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Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia

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Summary. *Objectives*: To evaluate and compare the drug response and side effects of adolescents with schizophrenia treated with olanzapine, risperidone, and haloperidol.

Methods: Forty-three patients were treated with olanzapine (n = 19), risperidone (n = 17) and haloperidol (n = 7) for 8 weeks in an open clinical trial. Clinical improvement was evaluated with the Positive and Negative Syndrome Scale (PANSS), and side effects with the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale.

Results: Significant clinical improvement was observed by week 4 for all medications. Olanzapine and haloperidol induced fatigability more frequently than risperidone. Haloperidol was associated with a higher frequency of depression and more severe extrapyramidal symptoms.

Conclusions: To the best of our knowledge this is the first study in adolescents to compare the efficacy and side effects of three most commonly prescribed antipsychotic medications. Olanzapine, risperidone and haloperidol appear to be equally effective for the treatment of schizophrenia in adolescent inpatients but have different side effect profiles.

Keywords: Adolescents, antipsychotics, olanzapine, risperidone, haloperidol, side effects.

Introduction

About one-third of patients with schizophrenia present in childhood or early adolescence (Beratis et al., 1994; Loranger, 1984). These cases are generally

characterized by insidious onset, prominent negative symptoms and poor outcome (Remschmidt, 2002; Werry et al., 1991). Some authors claim that children and adolescents are more prone than adults to side effects of neuroleptic treatment, and have higher rates of nonresponse (Remschmidt et al., 2000; Toren et al., 1998). Despite these findings, psychopharmacological research in this patient population lags far behind that in adults. This has particular importance in light of findings that early intervention has a significant impact on outcome (DeQuardo, 1998).

In the pre-atypical neuroleptic era, studies of haloperidol in adolescents with schizophrenia were particularly scanty. Pool et al. (1976), in a four-week trial, found the neuroleptics haloperidol and loxapine to be superior to placebo in improving the psychotic symptoms of the more severely ill patients. Extrapyramidal symptoms (EPS) developed in 72% of the haloperidol-treated patients. The efficacy of haloperidol has been shown in a double blind, cross-over study of 16 hospitalized children and adolescents with schizophrenia, using haloperidol doses of 0.02–0.12 mg/kg/day (Spencer et al., 1992).

Among the atypical neuroleptics, clozapine has been investigated most often in children and adolescents with schizophrenia. Kumra et al. (1996) compared the efficacy of clozapine to haloperidol in a 6-week randomized double-blind study of treatment-refractory children and adolescents with schizophrenia. The clozapine-treated patients showed significantly more improvement in both positive and negative symptoms. Besides this study, 10 open-label trials of clozapine in children and adolescents have been published (Toren et al., 1998).

Unfortunately, there are only very few retrospective and open studies of risperidone in adolescents with schizophrenia (see Table 1). Grcevich et al. (1996) conducted a chart review of 16 schizophrenia patients of mean age 14.9 years treated with risperidone. Mean daily dose was 5.9 mg. There was a significant improvement in total and negative symptom scores in the Brief Psychiatric Rating Scale. The most common side effect was transient sedation (31%), followed by EPS (19%). Armenteros et al. (1997) studied the effect of risperidone in 10 schizophrenia patients of mean age 15.1 years. Mean dose was 6.6 mg per day, and the study was conducted for 6 weeks. On average, the patients' positive as well as negative symptoms improved significantly, as documented by the Positive and Negative Syndrome Scale. Side effects were transient sedation (8 patients), parkinsonian symptoms (3 patients) and dystonic reaction (2 patients). Several studies reported that risperidone is effective in the treatment of children and adolescents with other psychopathologies including Tourette's syndrome (Lombroso et al., 1996), pervasive developmental disorders (Findling et al., 1997; Masi et al., 2001; McDougle et al., 1997; Nicolson et al., 1998; Perry et al., 1997; Zuddas et al., 2000), conduct disorder (Findling et al., 2000), and for behavioral problems of children with borderline intelligence and mental retardation (Buitelaar et al., 2001; Van Bellingen and De Troch, 2001).

