7267 Vol. 9 (2), pp. 001-009, February, 2020.
Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Efficacy and safety of long-acting risperidone on early onset schizophrenia in adolescent patients

Liming Ruan, Shaohua Hu, Manli Huang, Jianpo Hu and Wei Cai*

The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China

Accepted 13 October, 2019

The present study is aimed at evaluating the efficacy and safety of long-acting risperidone on early onset schizophrenia in adolescent patients. A total of 31 adolescent patients (13 - 18 years) with schizophrenia met the DSM-IV-TR criteria for schizophrenia and their symptoms were stable when orally taking risperidone or olanzapine. They were admitted into a 24 week, open-label study on the long-acting risperidone. Risperidone was administered every 2 weeks at a dose of 25, 37.5 and up to a maximum dose of 50 mg. The Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) and the Extrapyramidal symptom rating scale (ESRS) were used to assess the improvement in the symptoms. Improvements in the symptoms of schizophrenia occurred in patients treated with long-acting risperidone at week 6 and continued throughout the study with significant reduction in total PANSS score at week 24 (-4.2 ± 0.2, P < 0.01). At the same time, 51.6% of patients were rated as clinical improvement at the end of study. Among these 31 cases, the most frequently reported adverse events were depression (12.9%), anxiety (9.7%), headache (9.7%) and insomnia (6.4%). ESRS scores were reduced during the treatment with long-acting risperidone. The mean decrease in serum prolactin and body weight was 13.1 ng/ml and 4.5 kg, respectively. Intramuscular administration of long-acting risperidone was safe and well tolerated in adolescent patients. Long-acting risperidone also could improve the symptoms of schizophrenia in adolescent patients.

Key words: Long-acting risperidone, early onset schizophrenia, oral risperidone, olanzapine, adolescents.

INTRODUCTION

Schizophrenia with onset during childhood or adolescence often refers to early onset schizophrenia (Werry et al., 1991), which presents more neuro-developmental problems and greater chronicity (Armenteros et al., 1995), as compared with adult onset disorder. Atypical antipsychotics have both significantly improved positive and negative symptoms (Kumra et al., 1996), as well as patients cognition (Toren et al., 2004). Also, clinical trials with new atypical antipsychotics risperidone and olanzapine demonstrated significant improvement in the symptoms of schizophrenia in children and adolescent patients (Gothelf et al., 2003; Zalsman et al., 2003). However, compliance with oral agents is variable (Rosa et al., 2005) due to their intolerability in long-term antipsychotic therapy (Yamada et al., 2006). Moreover, when compared with adults, children and adolescents are more vulnerable to adverse effects of antipsychotics, including EPS, sedation, weight gain and increase in the prolactin level (McConville and Sorter, 2004; Strassnig et al., 2007; Benedetto et al., 2009). Non-adherence and partial adherence to antipsychotics are major risk factor of (Leucht and Heres, 2006) and will result in high relapse incidence (Robinson et al., 1999). Besides, non-adherence to medication also leads to incomplete or unsustainable remission (Andreasen et al., 2005), but remission may represent the long-term goal of treatment for patients with

*Corresponding author. E-mail: hehesmiling@163.com. Tel: +86571-87236332.

Abbreviation: PANSS, Positive and negative syndrome scale; **ESRS**, extrapyramidal symptom rating scale; **CGI**, clinical global impressionsl; **EPS**, extrapyramidal symptoms, **BMI,** body mass index ; **ECG,** electrocardiogram.

schizophrenia as well as for further functional recovery (Kane, 2001).

Therefore, in the treatment of chronic disease such as schizophrenia, pharmacologic advantages (Ereshefsky et al., 1984) of long-acting antipsychotics including consistent and reliable serum concentrations, are not associated with first-pass metabolism and can be adjusted more reliably to the lowest effective dose markedly reducing the risk of unwanted effects. In addition, non-self-administered medication will allow clinicians to reliably determine when patients are suboptimally compliant with therapy. Studies on antipsychotics have concluded this administration was associated with significantly lower relapse incidence than oral administration (Schooler, 2003; Möller, 2005; McEvoy, 2006) . It is also suggested that patients who intramuscularly received long-acting antipsychotics achieved sustained remission (Emsley et al., 2008).

Recent studies have demonstrated the efficacy and safety of intramuscular long-acting risperidone in adult patients with stable schizophrenia or schizoaffective disorder (Kane et al., 2003; Fleischhacker et al., 2003; Knox and Stimmel, 2004; Möller, 2007), but little is known on the intramuscular long-acting risperidone in adolescent patients with early onset schizophrenia. The present study aimed to assess the efficacy and safety of long-acting risperidone on the early onset and stable schizophrenia in adolescent patients.

PATIENTS AND METHODS

Patients

Patients (13 - 18 years) with schizophrenia (DSM- IV-TR criteria) were recruited from the Department of Psychosis, First Affiliated Hospital, Medical College, Zhejiang University, China. They had been treated with oral olanzapine and risperidone for a minimum duration of 4 weeks before study. Diagnosis was confirmed using a structured clinical interview based on positive and negative syndrome scale (PANSS) (Kay et al., 1987). Patients were at symptomatically stable stage with current treatment at baseline which was defined as a total PANSS score 80 and a score 4 on each items in the PANSS: conceptual disorganization, hallucinatory behavior, suspiciousness and unusual thought content. The symptomatic stability was determined by the principal investigator and the medication was not altered within at least 1 month prior to screening. The body mass index of these patients was 35 kg/m^2 or less before study (Keks et al., 2007; Turner et al., 2004). The clinical laboratory results were within the reference range.

