An Open Trial of Risperidone in the Treatment of Schizophrenia In the University of Malaya Medical Centre

Stephen T. Jambunathan, Aili Hanim Hashim

Objective: To apalyze the pattern of use and outcome of patients with Schizophrenia treated with Risperidone over a minimum period of one year In an open label longitudinal descriptive study.

Key words: Treatment of psychotic disorders, risperidone, Asian patients, **CGI, GE**

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Methods: The first 94 patients aged 14 — 72 years with schizophrenia were recruited from the University of Malaya Medical Centre. Patients were treated with risperidone and assessed at baseline (week 0), week 1, week 4, week 24, and week 52. Data was collected using the Risperidone Study Questionnaire. The response was assessed using the Clinical Global Impression (CGI) and Global Evaluation (GE) scales and the rate ofreduction ofnumberofhospitalization comparing the year before and after the onset of treatment. The outcome was assessed by evaluation -of factors leading to discontinuation of treatment. Safety was assessed by investigating the side effects that led to discontinuation of treatment and the eventual outcome of all patients.

Results: 62 patients with a mean age of 33.7 ± 12.0 yrs (range 14 to 72) were analyzed. The sex distribution was 29 male patients (46.8%) and 33 femalepatients(53.2%) with racial distributionbeing 34 Chinese (54.8%),16Malay(25.8%)and 12Indian patients (19.4%). Out of 94 patients put on risperidone, 62(66.0%) were still on medication after one year. The initial clinical status of the recruited patients were treatment refractory (42%), chronic controlled (12%), acute exacerbation (21%), BPS prone (15%), 1° episode (2%), elective switch-over (8%) and with combination of reasons (15%). Over aperiod ofone year, there was a discontinuation rate of34.0%. Mean CGI score reduced from 4.9 f 1.0 at week 0 (baseline) to 2.5 f 0.8 at week 52 (endpoint), p < 0.001. Mean Global Evaluation by Investigator (GEI) score improved from 5.7 f 0.9 at week 4 (baseline) to 6.5 * 0.9 at week 52 (endpoint), p 0.001. Mean Global Evaluation by Patient (GEP) score improved from 5.7 ± 0.9 at week 4 (baseline) to 6.5 t 1.0 at week 52 (endpoint), P ᶜ 0.001. There was a 76.9% reduction in the number of admissions one year post-treatment (endpoint) as compared to baseline of the study, p ᶜ 0.001.

Conclusions: Overall, the therapy of schizophrenia with risperidone was significantly effective and safe. However in order to maximize patient benefit doctors should take into consideration various influencing factors that may lead to early discontinuation of the medication.

Introduction

The advent ofantipsychotics began with the discovery of reserpine, a constituent of the Rawolfia shrub which was found to be effective in the treatment of psychosis. In 1952, chlorpromazine was discovered as an effective antipsychotic and this was followed by the introduction of many other antipsychotic drugs. The use of these drugs began to revolutionize the treatment of psychosis with 50% - 75% of the patients showing significant clinical response. However, the early antipsychotics also have many major limitations such as extrapyramidal side effects, neuroleptic malignant syndrome and tardive dyskinesia. In addition, these drugs are not effective in the treatment of the negative symptoms of schizophrenia. There is also a h igh percentage ofnon-responders which is a major public health concern

Stephen T. Jambunathan, Lecturer, Dept. of Psychological Medicine, University Malaya Medical Centre, Kuala Lumpur.

because of the debilitating effects of the illness.

The high incidence ofextrapyramidal symptoms (EPS) with the conventional antipsychotics often• lead to poor compliance and thus an increased risk of relapse. Approximately 20% - 30% of patients develop tardive dyskinesia (TD) and about 0.5% - 1.5% suffer from neuroleptic malignant syndrome (1). The need for safer and better drugs led to the discovery of atypical or novel antipsychotics such as clozapine, risperidone, olanzapine, sertindole, zotepine, quetiapine and ziprasidone (2,3). With the discovery of numerous atypical antipsychotics, the clinical implications have increased tremendously.

We now have more effective medications for the treatment refractory schizophrenia and for the treatment of negative symptoms. Compliance has increased due to better response, improved insight, find better side effect profile. Patients on atypical antipsychotics have a much lesser risk of developing tardive dyskinesia (TD). In addition, in many cases, a reduction in TD has been reported (4,5,6). With a lower incidence ofEPS, the need for anticholinergics has been greatly reduced. These antipsychotics are therefore more appropriate for patients with organic brain syndromes, who are more susceptible to the side effects ofanticholinergics. Anticholinergics have also been implicated as the cause of significant cognitive deficits in patients with schizophrenia (7). Apart from a decreased need for anticholinergics, atypical antipsychotics also play a role in the amelioration of neurocognitive deficits in schizophrenia (8).

