FIRST GENERATION ANTIPSYCHOTICS SWITCH WITH RISPERIDONE IN THE TREATMENT OF CHRONIC SCHIZOPHRENIC PATIENTS

Irena Popović 1, Dragan Ravanic 2, Vojin Popović 1, Snežana Vladejić 1, Albina Stanojević 1 & Miodrag Stojanović 3

1Specialized Hospital for Psychiatric Disorders “Gornja Toponica” Niš, Serbia
2Department for psychiatry, Medical faculty, University of Kragujevac, Serbia
3Department for Social medicine and statistics, Medical faculty, University of Niš, Serbia

received: 13.6.2011; revised: 18.10.2011; accepted: 24.10.2011

SUMMARY

Background: Schizophrenia is a severe chronic psychiatric disorder for which treatment compliance is important in the prevention of relapse. Second generation antipsychotics (SGA), such as Risperidone, have been found to be more effective in the treatment of such patients than the high potency first generation antipsychotics (FGA). This is an open study where the same group of patients was first treated with FGA and then were switched to Risperidone, in controlled hospital conditions, after a wash-out period. The aim of the study was to examine whether patients with schizophrenia who were judged to be stable on long-term treatment with FGA would further benefit from a switch to an atypical antipsychotic drug.

Subjects and methods: Eighty hospitalized patients suffering from Schizophrenia or Schizo-affective disorder (male 54, female 26) were first treated with Haloperidol (N=60) or Fluphenazine (N=20), and then were switched to Risperidone. Their clinical state was monitored using the PANSS scale for Schizophrenia, measuring the Total PANSS score. The KLA-WANS scale for assessment of extrapyramidal syndrome (EPS) was also used. Administration and dosage of Trihexiphenidil (THF) was recorded. The study lasted for 8 weeks, with 4 screenings (Visit 0-baseline- FGA, Visits 1-3 Risperidone on Day 14, 28 and 56, respectively).

Results: The average age was 38. Patients usually suffered the paranoid form of Schizophrenia (55%). The duration of illness was more than 5 years (38.8%). During the eight-week trial on Risperidone, using the PANSS total scores, we observed clinical improvement where the therapy switch had caused an initial worsening (p<0.05). Also, the compared baseline (FGA) and last visit showed a low, but statistically significant benefit in favor of Risperidone (t=5.45, df=79, p<0.005). Intensity of EPS measured by KLA-WANS scores significantly decreased during time (F=4.115; p=0.016; Partial Eta Square=0.058). Average Trihexiphenidil doses followed Risperidone in a dose dependent manner (r=0.748, r=0.661, respectively, p<0.01) with the consequent decrease of patients needing THF corrective therapy (68.8% at the baseline toward 22.5% on last visit).

Conclusion: 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 in this population of chronic schizophrenic patients.

Key words: psychiatric status rating scales - psychotic disorders - risperidone - treatment outcome - dose response relationship

* * * * *

INTRODUCTION

The antipsychotic action of high potency first-generation antipsychotics such as Haloperidol, is essentially derived from their D2 antagonistic properties, as are their extrapyramidal side effects (EPS). Also, the efficacy of these substances is generally restricted to the positive symptoms of schizophrenia. In the 1980s, antipsychotics that block D2 and 5-HT2 receptors simultaneously were successfully developed, in line with the serotoninergic hypothesis of schizophrenia (Meltzer 1987). Risperidone, in contrast to Haloperidol, is characterized by a high antiserotonergic activity. In vitro binding studies show that Risperidone possesses a great affinity for 5-HT2A and 5-HT2 receptors. At the same time, it binds strongly to dopamine D2 and α1 and α2 adrenoceptors. With its high 5-HT2A/D2 ratio Risperidone shows the characteristic receptor profile of an atypical antipsychotic, which is a likely reason for its lower reported rate of EPS (Extrapyramidal symptoms). In addition, the lower dose-related increase in occupancy of the D2 compared with the 5-HT2A receptor is likely to influence these properties (Schotte et al. 1996). Risperidone has a lower affinity for nistrostral D2 receptors potentially contributing to the reduced probability of EPS.