Exclusion criteria included a diagnosis of substance dependence within 3 months before the study; moderate or severe tardive dyskinesia; a history of neuroleptic malignant syndrome; documented organic disease of the central nervous system; current seizure requiring medication; severe drug sensitivity/allergy; non-response to risperidone; clinically severe abnormalities in the electrocardiogram (ECG); an acute, unstable, or severe untreated medical illness; serious suicidal ideation or behavior within the past 6 months; high risk for violent behavior toward others. Also excluded were women who were pregnant or likely to be pregnant and breast-feeding women.

Patients voluntarily participated in the present study and written informed consent was obtained from the patients or their relatives, guardians or legal representatives at the study entry. This study was conducted in accordance with the 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects' in the declaration of Helsinki (1989) . The study was also approved by the local ethics committee of School of Medicine, Zhejiang University.

Medication

In this 24-week, open-label trial, adolescent patients were diagnosed with schizophrenia and at the symptomatically stable stage after treatment with oral atypical antipsychotics (olanzapine or risperidone). The medication was switched to 25 or 37.5 mg of intramuscular long-acting risperidone once every 2 weeks. Initial dose of long-acting risperidone prescribed was mainly based on oral administration or clinicians' decision. Patients completed a 4-week prospective run-in period before being switched to the long-acting risperidone.

Once patients met the inclusion criteria, they entered a run-in period of 4 weeks during which they continued to receive the same dose of current oral antipsychotics and other concomitant psychotropics (antidepressants, benzodiazepines, anti-parkinsonian agents, mood stabilizers, or hypnotics). During the 24-week treatment period, the medication was switched from previous oral antipsychotics to intramuscular long-acting risperidone once every 2 weeks. At baseline, patients received an initial dose of long-acting risperidone of 25 or 37.5 mg which was based on oral antipsychotic medication in the run-in period. If patients experienced insomnia, 5 - 10 mg benzodiazepine was given and if extrapyramidal reaction occurred, trihexyphenidyl was added, without other combination therapies. According to investigator's judgment (disease condition or symptoms), the dose of long-acting risperidone could be increased gradually by 12.5 mg increments up to maximum of 50 mg if the patient experienced deterioration in the psychotic symptoms. However, the dose was adjusted only at scheduled visits and patients were treated with each dose for at least 4 weeks.

Oral supplementations were required during the first two weeks of treatment with long-acting risperidone because achieving therapeutic serum level would cost several days. Then, the dose of oral supplementations was titrated down and oral medication was discontinued during week 3. Thereafter, temporary oral supplementation was also permitted during the remainder of the trial when considered by the investigator to be clinically necessary for the treatment of breakthrough psychosis. Concomitant psychotropics were permitted if the patients were taking the medication before the trial. Ideally, the dose of psychotropics was maintained constant throughout the study, but the dose adjustment should be performed if necessary.

Assessments

Assessments of safety and efficacy were performed at baseline (beginning of long-acting risperidone treatment) and at designed time points during the long-acting risperidone treatment. Efficacy was assessed by the PANSS scale, of which there are five symptom domains previously defined by one factor analytic method. Total score of PANSS scale is the sum of scores from five symptom domains and ranges from 30 to 210. Patients were interviewed using the structured clinical interview-PANSS at the beginning of long-acting risperidone treatment and 6, 12, 18 and 24 weeks after long-acting risperidone treatment. Additionally, the severity of illness was evaluated with the Clinical Global Impressions (CGI) (Guy, 1976) severity scale at baseline and thereafter every 2 weeks.

Spontaneously reported adverse events were recorded by the investigators at each visit and at endpoint. Severity of movement disorders was evaluated with the 10-item Extrapyramidal Symptom

Table 1. Characteristics of the patients receiving Long-Acting Risperidone at baseline.

Characteristic	Pre-antipsychotic treatment		
	Olanzapine (n=18)	Risperidone (po) (n=13)	Total (n=31)
Male (%)	38.8	46.1	41.9
Age (year)	16.3 ± 2.6	15.4 ± 3.2	15.9 ± 3.3
Body weight (kg)	52.3 ± 12.7	47.9 ± 13.6	50.2 ± 14.1
BMI (kg/m^2)	27.1 ± 8.5	25.6 ± 6.7	26.3 ± 7.6
Schizophrenia diagnosis, %(n)			
Paranoid	77.8(14)	76.9 (10)	77.4 (24)
Undifferentiated	5.6(1)	7.7 (1)	6.5 (2)
Disorganized	11.1 (2)	15.3 (2)	12.9 (4)
Catatonic	5.6(1)	0	3.2 (1)

Rating Scale (ESRS) (Chouinard et al., 1980) before the study and at each visit. Results from standard clinical laboratory tests and electrocardiography and body weight were assessed at baseline and 6, 12, 18 and 24 weeks after long-acting risperidone treatment. Vital signs were measured at each visit. Patients completed an assessment for pain with a 100 mm visual analogue scale (VAS) 5 min after each injection and investigators rated injection-site pain, redness, swelling and in duration with a categorical scale (absent, mild, moderate, or severe) at each injection; both assessments were performed at baseline and every 2 weeks from week 2 to 24.

Statistical analysis

Safety was assessed in all patients who received at least one injection of long- acting risperidone and efficacy in patients who received at least one injection and completed at least one post-baseline PANSS assessment. Descriptive statistics, including clinical characteristics and treatment-emergent adverse events were summarized for all treated subjects according to initial oral antipsychotic treatment group at all time points. Changes in the vital signs, body weight and body mass index, electrocardiography and ESRS scores. Means were presented as means ± standard deviation (SD). The variable of primary efficacy was defined as the changes in total PANSS score from baseline to endpoint and that of secondary efficacy as a CGI severity rating at each assessment. The changes in the rating scale score from baseline to each visit and endpoint were analyzed with Wilcoxon signed-rank (PANSS) and paired *t*-tests (ESRS). A value of $P < 0.05$ was considered statistically significant. A last-observation-carried-forward (endpoint) analysis was performed on data from PANSS and ESRS.