Studies with ritanserin, a specific $5HT_2$ receptor antagonist in the early 1980's demonstrated the role of$5HT_2$ receptorantagonism in ameliorating negative symptoms and decreasing the incidence ofEPS. With further research, the Serotonin-Dopamine Antagonist (SDA) group of antipsychotics was discovered. In 1984, risperidone was chosen for further testing and was first used in the USA in 1994. This drug was introduced in Malaysia in January 1997. Risperidone belongs to anew group of drugs called benzisoxazole derivatives. It acts through D_2 receptor antagonism in the mesolimbic pathway leading to the reduction of positive symptoms. $5HT_2$ receptor antagonism leads to the reduction of negative and affective symptoms, as well as increases dopamine in the nigrostriatal region thus resulting in a reduction of EPS (9). With the serotonin-dopamine antagonism mechanism of action, risperidone is said to be more effective than older antipsychotics. It is also more tolerable due to theadd iti onal advantage of having no affinity to the cholinergic muscarinic receptors.

Objectives of the study

The aim of the study is to assess the following:

1. The various indications of use of Risperidone.
2. The efficacy in terms of doctor and patient satisfaction.
3. The outcome in terms of side effects, dosages and reduction in the rate of re-hospitalization.
4. Methods.ofmore effective switching over from one antipsychotic to another.
5. The varying prescribing philosophies and their shortcomings in order to improve on the methods of use of atypical antipsychotics.

Methods

This was a descriptive, 52-week, open label flexible dose study designed to evaluate the efficacy and safety of risperidone in the treatment of patients with schizophrenia in the University of Malaya Medical Centre.

Patients

Male and Female adult inpatients and outpatients diagnosed according to DSM IV criteria for schizophrenia disorder were recruited. As this was an open labeled trial of a then new drug, the first hundred patients put on Risperidone were included.

Assessment Parameters

The primary efficacy parameters wereClinical Global Impression (CGI) and Global Evaluation (GE) by the investigators and patients.

Secondary efficacy parameters were evaluation of factors leading to discontinuation of treatment and effectiveness ofrisperidone in terms ofreduction in the number of hospitalizations.

The safety and tolerability of risperidone was assessed by monitoring the side effects that led to discontinuation.

Treatment and Assessment Schedule

The first 94 patients put on risperidone were followed up and assessed at baseline (week 0), week 1, week 4, week 24, and week 52. They were assessed by the same doctors using the Clinical Global Impression (CGI) and Global Evaluation (GE) scales. Data collected also included thenumberofadmissions one year prior to and one year after starting risperidone, diagnosis, initial clinical status, as well as side effects. The side effects noted were based on subjective and objective observations. For patients who discontinued UnNatmentwith risperidone, the reasons for stopping were noted and data concerning the previous medication, titration schedule and dosages were collected. Data was collected using the Risperidone Study Questionnaire. Changes in side effects encountered while on the previous antipsychotics were also noted.

Statistical Analysis

Measured values are expressed as means +/-SD (standard deviation). Characteristics and clinical ratings were compared using Wilcoxon's signed rank test. All statistical tests were interpreted at the 5% significance level (two-tailed).
Additional statistical analysis included summaries of demographics and baseline data. Demographic variables (age, sex, race, initial clinical status) were summarized using frequency tables.

Results

In total 94 patients entered the study and data from 62 patients were used for statistical analysis as 32 patients discontinued. Reasons for treatment discontinuation will be discussed in thenextsection.

Demographics

Of the 62 evaluated patients, 34 were Chinese (54.8%), 16 were Malays (25.8%), and 12 were Indians (19.4%). Thirty-three patients (53.2%)were female and 29 patients (46.8%) were male.
The initial clinical status were treatment refractory (42%), chronic controlled (42%), acute exacerbation (21%), EPS prone (15%),1 episode (2%), elective switch-over (8%) and with combination of reasons (1.5%). Out of the 62 patients with schizophrenia, 42 patients (67.7%) were treatment refractory. Eleven patients of the treatment refractory group discontinued the trial while 31 patients (73.8%) completed the one-year treatment. The patients mean age was 33.7 ± 11.9 yrs. (range 14 to 72). Risperidone mean final dosage was 4.3 + 1.8 mg (mode = 4 mg).