Like for risperidone, there are a paucity of data on the efficacy and safety of olanzapine in children and adolescent with schizophrenia (see Table 1). Only two retrospective, open-label studies have been conducted. Kumra et al.

Table 1. Previous studies with risperidone and olanzapine in children and adolescents with schizophrenia

N	Mean age (years)	Mean dose mg/d	Results	Most common side effects	Reference
Risperidone					
16 (Retrospective study)	14.9	5.9	Mean improvement of 39% in BPRS scores	Sedation 31% EPS 19%	Grcevich et al. (1996)
10 (Open trial)	15.1	6.6	Mean improvement of 30% in BPRS scores	Transient sedation 80% Parkinsonism 30% Dystonia 20%	Armenteros et al. (1997)
Olanzapine					
8 (Open trial)	15.3	17.5	Mean improvement of 17% in BPRS scores	Transient elevation in liver transaminase 87.5% Insomnia 87.5%	Kumra et al. (1998)
15 (Open trial)	9.4	5	67% moderate to great improvement in psychotic symptoms	Transient sedation (rates not specified)	Sholevar et al. (2000)

BPRS Brief Psychiatric Rating Scale; *EPS* extrapyramidal symptoms

(1998) studied the effect of olanzapine, 17.5 mg per day, on 8 treatment-refractory children and adolescents with schizophrenia. Mean age was 15.3 years, and duration of follow-up was 8 weeks. On average, there was a negligible improvement (6%) in positive symptoms, but a 21% improvement in negative symptoms. Side effects included a transient elevation in liver transaminase levels and insomnia (7 patients each); increased appetite, nausea or vomiting, headache, tachycardia and increased agitation (6 patients each); and constipation and concentration difficulties (5 patients each). In a more recent study, Sholevar et al. (2000) examined 15 inpatient children (mean age 9.4 years) treated with olanzapine by clinical observation. Most of the patients were maintained on 5 mg per day. They found that 10 patients (67%) showed moderate to great improvement following an average of 11.3 days of treatment. The only side effect was significant sedation that lasted up to 4 days.

To the best of our knowledge, there are no reported studies in children or adolescents comparing the efficacy and tolerability of risperidone with olanzapine, or either of these drugs with haloperidol. In a 28-week double-blind prospective comparison of olanzapine and risperidone in adult patients with schizophrenia, Tran et al. (1997) found an apparently equal efficacy of the drugs in the alleviation of positive symptoms, and a greater efficacy of olanzapine in alleviating negative symptoms. Significantly more risperidone-treated patients had side effects, namely, EPS, hyperprolactinemia, sexual dysfunction, early waking, and increased dreams. Another study in an adult population (Conley and Mahmoud, 2001) noted a greater reduction in positive and affective symptoms with risperidone than olanzapine, with the same frequency and severity of EPS. Several studies have also compared risperidone and olanzapine with haloperidol in adults (e.g., Carman et al., 1995; Tollefson and Sanger, 1997). Generally, results showed a higher clinical effectiveness for the atypical antipsychotics, especially with regard to negative symptoms, in addition to significantly lower association with EPS (Tandon et al., 1999).

The aim of the present open clinical trial was to compare three most commonly prescribed antipsychotic medications (olanzapine, risperidone, and haloperidol) in adolescents with schizophrenia.

Materials and methods

Patients

In a previous study with the same subjects (Ratzoni et al., 2002) we focused on weight gain induced by antipsychotic medications. In the present paper, we report on clinical response and other side effects. The study was conducted prospectively from January to August 2000 in 43 adolescent patients hospitalized in two mental health centers in the Tel Aviv area of Israel.

The diagnosis of schizophrenia was established according to DSM-IV criteria following a structured psychiatric interview, the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime (K-SADS-PL) (Shanee et al., 1997) and on past medical records, and observations of the patient's behavior during hospitalization. A consensus between at least two senior child psychiatrists was required.