RESULTS

A total of 31 adolescent patients with early onset schizophrenia were enrolled. They completed the run-in period on current oral antipsychotics and received at least one injection of long-actingrisperidone. Baseline demographics and other clinical characteristics of these 31 patients are summarized in Table 1. Patients were predominantly female (58.1%), with a mean age of 15.9 years and 77.4% had a diagnosis of paranoid schizophrenia. Pre-study antipsychotics in the 31 patients included oral risperidone in 13 patients and olanzapine in 18 patients. Twenty-five (80.6%) patients completed the 24-week trial. The reasons for discontinuation included withdrawal of consent in two patients, noncompliance in one, adverse events in one, insufficient response in one and lost to follow-up in one.

Medication

During the 24-week treatment period, 25 patients (80.6%) received all 12 scheduled injections which were performed at a 2-week interval. The final dose (LOCF) of long-acting risperidone was 25 mg in 54.8% (n = 17), 37.5 mg in 29.0% (n = 9) and 50 mg in 16.1% (n = 5) of patients. Oral administration of risperidone was done in 3 patients, for 21, 28 days and 7 weeks and at a dose of 1.0, 1.5 and 1.0 mg/d, respectively. In terms of concomitant medications, during the 24-week trial, antidepressants were applied in 12.9%, anti-parkinsonian agents in 6.5% and sedative/hypnotics in 3.2% of patients.

Efficacy

Symptom severity (PANSS scores) in these symptomatically stable patients was generally low at baseline. Nevertheless, in all patients treated with long-acting risperidone, mean PANSS total score (± SE) was significantly improved at week 6 (-1.3 ± 0.5, $P < 0.05$), week 12 (-2.8 ± 0.6, $P < 0.05$), week 18 (-2.4 ± 0.3, $P < 0.01$), week 24 (-4.2 ± 0.2, $P < 0.01$) and the end of treatment (-3.3 ± 0.7, $P < 0.01$) when compared with baseline score. At the end of treatment, when compared with baseline, significant reduction in the mean PANSS score was observed across all five symptom domains: positive symptoms (- 1.0 ± 0.7, $P < 0.01$), negative symptoms (-0.9 ± 0.9, $P < 0.05$), disorganized thoughts (-1.1 ±

Table 2. Mean PANSS total scores and positive and negative factor scores at baseline and mean changes at the end of treatment with long-acting risperidone.

Variable	Pre-antipsychotic treatment		
	Olanzapine (N = 18)	Risperidone (po) (N = 13)	Total (N = 31)
PANSS total score			
Baseline	58.1 ± 1.9	57.3± 1.6	57.8 ± 1.8
Change at the end of treatment	-4.3 ± 0.5**	-4.5 ± 0.7**	-4.4 ± 0.2**
Positive symptom score			
Baseline	16.8 ± 0.7	17.2 ± 0.5	17.0 ± 0.8
Change at the end of treatment	-1.0 ± 0.5**	-1.1 ± 0.7**	-1.0 ± 0.7**
Negative symptom score			
Baseline	15.2 ± 0.5	14.7± 0.4	15.0 ± 0.6
Change at the end of treatment	-0.8 ± 0.4*	-0.9 ± 0.6**	-0.9 ± 0.9*
Disorganized thought score			
Baseline	12.6 ± 0.5	13.7 ± 0.4	13.2 ± 0.6
Change at the end of treatment	-1.1 ± 0.6**	-1.1 ± 0.5**	-1.1 ± 0.7**
Uncontrolled hostility/excitement score			
Baseline	5.8 ± 0.8	6.1 ± 0.3	5.9 ± 0.6
Change at the end of treatment	-0.4 ± 0.6*	-0.4 ± 0.5*	-0.4 ± 0.8*
Anxiety/ depressiion score			
Baseline	7.7 ± 0.3	5.6 ± 0.3	6.8 ± 0.8
Change at the end of treatment	-1.0 ± 0.7**	-1.0 ± 0.5**	-1.0 ± 0.6**

*? Difference in least squares means. *P < 0.05 *vs* baseline. ** P < 0.001 vs baseline.

0.7, P < 0.01), uncontrolled hostility/excitement (-0.4 ± 0.8, P < 0.05), anxiety/depression (-1.0 ± 0.6, P < 0.01) (Table 2, Figures 1 - 3). Figure 4 showed the percentage of patients who achieved 20, 40 or 60% improvement in total PANSS score following treatment. In these stable patients, the PANSS total score at the end of treatment was improved by 20% in 21 (67.7%) patients, 40% in 12 (38.7%) patients and 60% in 6 (19.4%) patients.

CGI- severity rating was substantially improved at the end of treatment (Figure 5). The proportion of patients with very mild to mild CGI was increased from 45.6 at baseline to 58.8% at the end of treatment. The mean CGI- severity score (± SD) was also reduced by 0.3 ± 1.3 (P < 0.001) from baseline to endpoint.

Safety and tolerability

In all the patients, adverse events were observed in 5% of patients including depression(12.9%), anxiety (9.7%), headache (9.7%) and insomnia (6.4%) (Table 3). Most of these were considered by the investigator to be mild to moderate in severity and only one patient experienced adverse events leading to withdrawal from the study. No newly-onset adverse events related to extrapyramidal symptoms (EPS) were reported during run-in period. EPS related adverse events during treatment with long-acting risperidone included akathisia in 1 patient and non-acute dystonia in 2 patients. Severity of movement disorders (ESRS scores) was low at baseline in all patients and was further reduced during treatment in patients previously treated with oral risperidone (Table 4). No clinically significant change in ECG findings including QTc was encountered.

