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Risperidone in the Treatment of First Episode Psychosis

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ABSTRACT

Objective: To evaluate the efficacy and safety of risperidone in Singapore patients with first-episode psychosis in an eight-week open label prospective study.

Method: Previously untreated male and female patients aged 18 - 65 with DSM IV schizophreniform disorder or DSM IV schizophrenia for no longer than 12 months were recruited from Woodbridge Hospital and Geylang Psychiatric Outpatient Clinic. Patients were treated with risperidone for 56 days. Outcome was assessed with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression scale (CGI). Safety was assessed by monitoring of vital signs and by comparing the frequency of adverse events (AEs) before and after treatment.

Results: 24 patients with a mean age of 33.29 ± 9.12 years and a mean duration of illness of 166.5 ± 111.4 days (median 180 days) were included. The mean risperidone dosage was 2.7 mg ± 1.0 at day 56. Mean PANSS total scores reduced by 50.21% from 88.29 ± 21.55 at baseline to 43.96 ± 7.5 at endpoint ($p < 0.001$). The responder rate (≧ 20% reduction in the total PANSS score) was 87.5%. 13 patients (54.2%) exhibited a 50% or greater reduction in total PANSS score. Except for item G5 (mannerisms and posturing) all single PANSS items were reduced significantly. The CGI scores of all patients improved at endpoint. No serious adverse events were reported.

Conclusions: Overall the therapy of first-episode psychosis patients with risperidone was effective and safe.

Keywords: Treatment of first-episode psychosis, risperidone, Asian patients, PANSS, CGI

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INTRODUCTION

Risperidone is a novel benzisoxazole antipsychotic agent with potent serotonin 5-HT2A and dopamine D2 receptor blocking effects. Risperidone has been shown in a series of six to eight-week double blind trials[1-3] to improve the positive and negative symptoms of schizophrenia measured by the PANSS score. A previous study conducted in Singapore at Woodbridge Hospital revealed the efficacy and safety of risperidone in patients with a longstanding diagnosis of schizophrenia[4].

AIM

The aim of this study was to evaluate the efficacy and safety of risperidone in patients with first episode psychosis over an eight-week treatment period.

PATIENTS AND METHODS

This was a Phase IV, eight-week, open label, flexible dose study. Male and female inpatients and outpatients aged 18 - 65 years fulfilling criteria for DSM-IV schizophreniform disorder or DSM IV schizophrenia with an illness duration of no longer than 12 months were recruited into the study. Except for emergency treatment with antipsychotics for a maximum period of three days, patients had not previously ben treated with antipsychotic drugs. Written informed consent was obtained. Pregnant and lactating female patients were excluded from the study. Other exclusion criteria were current and clinically relevant organic, neurological or cardiovascular disease, alcohol or drug abuse within the last 12 months and emergency antipsychotic treatment lasting for more than three days prior to study inclusion.

The primary efficacy parameters were shift of the total PANSS score from baseline (visit 1) to endpoint (visit 5) and the percentage of subjects showing clinical improvement as measured on the PANSS scale. Clinical improvement was defined as ≧ 20% reduction in the total PANSS score.

Secondary efficacy parameters were:

- Shift from baseline to endpoint of the PANSS Positive Subscale Score
- Shift from baseline to endpoint of the PANSS Negative Subscale Score

- Shift from baseline to endpoint of the PANSS General Psychopathology Subscale Score
- The overall severity, measured in the Clinical Global Impression Scale
- The overall change, measured in the Clinical Global Impression Scale

The safety and tolerability of risperidone was assessed by monitoring the vital signs, the body weight and the occurrence of adverse events which were recorded over the five visits. The adverse events monitored were insomnia, agitation, anxiety, headache, somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea, blurred vision, erectile dysfunction, ejaculatory dysfunction, rhinitis, rash and "others".

The patients were scheduled for five visits: visit 1 (screening and baseline, day 0); visit 2 (day 7); visit 3 (day 14); visit 4 (day 28); and visit 5 (day 56, end of treatment). At day 0 patients were assessed for eligibility and after inclusion treated with risperidone 0.5 mg b.d. or 1 mg o.d. in the morning (0800 hours) or evening (2000 hours) at the investigators discretion. The chosen time of dosing should, if possible, have remained constant throughout the trial. Starting on Day 8, the dosage of risperidone could be increased by increments of 0.5 mg/day to 1 mg/day, but no more than 1 mg/day per week depending on the patient's response to the therapy. The maximum dose was 6 mg per day. If the patient had reached this maximum dose and he/she did not show sufficient response (condition of patient unchanged or worsened in the opinion of the investigator) and the patient had no extrapyramidal side effects (EPS), the dose could be further increased by 1 mg weekly up to a maximum of 8 mg per day.