Seven patients were drug-naive, and 36 had been previously treated with antipsychotic agents, either classical haloperidol, perphenazine, thioridazine, clothiapine, sulpiride, levropromazine or zuclopenthixol, or atypical (risperidone and clozapine). The psychotropic medications were discontinued before the initiation of the study drugs. Details regarding previous neuroleptic treatments and neuroleptic washout periods are presented in Table 2. Besides the study neuroleptic the only medications that were used during the study period were lorazepam and anticholinergic agents (trihexyphenidyl, biperiden). Seventeen patients were assigned to receive risperidone, 19 olanzapine and 7 haloperidol. All three drugs were started at a low dose, with stepwise increments. The allocation of the patients to the three study groups and the dosages required were based on the clinical judgment of the departmental directors (A.A., G.R.).

Choice of medications for each individual patient was based on the treating physician recommendation. Many patients were initially started on risperidone since this was the only atypical antipsychotic available in Israel at the beginning of the study. Later on, as olanzapine became available for use many patients were assigned to this agent. Thus, there may well have been some bias limiting the validity of the study. However, no significant association was found between previous antipsychotic treatment and the medications used in the present study ($\chi^2_6 = 8.0$, $p = 0.24$).

Assessment

The severity of the psychiatric symptomatology was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991), and the neuroleptic side effects with the comprehensive Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987). The UKU is composed of 48 adverse effects items, divided into 4 categories: psychic, neurologic, autonomic, and other. Each item is rated on a 4-point scale: 0 – no side effects, 1 – mild, 2 – moderate, 3 – severe. It has been found to be reliable and valid (Lingjaerde et al., 1987) and has been used in many studies of antipsychotic drugs (e.g., Cabeza et al., 2000; McConville et al., 2000; Huttunen et al., 1995). In the present trial, UKU adverse effect was categorized as appeared or disappeared: appearance of a side effect was recorded if it had not been present at baseline but was noted in week 4 or 8, or it had been present at baseline but was exacerbated in week 4 or 8; disappearance was recorded if, following an appearance of the side effect, its score was zero at week 8.

The clinical assessment was carried out by two senior child psychiatry fellows (JR, AB). They were trained in assessment procedures by the senior author (DG) until a satisfactory inter-rater reliability was obtained. The concordance rates on the PANSS between the 2 fellows and between each of them and the senior author was satisfactory as defined by Kay (1991), that is, agreement on more than 80% of the items and total score deviations of less than 20%. The concordance rates on the UKU were above 90%.

Procedure

The study was approved by the Review Boards of the Geha and Shalvata Mental Health Centers, and written informed consent was obtained from all patients and their parents after the nature of the study was fully explained to them.

Psychiatric assessment using the PANSS as a primary outcome measure and the UKU as a measure of side effects were performed at baseline, just before initiation of the antipsychotic medication, and after 4 and 8 weeks of treatment.

Statistics

The effects of the drugs on psychotic symptoms were assessed statistically using 3×3 ANOVA, with drug (risperidone, olanzapine, haloperidol) as the between-subjects factor and time (baseline, week 4, week 8) as the repeated-measurement factor. The

Table 2. Characteristics of study sample

	Risperidone (n = 17)	Olanzapine (n = 19)	Haloperidol (n = 7)	Statistics
Subtype of schizophrenia				$\chi^2_4 = 0.63$
Paranoid	8	10	3	
Undifferentiated	5	6	2	
Disorganized	4	3	2	
Age (yrs) (mean ± SD)	17.0 ± 2.1	16.8 ± 1.6	17.1 ± 1.3	F(2,40) = 0.1
Sex (M/F)	9/8	13/6	5/2	$\chi^2_2 = 1.19$
Duration of illness (months)	16.9 ± 13.9	17.6 ± 17.0	12.0 ± 12.9	F(2,40) = 0.4
Age at first hospitalization (yrs)	14.3 ± 3.2	15.1 ± 2.1	14.2 ± 1.8	F(2,40) = 0.7
Previous neuroleptic treatment				
Number of previous neuroleptics	2.1 ± 1.8	1.8 ± 0.8	1.5 ± 0.6	F(2,33) = 1.2
None	3	2	1	
Risperidone	–	10 (1–4 mg/d)	3 (1–4 mg/d)	
Olanzapine	4 (20 mg/d)	–	–	
Clozapine	–	1 (450 mg/d)	–	
Haloperidol	7 (5–10 mg/d)	8 (5–12.5 mg/d)	–	
Perphenazine	7 (20–40 mg/d)	3 (24–32 mg/d)	3 (24–32 mg/d)	
Levopromazine	4 (200–300 mg/d)	3 (75–200 mg/d)	1 (150 mg/d)	
Thioridazine	2 (250–550 mg/d)	2 (150–450 mg/d)	1 (200 mg/d)	
Clothiapine	2 (120 mg/d)	2 (80–120 mg/d)	–	
Zuclopenthixol	2 (25 mg/d)	2 (25 mg/d)	–	
Sulpiride	1 (800 mg/d)	–	1 (1,200 mg/d)	
Study medication				
Dose (Mean ± SD)	3.3 ± 1.1	12.9 ± 3.1	8.3 ± 3.8	
Dose in mg/kg	0.05 ± 0.02	0.2 ± 0.1	0.1 ± 0.1	
Washout period in days (Mean ± SD)	5.2 ± 10.0	4.8 ± 5.6	6.5 ± 8.1	F(2,33) = 1.1