Adverse effects potentially attributable to elevated prolactin level were reported in 5 patients (16.1%) (non-puerperal lactation in 2 and dysmenorrhea in 3) . Prolactin level was elevated in 17 (54.8%) patients at baseline. Mean (± SE) serum prolactin concentration in patients with previous oral risperidone treatment was decreased from 87.4 ± 15.5 ng/ml at baseline to 40.2 ± 14.8 ng/ml at the end of treatment (P < 0.001), while significant increase in the mean serum prolactin concentration was observed in patients with previous olanzapine treatment

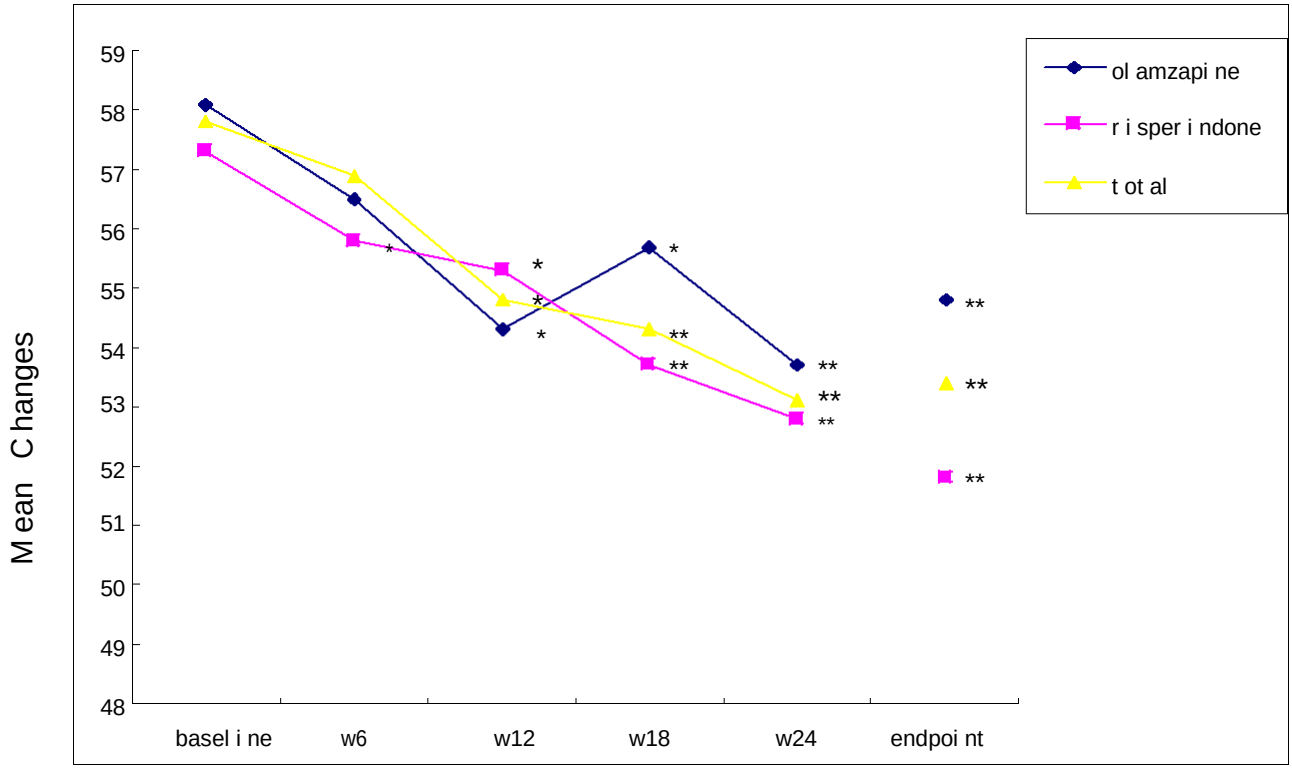

Figure 1. Mean changes in the PANSS total score from baseline to the end of treatment (LOCF).
*P < 0.05 vs baseline. **P < 0.001 vs baseline.