Except for the study medication, no other antipsychotic drugs were allowed. If a subject required sedation, benzodiazepines were allowed at the minimum doses necessary. Benzhexol was allowed if needed for the treatment of extrapyramidal symptoms.

The statistical comparison of symptom scores before and after treatment was done by means of non-parametric tests, the Wilcoxon matched pairs signed rank test. All statistical tests were interpreted at the 5% significance level (two-tailed). All numerical results were expressed as means +/-SD. Patients were analysed on an intent-to-treat basis. Missing data were carried forward for the main efficacy evaluation according to intention-to-treat policy.

RESULTS

A total of 25 patients entered the trial but only data from 24 were used for statistical analysis as one patient was a protocol violator. This patient had a history of schizophrenia for more than 12 months. 18 patients returned for all visits and had the PANSS scores taken for all five visits as asked for in the protocol. Four patients did not return for the last visit and had only four PANSS scores taken, one patient did not return after visit 3 and had only three PANSS scores taken and one patient did not return after visit 2 and had only two PANSS scores taken.

Of the 24 patients, 19 were Chinese (79.2%), 3 were Malay (12.5%), and 2 were Indian (8.3%). 8 patients (33.3%) were female and 16 patients (66.7%) were male. 18 patients had schizophrenia and 6 patients had schizophreniform disorder. The mean age was 33.29 $\pm$ 9.12 years (range 21 to 57). The mean duration of illness was 166.5 $\pm$ 111.4 days median of 180 days (range 8 to 360), with a mean age of onset at 33.21 $\pm$ 9.18 years (range 21 to 57).

The risperidone dosage increased from 1.0 mg to 2.7 mg $\pm$ 1.0 ($p<0.001$). No patient needed a dose higher than 4 mg/day. Nine subjects received benzodiazepines (five patients diazepam and four patients lorazepam) at baseline. In six patients, the benzodiazepine could be withdrawn throughout the study course. Four patients developed mild extrapyramidal symptoms (dyskinesia and parkinsonism) and three of those required medication (benzhexol 2 mg/day).

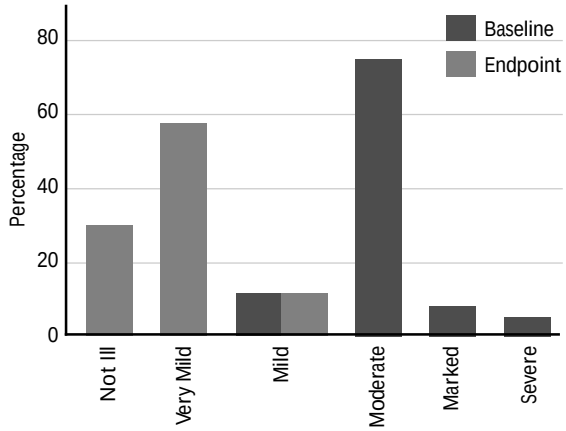
EFFICACY

The PANSS total scores were reduced from a mean of 88.29 $\pm$ 21.55 (Min 50, Max 153) at baseline to 43.96 $\pm$ 7.5 (Min 33, Max 58) at endpoint ($p<0.001$). This was an overall reduction of 50.21%.

Responders were defined as subjects showing clinical improvement with a reduction in the total PANSS score of 20% or more between baseline and endpoint. The responder rate was 21 of 24 patients or 87.5%. 13 patients (54.2%) exhibited a 50% or greater reduction in total PANSS score. There were no differences in age, age of onset age, duration of illness, mean daily dose between responders or non-responders. However there was a significant difference for the mean PANSS total score at baseline with 92.14 $\pm$ 20.07 for responders and 61.33 $\pm$ 8.08 for non-responders ($p=0.014$) i.e. the responders were more ill at the beginning of treatment than non-responders.

The individual PANSS positive subscale scores were reduced from a mean of 2.88 $\pm$ 1.50 (Min 1, Max 6) at baseline to 1.36 $\pm$ 0.72 (Min 1, Max 4) at endpoint ($p<0.001$). This was an overall reduction of 52.78% in the individual subscale scores. The individual PANSS negative subscale scores were reduced from a mean of 2.95 $\pm$ 1.27 (Min 1, Max 6) at baseline to 1.57 $\pm$ 0.82 (Min 1, Max 4) at endpoint ($p<0.001$). This was an overall reduction of 46.78% in the individual subscale scores. The individual PANSS general psychopathology

Fig. 1 Clinical Global Impression at baseline (Visit 1) and endpoint (Visit 5).



subscale scores were reduced from a mean of 2.61 ± 1.37 (Min 1, Max 6) at baseline to 1.26 ± 0.64 (Min 1, Max 6) at endpoint ($p<0.001$). This means an overall reduction of 51.72% in the individual subscale scores.