dependence between drug treatment and appearance of symptoms according to the UKU was determined by chi-square test.

Results

The characteristics of the study population are presented in Table 2. There were no significant differences among these three groups in subtype of schizophrenia, age, gender distribution, duration of illness and age at first hospitalization. All previous neuroleptic medications and dosage ranges prescribed for these neuroleptics are also summarized in Table 2.

Starting doses were 0.5 mg per day for risperidone and haloperidol, and 5 mg per day for olanzapine. Dosage increments were stepwise and slow to minimize the rate of side effects. Risperidone and haloperidol were increased by 0.5 mg and olanzapine by 2.5 mg every one to two days. The final dose was based on clinical judgment. The final mean doses (±SD) for risperidone were 3.3 ± 1.1 mg per day (range 1–5), for olanzapine 12.9 ± 3.1 mg per day (range 10–20), and for haloperidol 8.3 ± 3.8 mg per day (range 5–15).

The small number of patients on halopreidol reflects the switch in practice from the typical to the atypical neurolpetics by child psychiatrists in Israel. Considering this tendency, it was quite difficult to recruit subjects receiving haloperidol.

Clinical response

Of the 43 patients who started the study, 39 completed the full 8 weeks of treatment. Four patients dropped out before the end of the study period. Two (1 from the risperidone and 1 from the olanzapine group) had a psychotic excacerbation and 2 (1 risperidone and 1 olanzapine) refused to continue hospitalization and were noncompliant with treatment. None of the patients discontinued a medication because of side effects.

The PANSS positive, negative and total scores at baseline, week 4 and week 8 are shown in Table 3 and Fig. 1. At baseline, there were no significant differences among the 3 groups of patients in the subclass or total scores. However, the total PANSS score was slightly higher in the risperidone than the olanzapine group [$F(2,40) = 2.64$, $p = 0.08$], and the positive symptom score was slightly higher in the haloperidol than the olanzapine group [$F(2,40) = 2.47$, $p = 0.01$].

On 3 × 3 ANOVA, there was a significant effect of week on positive [$F(2,72) = 16.9$, $p < 0.001$], negative [$F(2,72 = 5.3$, $p < 0.01$], and total scores [$F(2,72 = 12.7$, $p < 0.001$]. None of the drug × week interactions was significant ($p = 0.14$; $p = 0.99$; $p = 0.77$, respectively). Further comparison of the 3 time points by Duncan post hoc analysis confirmed that scores for positive and negative symptoms and total scores were lower at weeks 4 and 8 than at baseline ($p < 0.01$ for all). There was no difference in scores between week 4 and week 8 ($p > 0.88$ for all).

