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ORIGINAL PAPER

Risperidone in the Treatment of Schizophrenia

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Background: Risperidone is a second generation antipsychotic agent, with potent serotonin 5-HT2A and dopamine D2 receptor blocking effects. Specifically, risperidone possesses a unique balance of serotonin and dopamine antagonism, namely that its affinity for 5-HT2A receptors is significantly greater than its affinity for D2 receptors. Risperidone is well-established medication, with the proven effects on positive and negative symptoms of schizophrenia. The aim of research was to establish the effectiveness and safety of risperidone in patients with schizophrenia. **Subjects and Methods**: The sample consisted of 60 subjects, age ranged was between 18-60 years, both genders, who met the criteria for the diagnosis various types of schizophrenia, according to ICD-10 (International Statistical Classification of Diseases). They were enrolled in the study as outpatient and inpatient setting. All subjects signed informed consent before entering into this study which had been conducted at the Psychiatric Clinic, University Clinical Center Sarajevo. Study was designed for 8-week, open-label, flexible-dose observational study. The subjects had to have a total score >-40 on Positive and Negative scale –two parts of the Positive and Negative Syndrome Scale (PANSS), and to be able to discontinue current antipsychotic medications. The primary efficacy parameter was the percent of score difference between baseline and week 8 of therapy on two above–mentioned PANSS subscales. The difference was considered as significant improvement if decrease from the baseline was 20% or more. The secondary efficacy parameter was subjective clinical evaluation of efficacy with five possible answers: very good, good, moderate, not satisfactory, not possible to evaluate. It was measured at the end of observational period by the investigator. **Results:** All 60 enrolled patients completed the study. After the 8 weeks of treatment, 54/60 patients (90%) had clinically significant improvement of 20% or more decreased total PANSS score (Positive and Negative subscale). In 6/60 patients (10%) clinical improvement was also reported with less of 20% decreased total PANSS score. The side effects were registered in 8/60 patients(13,32%). The mild extrapyramidal symptoms registered in 1/60 (1,66%) patients, whom dose of risperidone was reduced. Increase of prolactine in 7 /60 (11,66 %), patients, whose dose of risperidone also were reduced. Average weight gain was 0.84 kg. **Conclusion:** In this study Risperidone has shown very good effectiveness and safety. **Key words:** Risperidone, Schizophrenia.

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1. INTRODUCTION

The treatment of schizophrenia has been significantly improved in recent years by the introduction of second generation antipsychotics, with clinical characteristics such as propensity for or lack of motor side effects such as extrapyramidal side effects (EPS) and tardive dyskinesia, can separate second generation antipsychotics from the first generation antipsychotics. Underlying the different clinical profiles are differences in receptor binding, especially at dopamine-2 (D2) and serotonin-2A (5-HT2A) receptors. While these drugs are bound to a receptor, that receptor is blocked from the naturally occurring substance, in this case,dopamine or serotonin. The improved tolerability of second generation antipsychotics is linked to reduced D 2 receptor blockade in parts of the brain where side effects are mediated. This reduced blockade, in turn, may be linked to antagonism of 5-HT2A receptors, a drug's ability to quickly dissociate from D2 receptors, or both (1).Risperidone is a second generation antipsychotic agent, with potent serotonin 5-HT2A and dopamine D2 receptor blocking effects. Specifically, risperidone possesses a unique balance of serotonin and dopamine antagonism, namely that its affinity for 5-HT2A receptors is significantly greater than its affinity for D2 receptors (2, 3). Risperidone is well-established medication, with the proven effects on positive and negative symptoms of schizophrenia (4, 5). Risperidone have been subject to numerous studies to assess their safety, efficacy, tolerability, and patients' satisfaction and positive attitudes with treatment (6, 7, 8, 9). Risperidone is currently one of the most widely prescribed antipsychotic medications, used for both acute and long-term maintenance in schizophrenia. Risperidone fares better than first-generation antipsychotics in the treatment of negative symptoms(10). Risperidone has a higher risk of hyperprolactinemia comparable to first-generation antipsycho-

tics, but fares better than many second-generation antipsychotics with regards to metabolic side effects. The following risperidone dose dependent extrapyramidal symptoms are usually mild and reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary (11, 12). The aim of this study was to establish the effectiveness and safety of risperidone in patients with schizophrenia.