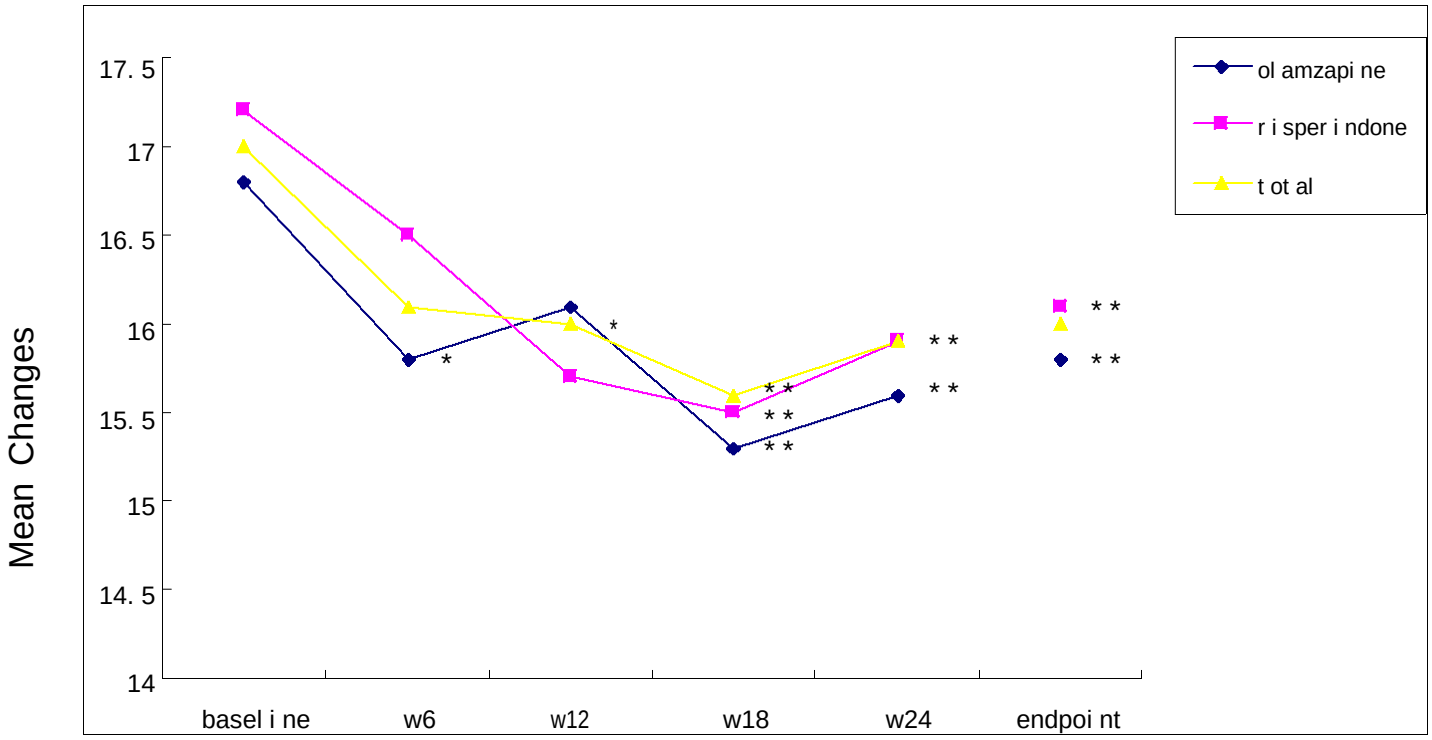

Figure 2. Mean changes in the scores on positive syndrome scale of PANSS from baseline to endpoint (LOCF). *P < 0.05 vs baseline. **P < 0.001 vs baseline.

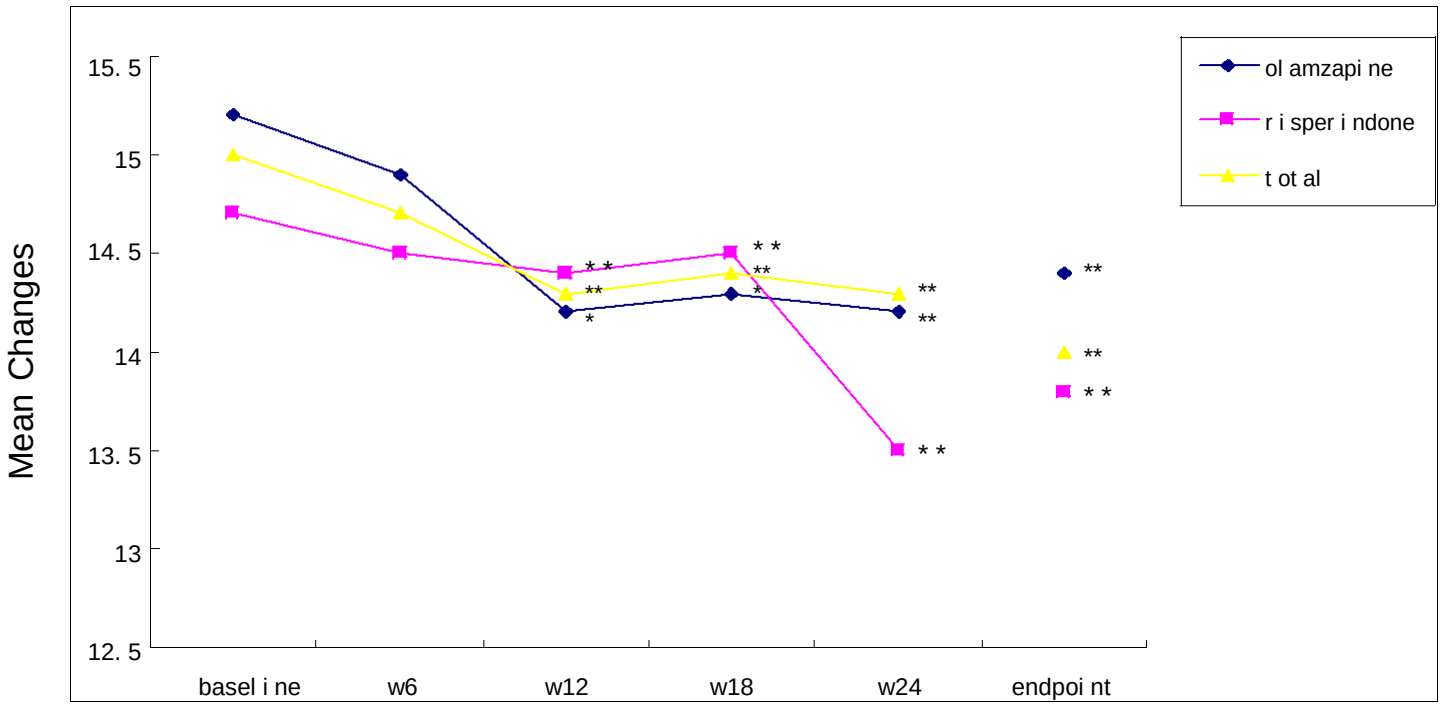

Figure 3. Mean changes in the scores on negative syndrome scale of PANSS from baseline to endpoint (LOCF). * P < 0.05 vs baseline. **P < 0.001 vs baseline.