Table 3. Effects of risperidone, olanzapine and haloperidol on PANSS scores (mean ± SD)

	Baseline	Week 4	Week 8
	Positive symptoms		
Risperidone (n = 15)	17.4 ± 6.9	12.8 ± 3.4	13.2 ± 3.8
Olanzapine (n = 17)	15.0 ± 4.9	11.7 ± 4.2	13.3 ± 8.0
Haloperidol (n = 7)	21.3 ± 8.9	14.1 ± 6.3	13.0 ± 5.8
Effects of Week		$F(2,72) = 16.9$, $p < 0.001$	
Drug X week interactions		$P = 0.14$	
	Negative symptoms		
Risperidone (n = 15)	24.2 ± 9.3	20.3 ± 8.8	20.8 ± 8.4
Olanzapine (n = 17)	18.1 ± 11.0	13.8 ± 6.4	14.9 ± 8.0
Haloperidol (n = 7)	20.3 ± 8.0	16.0 ± 9.1	16.4 ± 8.5
Effects of week		$F(2,72) = 5.3$, $p < 0.01$	
Drug X week interactions		$P = 0.99$	
	Total Scores		
Risperidone (n = 15)	90.2 ± 26.4	73.3 ± 9.2	73.9 ± 19.1
Olanzapine (n = 17)	71.6 ± 23.8	57.7 ± 14.8	61.6 ± 28.4
Haloperidol (n = 7)	86.1 ± 24.4	66.4 ± 19.6	66.3 ± 21.8
Effect of Week		$F(2,72) = 12.7$, $p < 0.001$	
Drug X week interactions		$P = 0.99$	

PANSS positive and negative syndrome scale

Side effects

The side effects, as rated by the UKU, are presented in Tables 4 and 5. Table 4 shows all the nonneurological side effects that occurred in at least 10% of the patients in at least one of the 3 study groups. Side effects with a lower rate of appearance are not shown; these included diarrhea, sweating, rash, menorrhagia, amenorrhea, galactorrhea, gynecomastia, increased sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, and headache. In addition, weight gain, which was the focus of our previous article (Ratzoni et al., 2002), is not reported on here.

Increased fatigability was present in most of the patients in the haloperidol group (71.4%), and was also common in the olanzapine group (42.1%); the rate in the risperidone-treated patients was considerably lower (11.8%). This association was statistically significant ($\chi^2_2 = 8.55$, $p = 0.013$). A similar pattern was observed for sedation and increased duration of sleep, which were present in more than 40% of the patents treated with olanzapine and haloperidol, but these results were not significant. In the vast majority of affected patients, these side effects did not disappear after 8 weeks of treatment.

Five patients receiving haloperidol (71.4%) became more depressed, a finding that was significantly more common ($p < 0.01$) in this group than in the risperidone (11.8%) and olanzapine (26.3%) groups ($\chi^2_2 = 8.82$, $p = 0.012$). Other cognitive side effects, that is, concentration difficulties and failing memory, were also relatively common in the olanzapine- and haloperidol-treated adolescents.