The scores for the Clinical Global Impression Scale (Fig.1) indicated that all of the patients improved at endpoint. 15 patients (62.5%) were very much improved, 8 patients (33.3%) much improved and 1 patient (4.2%) minimally improved.

SAFETY ANALYSIS

There was no significant change in the mean systolic and diastolic blood pressures and the mean heart rate. However, there was an increase in the mean body weight from 55.9 ± 12.9 at baseline to 57.3 ± 12.4 at the endpoint ($p=0.09$). The total number of adverse events experienced decreased over the course of the study from 47 to 22. The reduction occurred in anxiety (reduced from 5 to 1), insomnia (reduced from 9 to 1) and impaired concentration (reduced from 11 to 4). No serious adverse events were reported and no adverse event led to withdrawal from the study.

DISCUSSION

Compliance with antipsychotic medication is likely to have a strong influence on patients' attitude towards medication. Given that many patients with first episode psychosis will require continuous and possibly lifelong medication to control psychotic symptoms, using compounds that are less likely to give rise to or worsen pre-existing extrapyramidal side effects (EPS) becomes important. Those patients prone to spontaneous EPS may be more likely to develop drug-induced EPS when treated with typical neuroleptics. Asian patients have also been shown to be more sensitive to haloperidol-induced EPS[5]. In this study, only four patients developed mild EPS and only three of them had to be treated with low doses of benzhexol.

Anxiety and insomnia are well known side effects of risperidone. These side effects were reduced at the end of the study. Hence risperidone is well tolerated.

Double-blind studies[1,2] have shown that risperidone is effective in schizophrenia. A recent study[6] showed that risperidone is effective in first episode psychosis and that a lower does of risperidone is needed. DeQuardo[7] in his review of the management of first episode schizophrenia recommended that the dosage range for risperidone in this group of patients was 4 - 8 mg/day. On the other hand McGorry[8] reported that a lower dose range of 2 to 4 mg/day of risperidone and a slower rate of titration is effective in treating 60% of patients with first-episode psychosis. Another study[9] also suggests giving an adequate trial of risperidone in the 2 to 4 mg/dy dose range before proceeding to higher doses. Although the dosing schedule in this study allowed for up to 8 mg of risperidone per day, the mean dose of risperidone was only 2.7 mg ± 1.0 and no patient needed a dose higher than 4 mg/day. 87.5% of patients in this study responded to this treatment regimen. This would suggest that lower doses of risperidone and a slower rate of titration are as effective for first-episode psychosis. The advantage of using lower doses would be that EPS is avoided and patient compliance with treatment enhanced.

In addition, all PANSS subscales were significantly reduced and all single PANSS items showed a significant reduction besides item G5. The reductions in the PANSS scores were supported by the improvement in CGI scores, which showed a continuous shift towards mild disease stage or cessation of symptoms. These findings suggest that risperidone is even more effective across the symptom scale in first-episode psychosis patients than it was in a previous trial in Asian patients with long-standing diagnosis of schizophrenia[4].

The association of weight gain with both traditional and atypical neuroleptics has long been noted. Among the atypical agents two recent reviews[10,11] showed that clozapine was associated with the highest risk of weight gain, followed by olanzepine and quetiapine while risperidone was associated with a lower risk of weight gain. In Allison, Mentore & Heo et al's[11] review it was estimated that the mean increase in weight after 10 weeks of treatment at standard doses were clozapine, 4.45 kg; olanzepine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; and ziprasidone, 0.04 kg. In this study there was a gain in weight of approximately 2 kg.

This study has some limitations. The sample size is small and the selection of patients was not randomised. A selection bias could have inflated the response rate. Nevertheless the findings of this study are consistent with the suggestion that risperidone given at lower doses and increased at a slower titration rate is effective in

the treatment of first episode psychosis. Studies designed to compare low and high doses of antipsychotics in this group of patients are needed to confirm these findings

CONCLUSION

This study suggests that the dose of risperidone 4 mg/ day or less is effective and safe in the treatment of first-episode psychosis. Randomised controlled trials are needed to confirm to this finding.

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