The average dose of antipsychotics in the treatment of schizophrenic disorders has been considerably reduced over time. In an observational study, the average administered dose of Risperidone fell over a 5-year period, from 5-7 mg/day in 1996. to 4.5 mg/day in 2002 (Pajonk et al. 2003a, b). Other data for Risperidone indicate that the effective dose range is 4–6 mg for acute therapy and 3–4 mg for maintenance therapy (Williams 2001). This dose range is supported by findings from positron emission tomography (PET) studies investigating the D2 occupancy levels in different doses of Risperidone (Nyberg et al. 1999).
The aim of the study was to follow up the clinical and the side effects of Risperidone during time (8 weeks), on the same patient sample, also recording presence and dosage of the anticholinergic drug administration. The hypothesis to be tested was that Risperidone therapy results in at least equal clinical efficacy and a lesser degree of side effects which is dose related. Tolerability and safety of Risperidone among chronic schizophrenic patients should result in their better compliance with further ambulatory treatment, which means maintenance of the remission state.

SUBJECTS AND METHODS

Eighty hospitalized patients suffering from Schizophrenia or Schizoaffective disorder (male 54, female 26) were included in the study, diagnosed by the criteria of the International Classification of Diseases, 10th Revision (ICD-10). Mean age was 38.16±5.03 years, all of them were hospitalized in the Specialized psychiatric hospital “Gornja Toponica”, Niš, Serbia. The study was conducted during a three-month period in 2010. Patients gave their consent to participate the study in writing. The study was approved by the Local Ethics Committee, in accordance with the Helsinki Declaration. The patients were in the post-acute phase of the illness, had been hospitalized for at least for one month, and pharmacotherapy had not been changed within the last two weeks. As shown from the demographic data (Table 1), according to duration of the illness, we focused on chronic schizophrenic patients. At the start of the study, all of them were treated with one of the high potency first-generation antipsychotics, Haloperidol (N=60, average dose 6.75±1.9 mg pro die), or Fluphenazine (N=20, average dose 5.37±2.2 mg pro die), with low doses of benzodiazepines as co medication (up to 10 mg pro die). After a 3 days wash out period, in controlled hospital conditions, the atypical antipsychotic drug Risperidone was prescribed to all participants, starting from 1mg a day and titrating upwards progressively over three days, according to the clinical state.

Clinical state was monitored using the PANSS scale for Schizophrenia (Kay et al. 1987), assessing the Total PANSS score. The KLAWANS scale was used for assessment of extrapyramidal syndrome (Klawans 1969), which include 6 items (Rigidity, Tremble, Bradikinesia, Motion, Aspect, Stability). The items could be rate from 0-4, with range from 0 to maximally 24. This scale can also be used in neurology for measuring intensity of Parkinson’s disease symptoms.

Presence and dosage of the anticholinergic drug Trihexiphenidil (THF) was also recorded.

Basic screening (Visit 0, Day 0.) during FGA treatment, before the pharmacotherapy switch. Then, the therapeutic efficacy of the Risperidone was observed in next 3 visits: Visit 1- Day 14, Visit 2- Day 28., and Visit 3- Day 56., also by screening with the same scales, Risperidone dosage, need for anticholinergic therapy and doses of THF if it was administrated were all recorded.

Statistical analysis

The statistical analyses included methods of descriptive and analytical statistics: mean values with standard deviations, comparison of mean values using Student’s t-test and ANOVA for repeated measures, Pearson’s correlation test to assess dose dependence among Risperidone and Trihexiphenidile over time. Data collected were processed and analyzed by using SPSS program for Windows (version 18) and significance level was set at p<0.01 and p<0.05.

RESULTS

Demographic data are shown in Table 1. In the patient sample, the majority were male (67.5%, mean age 38.20±5.18 years), over female (32.5%, mean age 38.08±4.82 years). Most of them suffered from the Paranoid subtype of schizophrenia (55%). The length of illness was over five years equally with over 10 years (38.8% both subgroups), so that we can say that we were focused on chronic schizophrenic patients in our sample.