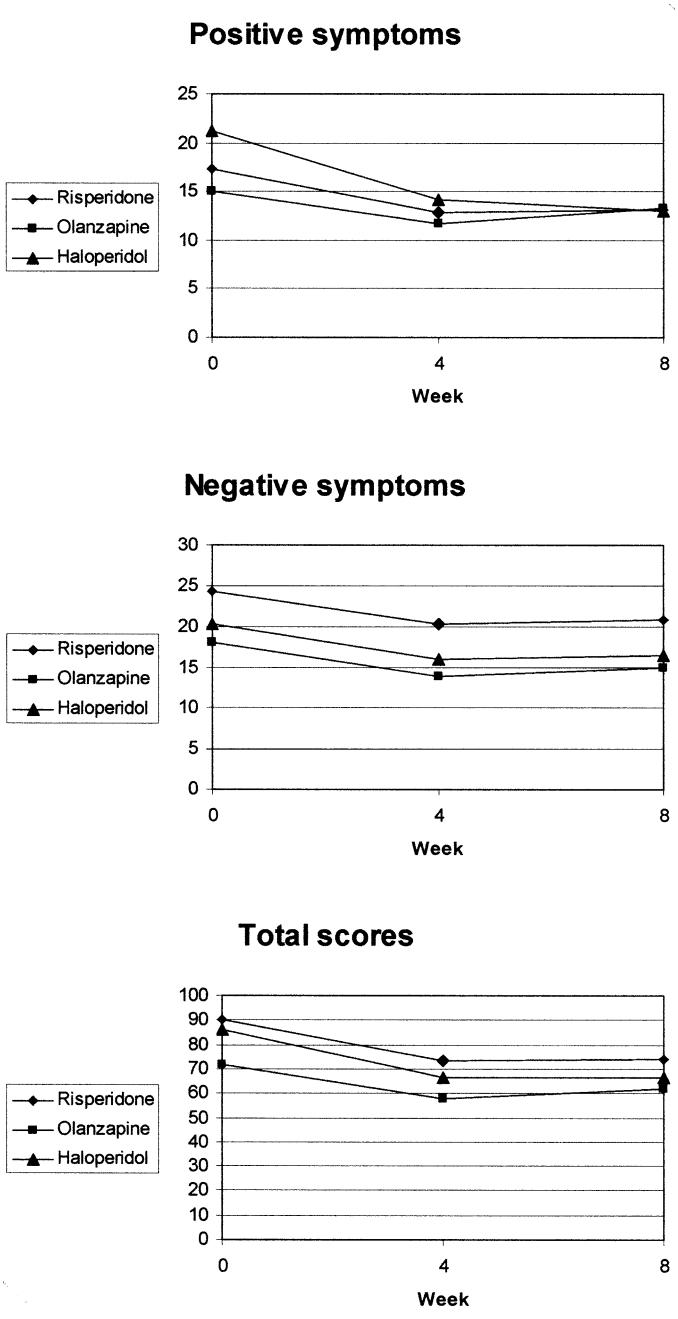

Fig. 1. PANSS scores (total, positive symptoms and negative symptoms) at baseline, week 4 and week 8 in adolescents treated with risperidone, olanzapine and haloperidol

The extrapyramidal side effects that occurred during the study period are presented in Table 5. None of the study patients had epileptic seizures. The symptoms that were observed significantly more often in patients treated with haloperidol were dystonia ($\chi^2_2 = 6.49$, $p = 0.039$), rigidity ($\chi^2_2 = 11.45$, $p < 0.01$), and akathisia ($\chi^2_2 = 11.53$, $p < 0.01$). In addition, the degree of EPS in

Table 4. Frequencies of UKU side effects in adolescent patients treated with risperidone, olanzapine and haloperidol

	Risperidone (n = 17)		Olanzapine (n = 19)		Haloperidol (n = 7)		
	n*	%	n*	%	n*	%	Chi-square
Concentration difficulties	2 (2)	11.8	7 (1)	36.8	3 (1)	42.9	3.73, p = 0.15
Increased fatigability	2 (1)	11.8	8 (2)	42.1	5 (0)	71.4	8.63, p = 0.01
Sleepiness/sedation	3 (1)	17.6	9 (2)	47.4	3 (0)	42.9	3.72, p = 0.16
Failing memory	2 (1)	11.8	7 (2)	36.8	2 (1)	28.6	3.00, p = 0.22
Depression	2 (1)	11.8	5 (1)	26.3	5 (2)	71.4	8.82, p = 0.01
Tension/inner rest	3 (1)	17.6	7 (2)	36.8	2 (1)	28.6	1.64, p = 0.44
Increased duration of sleep	4 (1)	23.5	9 (1)	47.4	3 (0)	42.9	2.29, p = 0.32
Reduced duration of sleep	1 (1)	5.9	4 (1)	21.1	0		3.11, p = 0.21
Increased dream activity	1 (0)	5.9	4 (0)	21.4	0		3.11, p = 0.21
Accommodation disturbances	1 (0)	5.9	2 (0)	10.5	0		0.92, p = 0.63
Increased salivation	5 (3)	29.4	4 (1)	21.1	1 (0)	14.3	0.73, p = 0.69
Reduced salivation	0		1 (1)	5.3	1 (0)	14.3	2.31, p = 0.31
Nausea/vomiting	1 (0)	5.9	2 (0)	10.5	1 (0)	14.3	0.48, p = 0.79
Constipation	1 (1)	5.9	3 (2)	15.8	2 (0)	28.6	2.22, p = 0.33
Micturition disturbances	3 (2)	17.6	1 (0)	5.3	1 (1)	14.3	1.40, p = 0.50
Polyuria/poydypsia	3 (1)	17.6	2 (0)	10.5	2 (1)	28.6	1.26, p = 0.53
Orthostatic dizziness	4 (1)	23.5	3 (1)	15.8	1 (1)	14.3	0.46, p = 0.79
Palpitations/tachycardia	2 (1)	11.8	4 (0)	21.1	0		2.00, p = 0.37
Pruritus	0		3 (0)	15.8	0		4.07, p = 0.13
Diminished sexual desire	1 (1)	5.9	4 (1)	21.1	1 (0)	14.3	1.72, p = 0.42