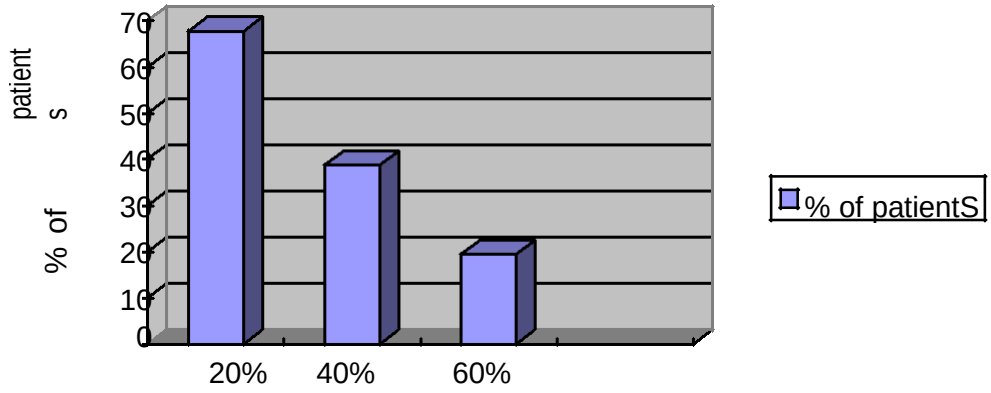

Figure 4. Percentage of patients with 20, 40 and 60% improvement in PANSS total score at the end of treatment (LOCF).

during the 24-week treatment.

Mean body weight was decreased from 54.3 ± 12.7 at baseline to 49.2 ± 11.5 kg at the end of treatment (P < 0.001) in patients with previous olanzapine treatment and from 47.9 ± 13.6 at baseline to 46.2 ± 11.5 kg in patients with previous oral risperidone treatment (P > 0.05). BMI in patients with previous olanzapine treatment was also decreased from 27.1 ± 8.5 to 25.7 ± 8.1 kg. After (31.3 ± 11.3 ng/ml at baseline and 42.9 ± 13.6 ng/ml at the end of treatment, P < 0.01). No other clinically significant changes in laboratory tests were encountered repeated gluteal intramuscular injections of long-acting risperidone, the self-ratings of local pain were low in both treatment groups throughout the trial and decreased over the 24-week study. Injection site responses were also uncommon based on the ratings of redness, swelling and indurations.

DISCUSSION

Our study demonstrated that adolescent patients with early onset schizophrenia at the stable stage achieved significant clinical improvements when their current

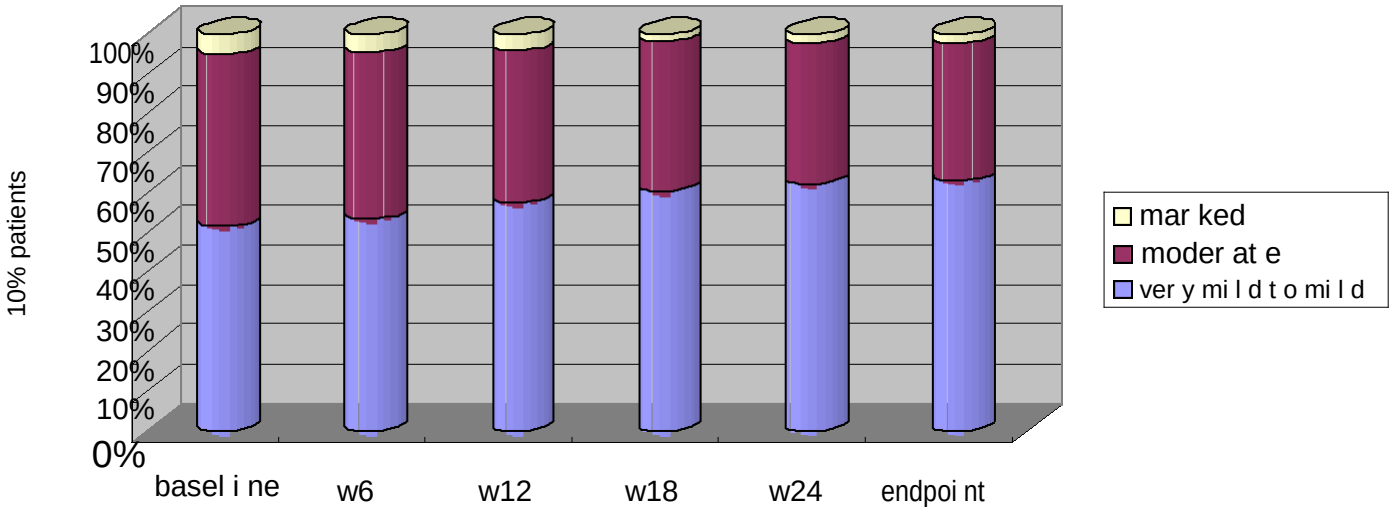

Figure 5. Percentage of patients whose illness were rated as very mild to mild, moderate and marked (severe?) at baseline and the end of treatment.

Table 3. Adverse events occurring in 5% of patients in each group.

Adverse event	Prior antipsychotic treatment		
	Olanzapine (n = 18) %	Risperidone (po) (n = 13) %	Total (n = 31) %
Insomnia	5.6	7.6	6.4
Anxiety	11.1	7.6	9.7
Headache	5.6	15.3	9.7
Depression	11.1	15.3	12.9

Table 4. Mean prolactin level, body weight, BMI and ESRS score at Baseline and at the end of treatment (LOCF) in patients with long-acting risperidone treatment.