Table 1. Demographic characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Age(mean)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>67.5</td>
<td>38.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>32.5</td>
<td>38.1</td>
<td>4.8</td>
</tr>
<tr>
<td>SCH type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paranoid</td>
<td>44</td>
<td>55.0</td>
<td>36.4</td>
<td>3.9</td>
</tr>
<tr>
<td>hebephrenic</td>
<td>14</td>
<td>17.5</td>
<td>36.5</td>
<td>4.7</td>
</tr>
<tr>
<td>residual</td>
<td>10</td>
<td>12.5</td>
<td>46.0</td>
<td>1.8</td>
</tr>
<tr>
<td>schizoaffective disorder</td>
<td>12</td>
<td>15.0</td>
<td>40.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Lenght of illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5yrs</td>
<td>18</td>
<td>22.4</td>
<td>32.8</td>
<td>3.11</td>
</tr>
<tr>
<td>5-10yrs</td>
<td>31</td>
<td>38.8</td>
<td>36.4</td>
<td>3.23</td>
</tr>
<tr>
<td>&gt;10yrs</td>
<td>31</td>
<td>38.8</td>
<td>43.0</td>
<td>2.63</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>100</td>
<td>38.2</td>
<td>5.0</td>
</tr>
</tbody>
</table>

N = number of patients; SD = standard deviation; yrs = years
Figure 1 shows PANSS total scores and Klawans scores over time. Pillai’s Trace Test shows significant changes of the PANSS total scores over time ($F=11.432$, $p<0.001$, Partial Eta Square=0.058), as so as Within Subjects Effects with Greenhouse-Geisser sphericity modification ($F=6.827$, $p<0.001$, Partial Eta Square 0.092). Average PANSS total score at Visit 0 (PANSS0) was 68.41±8.17, on the FGA therapy (average doses of Haloperidol 6.75±1.9 mg pro die $N=60$, or Fluphenazine - $N=20$, average dose 5.37±2.2 mg pro die). After switching to Risperidone at Visit1 - PANSS1 was 78.01±8.45, at Visit 2 - PANSS2 was 73.29±9.17; at the end of the study, Visit3 - PANSS3 was the lowest, 66.90±8.61.

![Graph showing PANSS total scores and Klawans scores over time](image.png)

Table 2. Trihexiphenidile (THF) and Risperidone doses correlation

<table>
<thead>
<tr>
<th></th>
<th>VISIT 1. (day 14.)</th>
<th>VISIT 2. (day 28.)</th>
<th>VISIT 3. (day 56.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone dose (mg) (M±SD)</td>
<td>5.28±1.65</td>
<td>3.84±1.31</td>
<td>2.84±0.93</td>
</tr>
<tr>
<td>THF dose (mg) (M±SD)</td>
<td>2.68±0.94</td>
<td>3.05±0.99</td>
<td>2.06±0.72</td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>0.748**</td>
<td>0.661**</td>
<td>0.247</td>
</tr>
</tbody>
</table>

THF - trihexiphenidile; **p<0.01

The average doses of Risperidone and Trihexiphenidil (THF) were statistically correlated over time. In Table 2 we demonstrate a statistically significant Pearson’s correlation coefficient at the start of Risperidone treatment (Visit 1, $r=0.748$) and after two weeks (Visit 2, $r=0.661$ $p<0.01$).