* The number of patients in whom the side effect disappeared by week 8 of treatment is shown in parenthesis

Table 5. Rate of extrapyramidal side effects in adolescent patients treated with risperidone, olanzapine and haloperidol

	Risperidone (n = 17)	Olanzapine (n = 19)	Haloperidol (n = 7)	Chi-square
Any EPS	4 (23.6%)	3 (11.8%)	4 (57.2%)	4.66, p = 0.01
Dystonia	1 (5.9%)	0	2 (28.6%)	6.48, p = 0.04
Rigidity	0	1 (5.3%)	3 (42.9%)	11.45, p = 0.003
Hypokinesia/akinesia	2 (11.8%)	1 (5.3%)	2 (28.6%)	2.70, p = 0.26
Tremor	2 (11.8%)	2 (10.5%)	1 (14.3%)	0.07, p = 0.96
Akathisia	1 (5.9%)	0	3 (42.9%)	11.52, p = 0.003

all 4 affected patients in the haloperidol group was severe enough to require lowering the dose of haloperidol and initiating anticholinergic medications. Anticholinergic medications were required in only 1 patient in the olanzapine group and 2 patients in the risperidone group. In all, 7 patients were treated with anticholinergic medications, 6 with biperiden (2 to 6 mg per day), and 2 with trihexyphenidyl (5 to 10 mg per day). Five patients were treated with lorazepam (1 to 3 mg per day) for agitation or insomnia.

Three patients (43%) treated with haloperidol reported dissatisfaction with the EPS side effects; especially upset were the 2 patients who experienced akathisia. Fourteen patients treated with olanzapine (82%) and 7 treated with risperidone (41%) were concerned about the drug-induced weight gain.

Antipsychotic treatment after the end of the study

We surveyed the medical records of the study patients to determine how many continued with study medications and how many stopped them two months after the end of the study. About two-thirds of patients treated with risperidone (10/15, 67%) and olanzapine (12/17, 71%) continued with the same treatment, but only 3 of the 7 haloperidol-treated patients did so (43%). Seven patients were switched to other antipsychotic drugs because of clinical inefficacy (risperidone- 3 patients, olanzapine- 3, and haloperidol- 1), and five patients discontinued the medication because of noncompliance (risperidone- 2, olanzapine- 2 and haloperidol- 1). Two patients were switched from haloperidol because of EPS (akathisia and parkinsonism).

Discussion

This open clinical trial is the first to compare three of the most commonly used antipsychotic medications, risperidone, olanzapine and haloperidol, in the treatment of adolescents with schizophrenia.

A significant improvement in both positive and negative symptoms was documented in all 3 groups of patients, in agreement with the few previous studies in this age group (Armenteros et al., 1997; Grcevich et al., 1996; Kumra et al., 1998; Pool et al., 1976; Sholevar et al., 2000).

The average decline in PANSS positive symptoms scores from baseline to week 8 was 11.3% for olanzapine, 24.1% for risperidone and 39.5% for haloperidol and in the negative symptoms 14.0% risperidone, 17.7% olanzapine and 19.2% haloperidol. Similar rate of improvement was reported in other neuroleptics studies in adolescents (Armenteros et al., 1997; Grcevich et al., 1996; Kumra et al., 1998) and in adults (Tran et al., 1997; Conley and Mahmoud, 2001).