Efficacy Analysis

Primary Parameters

Mean CGI score decreased from 4.9 ± 1.0 at week 0 (baseline) to 2.5 t 0.8 at week 52 (endpoint), $p < 0.001$. This was an overallreduction of49.0%. There was a significant reduction in the CGI scores when comparing the scores at week 0 with those at week 1, 4, 26 and 52, $p < 0.001$. A comparison ofthe mean CGI scores indicated that the maximum reduction in CGI scores occurred within the first 26 weeks. The mean Global Evaluation by Investigator (GET) score increased from 5.7 ± 0.9 at week 4 (baseline) to 6.5 t 0.9 at week 52 (endpoint), $p < 0.001$. This was an overall improvement of 14.0%. Mean Global Evaluation by Patient (GEP) score increased from 5.7±0.9 atweek4to 6.5* 1.0 atweek52 (endpoint), $p < 0.001$. This was an overall improvement of 14.0%.

Table 1 • CGI.and GE whose mean (:SD) clinical rating were reducedlmproved significantly

Item	Baseline	Endpoint
CGI	4.9±1.0	2.5±0.8
GEI	57±09	65±09***
GEP	5.7±0.9	6.5t1.0

CGI = Clinical Global Impression
GEI = Global Evaluation by Investigator
GEP - Global Evaluation by Patient
•" =p<0.001

Secondary Parameters

There was a 34.0% (n=32) discontinuation rate of risperidone treatment with 37.5% (n = 12) reported as having poor response, 3.1% (n = 1) having galactorrhea or amenorhea, 6.3% (n = 2) having headache, 3.1%(n = 1) died of asthma, 3.1%(n=1) having diarrhea, 3.1%(n = 1) having blurred vision, 3.1% (n = 1) having palpitations, 9.4% (n = 3) defaulted on follow-up, 15.6% (n = 5) due to cost factor, 15.7% (n = 5) having persistent EPS. Nine patients (28.1%) discontinued within the first month.

Of the 12 patients (37.5%) reported as poor responders, 10 patients (83.3%) were classified as having treatment refractory schizophrenia. Among these 10 patients who were treatment refractory, 4 patients were on risperidone 2mg b.d. for a period ranging from one to six months, 2 patients were on risperidone 3mg b.d. for a period of one to three months, 2 patients were on risperidone 4mg b.d. for a period of six months and 2 patients were on risperidone4mg b.d. and haloperidol 30mg/day.

There was a 76.9% reduction in the number of admissions one year post-treatment (endpoint) as compared to week 0 (baseline), $p < 0.001$.
Of the 94 patients put on risperidone, 11 patients (11.7%) discontinued the treatment because of side effects. Side effects reported but did not lead to discontinuation were weight gain (10 kg) ($n = 1$), tremors ($n = 1$), salivation ($n = 1$), transient allopecia ($n = 1$) and transient amenorrhoea ($n = 2$).

7 patients were put on risperidone due to the presence of tardive dyskinesia with 6 having a reduction in symptoms and one patient having no change. 5 patients were put on risperidone due to prolactin-related side effects caused by the previous neuroleptic with I patient completely recovering while 3 patients showed partial. improvement.

Discussion

From this study, it was seen that risperidone was significantly effective in the treatment of schizophrenia. Based on the CGI and GE scores, 67.5% ofthepatients with schizophrenia and 73.8% of the patients diagnosed as treatment refractory schizophrenia responded to the treatment.

As mentioned earlier, there was a 73.8% responder rate in treatment refractory schizophrenia in terms ofpatient and doctor satisfaction . In a study o f 74 patients by Addington et. al., there was a 63.5% drop-out rate over a one-year period (16). In this study, the drop out rate among treatment refractory patients was 26.2%. The significantly lower rate found here may be due to varying criteria used to define treatment refractory. The criteria for treatment refractory in this study was taken from the Food and Drug Administration (FDA) guidelines for the treatment of treatment-resistant schizophrenia. Treatment resistance is defined as the failure to respond to two adequate antipsychotics in trials over a minimum period offour to six weeks each with a dosage equivalent to 400mg per day of chlorpromazine, adequate for blocking 80% to 90% ofdopamine receptors (14). Similarly in other studies, risperidone was found to be significantly effective in treating refractory patients (10,15,16).

Compliance with antipsychotic medication is another important factor in the maintenance of the well being ofpatients. Factors influencing compliance are persistent psychosis, poor insight by patient and care givers, intolerable side effects and cognitive dysfunction (4). Risperidone increases patient compliance not only by reducing the severity of psychosis butalso because ofits low incidence oflow side effects (3,16,17). Out of the 94 patients put on risperidone, 11 patients (11.7%) discontinued the treatment due to side effects. In relation to this low side effect profile, 7 patients were switched to risperidone due to the presence oftardive dyskinesia (TD). 6 of the patients showed a reduction in TD within six months of using risperidone. One patient reported no change in the severity of TD. Of the 6 patients who demonstrated improvement in TD, 2 patients had complete cessation of the oro-buccal movement. Similar findings of improvement of TD have been reported in other studies (4,5,6).