Figure 2 describes the decrease in number of patients who needed THF therapy over time - only 22.5% of patients on Visit 3 up to 68.8% on Visit 0 (FGA therapy). Also, the Univariate logistic regression taken of the intensity of EPS measured by Klawans scores and presence of THF therapy administration (Table 3) shows a statistically high significance in all visits, particularly the FGA therapy at Visit 0 (highest Odds ratio: 4.394, 95%CI=2.273-8.492, $p<0.001$), and switch to Risperidone at Visit 1 (lowest Odds ratio: 2.074, 95%CI=1.456-2.954, $p<0.001$).
DISCUSSION

Risperidone is generally well tolerated. Its efficacy on the clinical symptoms of both chronic and acute patients with schizophrenia is as good as or better than that of conventional antipsychotics (Conley 2000). The benefits of Risperidone are evident in long-term therapy, as proved by the findings of a double-blind long-term trial (Csernansky et al. 2002). In our patient sample, after the eight-week observation of clinical Risperidone effects through PANSS total scores we observe a statistically significant improvement compared to Haloperidol or Fluphenazine medication registered on the basic measurement, whereas that FGA therapy was present for at least a two months before, and doses were not changed within two weeks before the beginning of the study. After the wash-out period, and initial worsening in clinical state measured by total PANSS score in Visit 1, when we started with Risperidone therapy, in next two visits the PANSS scores decline permanently to a stable state in the last visit, demonstrating a clinically slight but statistically significant improvement compared with the baseline.

For the indication schizophrenia, EPS is still a benchmark for the assessment of tolerability. Although it is known that Risperidone may induce EPS in a dose-dependent manner and that this may be true to a greater degree than for some other atypical antipsychotic agents, the extrapyramidal tolerability of Risperidone, even in relatively high doses, is significantly better than Haloperidol. A few studies have noticed that, at doses up to 4 mg, the EPS rate was found to be approximately equivalent to placebo or other atypical antipsychotics and is significantly lower than with conventional antipsychotics (Chouinard et al. 1993, Lemmens et al. 1999, Marder & Meibach 1994). Our data demonstrate a statistically significant decrease of EPS measured by KLAWS score over time. Intensity of extra-pyramidal side effects changes in a dose related manner when Risperidone doses decline over time, from average 5.28 mg±1.65 on the Visit 1 to average 2.84 mg±0.93 in Visit 3. Also, there is a significant correlation in average doses of Risperidone and Trihexiphenidile observed over the first month period of screening (Visit 1, Visit 2).

These results confirm our hypothesis that Risperidone is a potent antipsychotic drug with therapeutic efficacy even better than conventional antipsychotics, but with less side effects. Lack of absence of a comparative group of patients who would have maintained the FGA therapy restrict the authors in making the conclusion that switching to Risperidone is the only solution for the patients. It is certain that lowering FGA doses should result in EPS decrease, but disturbances in the clinical state would need to be followed and then compared to the Risperidone group.

Not only lower doses but low level of necessity for THF administration was a benefit of Risperidone therapy. Our results showed statistically the highest ratio between intensity of EPS and present Trihexiphenidil administration during the FGA treatment (Visit 0, Day 0), and the lowest ratio after switch to Risperidone (Visit 1, Day 14) respectively, whereas the average dose of Risperidone was highest. Davies et al. (1998) conducted a meta-analysis of six randomized double-blind comparative trials. The analysis revealed that the use of Risperidone in patients with chronic schizophrenia was associated with a significantly higher response rate, lower rate of concomitant anticholinergic medication, as so a lower relapse rate compared with Haloperidol.

Limitations of our study such as the small patient sample, the absence of a comparative group of patients and the need for monitoring PANSS subscales, especially for negative schizophrenia symptoms, suggest the need for further investigation in those directions. Apart from the fact that during the study time we did not observe any galactorrhea, lack of measuring of the prolactin serum levels is also one of the study limitations.

CONCLUSION

This was an open study whose aim was to establish whether psychopharmacotherapy switch from FGA to SGA in chronic schizophrenic patients resulted in at least equal clinical effects, side effects or corrective therapy administration needs. Despite a lack of blinding, on eighty examined patients in two months follow up period, we confirmed our hypothesis and demonstrated...
some further benefits for patients such as less intensity of extrapyramidal side effects, less need for corrective therapy. This data encourages our attitude, based also in clinical experience, that Risperidone administration in long-term schizophrenic patients as a first choice pharmacotherapy (also recommended by our National board of health) provides a much better quality of life for this category of patients.

REFERENCES