Patients' clinical scores at week 8 of treatment were similar to the scores at week 4, indicating that the improvement in positive and negative symptoms peaked already at week 4. This may suggests that the improvement in the negative symptoms occurred only in the secondary ones which were a result of the positive psychotic symptoms, and not in the core negative symptoms. Otherwise, the change would have been more gradual, and not so closely associated with the degree and timing of the change in the positive symptoms. This interpretation of the findings is in line with several studies in adult schizophrenia patients (Czobor and Volavka, 1996; Tandon et al., 1993).

In our study, the clinical response to the atypical antipsychotics risperidone and olanzapine was not superior to that of haloperidol. Similar results have been reported in recent meta-analyses of studies in adults (Geddes et al., 2000; Kapur and Seeman, 2001), namely that haloperidol, in doses of less than 12 mg per day, is equally effective to olanzapine and risperidone in alleviating both the positive and negative symptoms of schizophrenia. In addition, it has been shown that not only the classical neuroleptics, but also the atypical neuroleptics, achieve a robust antipsychotic activity only at doses that occupy at least 65% of D2 receptors (Kapur and Seeman, 2001). On the basis of the dose range in our study, marked D2 blockade seems to be the major mechanism for alleviating the symptoms of schizophrenia in adolescent patients.

The fact that none of the study patients discontinued antipsychotic treatment because of side effects indicates that all 3 medications are safe and well tolerated, at least in the short term. We rated the adverse effects with the UKU to ensure that none was missed or underreported. This was particularly important in our sample, as adolescents are known to have greater difficulty communicating their concerns (AACAP, 2001). The disadvantage of the scale is that it probably overestimates the rate of side effects, for example, by attributing random occurrences of constipation or palpitations to the antipsychotic treatment (Lingjaerde et al., 1987). Although cognitive problems, such as concentration difficulties, failing memory, and depression, could be side effects, they are also inherent components of schizophrenia, and their severity changes along the course of the disease.

Increased fatigability, sedation and increased duration of sleep were very common in the patients treated with olanzapine and haloperidol, and less so in the patients given risperidone. In most cases, these side effects did not subside during the study period. Thus, in sedated schizophrenic patients, risperidone is probably the best choice.

Increased depression was noted in most of the haloperidol-treated adolescents, with a significantly greater frequency than in the atypical neuroleptic

groups. Depressive-like symptoms associated with treatment with typical antipsychotics, were described previously and may be related to the akinetic and anhedonic effects of these agents (Harrow et al., 1994). Our results are consistent with previous reports and suggest that risperidone and olanzapine are more efficacious than haloperidol for affective symptoms in patients with schizophrenia (Peuskens et al., 2000; Tollefson et al., 1999). Moreover, olanzapine and risperidone were reported to display an antidepressive activity in some psychotic patients (Weizman and Weizman, 2001).

The more common and more severe EPS in the haloperidol group may stem from the higher equivalent doses these patients received compared to the other two groups. A similar, well replicated finding has also been reported in adults (Leucht et al., 1999). It is particularly noteworthy here because adolescents are more prone to EPS (Toren et al., 1998).

The similar decline in psychotic symptoms, as measured by the PANSS, observed in all three treatment groups could demonstrate either similar efficacy of the agents or could highlights the problem with open label, non-placebo controlled trials. The sample size in our study is relatively small.

The small sample precluded the identification of small differences in drug response and side effect parameters, and the 8-week duration of the study limited the findings to the short-term. There was also no randomization in the choice of medication, and the naturalistic, open-label design was used. The EPS and depression were examined using the UKU scale items and not by specific EPS and depression scales.

In conculusion, three commonly used antipsychotic medications in adolescents with schizophrenia, olanzapine, risperidone, and haloperidol – are equally effective in treating the acute symptoms of the disease. In our study the antipsychotic effect was already prominent after 4 weeks of treatment. Haloperidol induces more severe EPS and depression than olanzapine and risperidone. Further large-scale, randomized, double-blind comparative studies are needed to obtain data sufficient for evidence-based decision making regarding which antipsychotic medication to initiate for which schizophrenic adolescent patient.

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