Variable	Pre-antipsychotic treatment		Total (n=31)
	Olanzapine (n = 18)	Risperidone (po) (n = 13)	
Prolactin level (ng/ml)			
Baseline	31.3 ± 11.3	87.4 ± 15.5	54.8 ± 17.7
end of treatment	42.9 ± 13.6*	40.2 ± 14.8**	41.7 ± 16.5*
Body weight (kg)			
Baseline	54.3 ± 12.7	47.9 ± 13.6	51.6 ± 14.1
end of treatment	49.2 ± 11.5**	46.2 ± 11.5	47.9 ± 11.5**
BMI (kg/m^2)			
Baseline	27.1 ± 8.5	25.6 ± 6.7	26.5 ± 7.6
end of treatment	25.7 ± 8.1*	25.1 ± 7.4	25.4 ± 8.7*
ESRS score			
Baseline	0.39 ± 0.13	0.48 ± 0.13	0.43 ± 0.17
end of treatment	0.41 ± 0.16	0.40 ± 0.15*	0.41 ± 0.21

*P < 0.05 *vs* baseline. **P < 0.01 *vs* baseline.

medication was switched from oral antipsychotics to intramuscular long-acting risperidone. Despite the baseline severity of schizophrenia in most patients (89.2%) was very mild to moderate according to the CGI-severity scale, the mean PANSS total score was further improved in both groups. Over half (67.7%) of the subjects showed at least 20% improvements in PANSS total score. The treatment in most of patients (54.8%) was maintained with 25 mg of long- acting risperidone till the end of trial. Moreover, reduction in the mean PANSS score from baseline to the end of treatment was observed across all five symptom domains. Although PANSS total score was very low at baseline among all patients, most patients presented progressive improvements throughout the trial, particularly in disorganized thoughts, anxiety/ depression and negative symptoms. These clinically important findings in adolescent patients were in accord with previous studies on long-acting risperidone in adult patients with schizophrenia (Turner et al., 2004) and schizoaffective disorder (Lasser et al., 2007), suggesting benefits of long-acting risperidone in treatment of refractory chronic psychotic illnesses.

The results showed that, in patients with early onset schizophrenia at the stable stage, switching oral antipsychotics to intramuscular atypical long-acting risperidone was clinically feasible and beneficial for further symptomatic improvement. Of the 31 adolescent patients with early onset schizophrenia in the present study, 25 (80.6%) completed the open-label, 24-week trial in which the new long-acting risperidone was intramuscularly administered, with very low rate of premature discontinuation for either adverse events (3.2%), or insufficient response (3.2%). The present study also indicated that the medication in adolescent patients who were with stable schizophrenia on oral antipsychotics for at least 4 weeks could be safely switched to intramuscular administration of long- acting risperidone in combination with maintenance with oral antipsychotics for another 3 weeks. Adverse effects which may negatively affect the compliance were less reported. Based on physician-rated EPS, the severity of movement disorder in most patients was also steadily improved from baseline to the end of treatment. McEvoy et al. (2007) have reported that olanzapine could cause lethargy in 53% of adults and oral risperidone in up to 50% of patients. In the present study, results indicated that the incidence of long-acting risperidone-related drowsiness was very low and only 3 patients felt drowsy in the daytime affecting learning. Because of this advantage, long-acting risperidone would greatly improve patients' concentration in the daytime and therefore facilitate adolescents' returning to school and social life.

A typical antipsychotic drugs often lead to weight gain especially in adolescent patients (Sikich et al., 2004; Stigler et al., 2004; Ramaswamy et al., 2007). Clozapine and olanzapine were two major drugs causing weight gain, followed by risperidone and quetiapine. The present study showed that the body weight of adolescent patients was increased after switching oral risperidone to intramuscular long-acting risperidone, which was consistent with previous report on the effects of oral risperidone and long-acting risperidone on the body weight of adult patients (Chue et al., 2005). In addition, our results also revealed that body weight as well as BMI was markedly reduced when the medication was switched to long-acting risperidone. Our results indicated the mean weight loss in patients with previous olanzapine treatment was 4.5 ± 2.7 kg and that was 0.5 kg in adult patients (Lindenmayer et al., 2007) after switching to long-acting risperidone. This can be explained by prolonged treatment period or the difference in the study subjects suggesting adolescent patients might be more sensitive to adverse effects of risperidone (Ramaswamy et al., 2007).

In present study, hyperprolactinemia was reported only in 6 female patients (19.3%), which was not dose-dependent. In previous studies on the long-acting risperidone in adult patients, the prevalence of drug-induced hyperprolactinemia was discrepant, but generally low (Turner et al., 2004; Lasser et al., 2007). Lindenmayer et al. (2007) reported 7.9% of patients with hyperprolactinemia symptoms after switching medication from typical or atypical antipsychotics to long-acting risperidone. Our study indicated more prolactin-related side effects in all patients. This could be attributed to the majority (58.1%) of female adolescents recruited into the present study. Nevertheless, remarkable decrease in prolactin-related side effects was observed in these patients after switching to long-acting risperidone treatment. This result indicated that replacing olanzapine or oral risperidone with long-acting risperidone was a favorable treatment of choice for adolescent patients who were at risk for hyperprolactinemia and weight gain. After switching to long-acting risperidone treatment, the prevalence of depression and anxiety was 12.9 and 16.1%, respectively. A total of 12.9% of patients were additionally given antidepressants. However, the results from similar studies on adult patients had a higher prevalence of depression and anxiety (Lasser et al., 2007; Chue et al., 2005; Lindenmayer et al., 2007).

The major limitations of this study were its open- label design, the small sample size, the lack of controls and 24- week duration (prolonged duration). Long-term studies are required to confirm whether the beneficial effects of long-acting risperidone can be maintained for a prolonged period. Patients were not randomized according to doses, but were assigned to given dose based on clinician decision (disease condition), limiting the interpretability of our results on the relationship between dose conversion and dose-response.

REFERENCES

Andreasen NC, Carpenter WT Jr, Kane JM (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162: 441-449.

Armenteros JL, Fennelly BW, Hallin A, Adams PB, Pomerantz P, Michell M, Sanchez LE, Campbell M (1995). Schizophrenia in hospitalized adolescents: clinical diagnosis, DSM-III -R, DSM-IV and ICD-10 criteria. Psychopharmacol. Bull. 31: 383-387.