2. SUBJECTS AND METHODS

This postmarketing, 8-week, open-label, flexible-dose observational study was designed to assess the efficacy and safety of risperidone in the treatment of patients with schizophrenia. The sample consisted of 60 subjects, 34 male, 26 female, age ranged was between 18-60 years, who met the criteria for the diagnosis of various types of schizophrenia according to ICD-10 - 10th Revision). At the beginning of the study 48 subjects were in relapse, 12 subjects were in remission; further, 36 were inpatients, and 24 were outpatients. All subjects signed informed consent before entering into this study which had been conducted at the Department of Psychiatry of Clinical Center of University of Sarajevo. Also, they had to agree to discontinue current antipsychotic medications. The subjects were assessed using the following instruments: The baseline demographic characteristic of the subjects, designed by the authors. The reason for switching from previous therapy to risperidone, designed by the authors. Types of schizophrenia accoding ICD-10. The Positive and Negative syndrome scale (PANSS) for schizophrenia(13), to evaluate efficacy of risperidone in the treatment. Ratings were based on clinical interviews. Administrators of the PANSS rate the severity of 30 symptoms, 7 for positive syndrome subscale, 7 for negative syndrome subscale and 16 for general psychopathology subsale, using a 7 point ranging from 1=Absent to 7= Extreme. Only the patients with a total PANSS score (the sum of Positive and Negative subscale) at the baseline more or 40 were eligible for entering the study in outpatient and inpatient setting. The primary efficacy parameter of treatment was the percent of score difference between baseline and the end of observational period on two above - entioned PANSS subscales. The difference was considered as significant improvement if decrease from the baseline was 20% or more. The secondary efficacy parameter was subjective clinical evaluation of efficacy with five possible answers: very good, good, moderate, not satisfactory, not possible to evaluate. It was measured at the end of observational period by the investigator.

3. RESULTS

Baseline demographic characteristic of 60 subjects included in the study according age, height and weight are presented in Table 1. The reason for switching the SUBJECTS from previous therapy to risperidone: Resistant to previous antipsychotic therapy (N= 36/60; 60%); Serious side effects induced by previous therapy (N= 12/60; 20 %); Both (N=12/60, 20 %). Various types of schizophrenia of 60 included SUBJECTS in the study are presented in Table 2. The primary efficacy parameter was the difference from the baseline to the week 8 of two PANSS subscales, (sum of Positive and Negative subscales). It was determined that the difference between the baseline and week 8 of 20% or more on two PANSS subscale scores would be considered as significant clinical improvement. Positive PANSS Scale: The mean score of the all items of the positive scale was 29.87 at baseline, and 16.25 at the end of the study. The mean difference baseline to week 8 was 13.62. Negative PANSS Scale: The mean score of the all items of the negative scale was 32.88 at baseline, and 20.80 at the end of the study. The mean difference baseline to week 8 was 12.08. Sum of Positive and Negative scale mean score of the all items was 62.75 at baseline and 37.05 at the end of the study. The mean difference baseline to week 8 was 25.70 (Table 3).

Variable	N	Range	MEAN	SD
AGE (YEARS)	60	18-60	34.66	6.65
Height (cm)	60	159-192	178.46	8.26
Weight (kg)	60	58-106	84.65	16.59

Table 1. Baseline demographic characteristic of the subjects included in the study

Diagnosis	N	Percent
Schizophrenia simplex F20.6	3	5.0
Paranoid schizophrenia F20.0	30	50.0
Catatonic schizophrenia F20.2	3	5.0
Hebephrenic schizophrenia F20.1	12	20.0
Residual schizophrenia F 20.5	12	20.0
Schizophrenia total	60	Total 100.00

Table 2. Various types of schizophrenia of included SUBJECTS

The secondary efficacy parameter was subjective clinical evaluation of efficacy with five possible answers: very good, good, moderate, not satisfactory, not possible to evaluate. It was measured at the end of observational period of 8 weeks by the investigator.