Therewas a 34.0% discontinuation ofrisperidone treatment in this study. The duration of concomitant medications (antipsychotics and anticholinergics), duration of study with risperidone before discontinuation, and duration of the switch-over period were examined.

6 patients who showed poor response possibly might have had symptoms of breakthrough or rebound psychosis as the previous antipsychotic was withdrawn by the first week. Anotherpossible cause for the failure of treatment is the occurrence of ' cholinergic rebound'. This occurs when a low potency antipsychotic or an anticholinergic medication is withdrawn abruptly. This phenomenon is characterized by changes in mental status such as worsening psychosis, restlessness, agitation and insomnia. Patients may also complain of altered bowel motility, sialorrhea and excessive perspiration (5,18,19). Apart from the possibility of true poor response, because ofthe short switching-over period, the possibility of rebound psychosis, cholinergic rebound or agitation due to residual or reemergence of EPS should be considered (20). In these cases, a

longer switch-over period might have been more appropriate in order to prevent these avoidable causes ofthe discontinuation. A longer continuation of the anticholinezgics may also help in controlling the residual EPS and help patients cope with the transient side effects of the newer medication. One study involving 1,283 patients on risperidone showed that there wag a lower rate of discontinuation when patients were put on risperidone more gradually with dose increments of risperidone between 0.5 —2 mg per day. In that study there was a higher rate of discontinuation when patients were put on dose increments of 2 — 4mg per day. The study also showed that patients put through a longer period of "switching-over' had a better outcome (30). In this study, as mentioned earlier, 10 out of 32 patients who discontinued treatment (31.3%) geased all other medications by the first week suggesting that the switch-over period was too brief.

In this study, one patient developed galactoahoea and amenorrhoea. Galactorrhoea and amenorrhoea can occur as a result of raised prolactin secondary to dopamine antagonism. Dopamine is the prolactin inhibiting factor (PIF) that controls the release of prolactin from the anterior pituitary. Other stpdies have shown the incidence of prolactin related side effects with risperidone to be between 0.8% to 9% (21,22,23). Another side effect reported was palpitations. One patient developed this symptom when on 4mg daily after a period of one month. The incidence of palpitations was 14.4% and 22.7% (23,24) in two separate studies. In comparison, the incidence of palpitations was relatively low in this study (1%).

• Studies have shown that the average dosage of risperidone used was between 4 — 8mg per day with one study suggesting the optimal dose to be 6mg per day(12,17,26,27). In this study, themean final dose was 4.3 mg per day with the mode being 4mg per day. In treatment-resistant schizophrenia where patients require high doses of antipsychotics of at least two different groups, the study of risperidone of only 4mg per day could be considered inadequate. In view of treatment resistance, risperidone could have been used at a higher dosage and fora longer period of time before being discontinued (12,26). One study showed that patients continued to show improvement even after 32 weeks (24). Based on the CGI and GE scores as seen in this study, it is evident that our patients continued to show significant improvement up to 6 months, indicating that in addition to having a short onset of efficacy, risperidone continues to improve symptoms on a more gradual basis.

During this study, two patients were put on 6mg of risperidone daily for a period of one and three months respectively. They were on a previous dosage of chlorpromazine 600mg and 1700mg daily respectively.. Although there is no suggested equivalent dose ofrisperidone as compared to older antipsychotics, nor a minimum period of study beforepoorresponse can be claimed, ahigherdosage of risperidone is indicated when there is a lack of adequate response to a lower dose. Previous needs for higher doses ofneuroleptics too could indicate the need for higher doses ofrisperidone. A longer treatment period would have been optimum for these patients to benefit optimally from risperidone therapy.

A total of five patients discontinued treatment because of persisting EPS. Three did not administer any anticholinergics after stopping the previous antipsychotic, while one patient who wasneuroleptic naive took risperidone 4mg daily without any anticholinergic medication. In the above-mentioned four patients; adequate steps had not been taken to prevent the re-emergence ofEPS or prevent the initial transient intolerance ofrisperidone. The fifth patient could not tolerate risperidone despite adequate anticholinergics for approximately 2 months. Two studies have shown that approximately 4.8% to 20% of patients require anticholinergics concomitant to risperidone treatment (12,21).