Benedetto V, Christoph C, Barbara van ZB (2009). Antipsychotics in children and adolescents: Increasing use, evidence for efficacy and safety concerns. Eur. Neuropsychopharmacol. 19(9): 629-635.

Chouinard G, Ross-Chouinard A, Annable L (1980). Extrapyramidal symptom rating scale. Can. J. Neurol. Sci. 7: 233.

Chue P, Eerdekens M, Augustyns I, Lachaux B, Molcan P, Eriksson L, Pretorius H, David AS (2005). Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. Eur Neuropsychopharmacol. 15(1): 111-117.

Emsley R, Oosthuizen P, Koen L (2008). Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection. Int. Clin. Psychopharmacol. 23(6): 325-331.

Ereshefsky L, Saklad SR, Jann MW (1984). Future of depot neuroleptics therapy: pharmacokinetic and pharmacodynamic approaches. J. Clin. Psychiatry 45(5; 2): 50-59.

Fleischhacker WW, Eerdekens M, Karcher K (2003). Treatment of schizophrenia with long-acting injectable risperidone: a 12-month evaluation of the first long-acting second-generation antipsychotic. J. Clin. Psychiatry 64: 1250-1257.

Gothelf D, Apter A, Reidman J, Brand-Gothelf A, Bloch Y, Gal G, Kikinzon L, Tyano S, Weizman R, Ratzoni G (2003). Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. J. Neural. Transm. 110: 545-560.

Guy W (1976). ECDEU Assessment Manual for Psychopharmacology. Revised Edition. Rockville, MD: National Institute of Mental Health: US Department of Health Education and Welfare.

Kane J (2001). Progress defined – short-term efficacy, long-term effectiveness. Int. Clin. Psychopharmacol. 16: S1–S8.

Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 13: 261-276.

Keks NA, Ingham M, Khan A, Karcher K (2007). Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. Br. J. Psychiatry 191:131-139.

Knox ED, Stimmel GL (2004). Clinical review of a long-acting, injectable formulation of risperidone. Clin. Ther. 26(12): 1994-2002.

Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, Hamburger SD, Smith AK, Albus KE, Alaghband-Rad J, Rapoport JLn (1996). Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. Arch. Gen. Psychiatry 53: 1090–1097. Kane JM, Eerdekens M, Lindenmayer J-P (2003). Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am. J. Psychiatry 160: 1125-1132.

Lasser RA, Bossie CA, Zhu Y, Locklear JC, Kane JM (2007). Long-acting risperidone in young adults with early schizophrenia or schizoaffective illness. Ann. Clin. Psychiatry 19(2): 65-71.

Leucht S, Heres S (2006). Epidemiology, clinical consequences and psychosocial treatment of nonadherence in schizophrenia. J. Clin. Psychiatry. 67(5): 3-8.

Lindenmayer JP, Khan A, Eerdekens M, Van Hove I, Kushner S (2007). Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder. Eur Neuropsychopharmacol. 17(2): 138-144.

McConville BJ, Sorter MT (2004). Treatment challenges and safety considerations for antipsychotic use in children and adolescents with psychoses. J. Clin. Psychiatry 65(6): 20-29.

McEvoy JP (2006). Risks versus benefits of different types of long-acting injectable antipsychotics. J. Clin. Psychiatry 67(5): 15-18.

McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD (2007). Efficacy and tolerability of olanzapine, quetiapine and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am. J. Psychiatry 164(7): 1050-1060.

Möller HJ (2005). Antipsychotic agents. Gradually improving treatment from the traditional oral neuroleptics to the first atypical depot. Eur. Psychiatry 20(5-6): 379-385.

Möller HJ (2007). Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. Drugs 67(11): 1541-1566.

Ramaswamy K, Kozma CM, Nasrallah H (2007). Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. Drug Saf. 30(7): 589-599.

Robinson DG, Woerner MG, Alvir JM (1999). Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 156: 544-549.

Rosa MA, Marcolin MA, Elkis H (2005). Evaluation of the factors interfering with drug treatment compliance among Brazilian patients with schizophrenia. Rev. Bras. Psiquiatr. 27: 78-84.

Schooler NR (2003). Relapse and rehospitalization: comparing oral and depot antipsychotics. J Clin Psychiatry 64(16): 14-17.

Sikich L, Hamer RM, Bashford RA, Sheitman BB, Lieberman JA (2004). A pilot study of risperidone, olanzapine and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacol. 29(1): 133-145.

Stigler KA, Potenza MN, Posey DJ, McDougle CJ (2004). Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance and management. Paediatr. Drugs 6(1): 33-44.

Strassnig M, Miewald J, Keshavan M (2007). Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophr. Res. 93: 90-98.

Toren P, Ratner S, Laor N, Weizman A (2004). Benefit-risk assessment of atypical antipsychotics in the treatment of schizophrenia and comorbid disorders in children and adolescents. Drug Saf. 27: 1135-1156.

Turner M, Eerdekens E, Jacko M, Eerdekens M (2004). Long-acting injectable risperidone: safety and efficacy in stable patients switched from conventional depot antipschotics. Int. Clin. Psychopharmacol. 19(4): 241-249.

Werry JS, McClellan JM, Chard L (1991). Childhood and adolescent schizophrenic, bipolar and schizoaffective disorders: A clinical and outcome study. J. Am. Acad. Child Adolesc. Psychiat. 30: 457-465.

Yamada K, Watanabe K, Nemoto N (2006). Prediction of medication noncompliance in outpatients with schizophrenia: 2-year follow-up study. Psychiatry Res. 141: 61-69.

Zalsman G, Carmon E, Martin A, Bensason D, Weizman A, Tyano S (2003). Effectiveness, safety and tolerability of risperidone in adolescents with schizophrenia: An open-label study. J. Child Adolesc. Psychopharmacol. 13: 319-327.