Clinical Efficacy: After the 8 weeks of treatment, 54 of 60 patients (90%) had clinically significant improvement meaning that they had 20% or more decreased score of two PANSS subscales. In 6/60 patients (10%) clinical improvement was also reported with less of 20% decreased total PANSS score. Table 4 shows distribution of patients within range of the differences between the baseline and week 8 of PANSS total scores (Table 4). The average starting dose of Risperidone was 2 mg/day, and average dose at the end of the study was 4.56 mg/day. Minimal starting dose was 1.00 mg/day, and maximal starting dose was 4.00 mg/day. At the week

Variable	N	Mean Baseline	SD	Mean Week 8	SD	Mean difference baseline to week 8	SD
Positive scale	60	29.87	7.66	16.25	8.65	13.62	4.74
Negative scale	60	32.88	9.03	20.80	8.16	12.08	5.62
Positive and Negative scale	60	62.75	12.42	37.05	11.43	25.70	12.34

Table 3. The difference of positive and negative subscale scores (PANSS) scores between baseline and week 8

Difference (%)	N	Percent
0-10	3	5.0
11-20	3	5.0
20-30	18	30.0
31-40	30	50.0
41-50	6	10.0
Total	60	100.00

Table 4. The difference of PANSS total scores (Positive and negative scale) between the baseline and week 8 **p<0.01

8 minimal dose was 2.00 mg/day, and the maximal dose was 8.00 mg/day. The side effects were registered in 8/60 patients(13,32%). The mild extrapyramidal symptoms registered in 1/60 (1,66%) patients, whom dose of risperidone was reduced. Increase of prolactine in 7 /60 (11,66 %), patients, whose dose of risperidone also were reduced. Average weight gain was 0.84 kg.

4. DISCUSSION

In this observational study, results demonstrated that Risset treatment lead to clinically significant improvement (20% or more PANSS decrease) in 90 % of participants during 8 week of therapy. In the latest reviews risperidone may be more acceptable to patients with schizophrenia than antipsychotics older generation. Risperidone might be equally clinically effective as relatively high doses of haloperidol. It causes fewer adverse effects than the side-effect-prone haloperidol (14). In our observational study the mean score of the all items of the negative scale was 32.88 at baseline, and 20.80 at the end of the study. The mean difference baseline to week 8 was 12.08. This significant improvement of negative shizophrenia symptoms are comparable to numerous recent clinical trials have suggested that second-generation antipsychotic medications significantly enhance cognition in schizophrenia. In a multicenter trial comparing the novel antipsychotic risperidone with haloperidol and placebo in symptomatic schizophrenia, negative symptoms (assessed using the Positive and Negative Syndrome Scale) were reduced more by risperidone at a dose of 6, 10, and 16 mg/day than by placebo. Haloperidol at a dose of 20 mg/day was not significantly better than placebo. Risperidone 6 mg was the lowest dose that produced substantial change in negative symptoms and no increase in extrapyramidal symptoms and antiparkinsonian medication use (15, 16, 17). Many studies with second generation antipsychotics proved that clozapine and olanzapine caused the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol. The relative receptor affinities of the second generation antipsychotics for histamine H1 appear to be the most robust correlate of these clinical findings (16, 17). The results of weight gain in our study (the average weight gain was 0.84 kg) are comparable to results in other studies(18). It proves that weight gain with risperidone treatment is smaller then with other antipsychotics. Accoding the recent research switch to risperidone medication provided significant additional improvement in symptom severity, extrapyramidal side effects and need for anticholinergic medication. This suggests that one might expect better compliance in future treatment of schizophrenic patients (7). The results of our study according the side effects of risperidone are comparable to these above-mentioned results in other studies. We registered in our research the mild extrapyramidal symptoms in 1/60 (1,66%) participant whom dose of risperidone was reduced, increase of prolactine in 7 /60 (11,66 %), participants whose dose of risperidone also were reduced.

5. CONCLUSION

Risperidone appears to be very effective on positive and negative syndrom of schizophrenia, also very tolerable and safe antipsychotic. Majority of the subjects in our study were treated before with other antipsychotic medication, and potentially had saturation of its¢ receptors system with previously used antipsychotic medications. The reason for switching the subjects from previous therapy to risperidone were resistant to previous antipsychotic therapy in 60% of subjects, serious side effects induced by previous therapy in 20 %, and both of these in 20 % of subjects, so risperidone shown excellent efficacy on positive and negative syndrom of schizophrenia. The safety profile was very good, there were no serious side effects reported. The limitation of the study was non- comparative design. Anyway, this study shown that risperidone seems to be effective and safe medication in the treatment of schizophrenia.

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