Switching patients from one antipsychotic to another is sometimes necessary because ofinadequate or incomplete therapeutic response or intolerable side effects. Special precautions are necessary when switching antipsychotics especially from a low potency antipsychotic to a newer or atypical type. This is because of the possibility of a 'cholinergic rebound' which may mimic psychosis in its clinical presentation or lead to a relapse due to the resulting poor compliance (18,20). Neuroleptic intolerance as such could be possibly due to true intolerance or lack ofadequate anticholinergics medication.Inthis study, three out offive patients who complained ofpersisting EPS, and six out of twelve who had poor response, discontinued risperidone prematurely due to the persisting side effects and inadequate dosing that could have been prevented respectively. With the advent of atypical antipsychotics, the increasing

'number of patients undergoing the process of switching over to these newer medications will also be subjected to a higher risk ofrelapses ifthe switch-over is not done properly with appropriate precautions being observed.

Psychoeducation is another important issue that needs to be emphasized before the switch-over is made. The patient and his or her family should be made aware of the day to day consequences of symptom change and their effects on relationships, jobs and ability to function. The family and physician should be prepared to spend more time with the patient. More rehabilitative services are needed in keeping with expectations of increased recovery with the increased use of atypical antipsychotics. These changes although very much desired and expected could paradoxically become a stressor ifnot managed, eventually causing a relapse. Changes in symptoms and side effects should be explained carefully. Symptoms may flare up during the period of switching over as a result ofthe withdrawal ofthe previousneuroleptic. Transient increase in side effects too may occur especially during the initial phase. The patient and family should be educated on these possibilities before embarking on a treatment. It is important to explain to the family that improvement may be slow and that the degree ofimprovement may be limited as the response to a new drug is never fully predictable.

In this local setting, another important factor is the presence of differing "prescribing philosophy". Patients in the Kuala Lumpur and Selangor region have access to three different psychiatric institutes: the Kuala Lumpur Hospital, University of Malaya Medical Centre and the Ulu Kinta Hospital. Often, patients are admitted in one hospital with a subsequent follow.-up in another hosp ital. Very often, the reasons for a change in medication are not known by the subsequent following up doctor. Medications deemed as ineffective by one doctor may not have been in keeping with the practice of the other doctor. Unfortunately, the lack of continuity of treatment for the more difficult patients or those requiring longerperiodofhospitalization can leadto inadequate evaluation ofany one medication. Considering other compounding factors such as inadequate dosing, reemergence of side effects from the previous medication and the premature discontinuation due to transient side effects, it is therefore necessary to extend the period ofevaluation ofa drug while using anticholinergics and perhaps anxiolytics at the same time to deal with the side effects caused by the previous medication.

Limitations of this study

This study was affected by the following limitations. Firstly, the CGI and GEI assessments made by the treating doctor are subjected to biases of the doctor. Secondly, there was no matched control group to compare the varying responses to risperidone. Thirdly, changes in the positive and negative symptoms were not evaluated. Lastly, this study was not double blinded thus the results were subjected to biases.

Conclusion

In this study the treating doctor and the patient were both satisfied with the response seen with a statistically significant reduction in the CGI and GE scores by both parties and also a 76.9% reduction in the number of hospitalizations ($p<0.001$). Risperidone was also significantly effective in the treatmentoftreatment refractory Schizophrenia with a 73.8 % response rate.

The discontinuation oftreatment (34%) was due to various factors such as side effects, poor response and persistent EPS. There was a low incidence (11%) of discontinuation due to side effects and a low incidence ofEPS (5%). Some ofthese problems could have been avoided had the patients been put on adequate anticholinergics for the persistent EPS and a higher dose ofRisperidone for a longer period for the poor responders. Possible causes for the discontinuation also include breakthrough psychosis and cholinergic rebound often seen when switching over of treatment is done over too short period.

Based on the results of this study, Risperidone may have a role in the reduction o f tardive dyskinesia in some patients. However more evidence has to be found to support this finding. Over the one year on Risperidone there were no reports of patients developing tardive dyskinesia. The treatment with risperidone was safe as no serious side effects occurred.

Overall, based on these observations, the therapy with risperidone was highly effective and safe. Finally, considering the various influencing factors on the response of a patient to treatment as seen in this

study, it is important for us to have a more complete approach when using a particular medicine or switching a patient from one medication to another. The factors to be considered here is described in a 6 D approach. The "Delivery" of the medication in terms of compliance is the first factor to consider. "Dose" and "Duration" of the drug used, the "Drug" efficacy and eventually the "Diagnosis" are also factors to be considered when response to treatment is not satisfactory.. Finally, the "Distress" faced by the patient in terms ofpsychosocial stressors should be taken into consideration from the Very beginning as that is something that can perpetuate an illness often rendering a patient to be treatment refractory.

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