Efficacy and Tolerability of Risperidone in Chronic Schizophrenic Thai Patients

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Abstract

Risperidone is a novel serotonin-dopamine antagonist antipsychotic in a class of benzisoxazole derivative which has been shown to be effective in reducing psychotic symptoms in schizophrenia. The study was designed as perspective, 8-week, multicenter, open label study in schizophrenic patients from 6 psychiatric hospitals. One hundred and twenty cases were recruited and 105 patients completed the study. The average total PANSS score at the baseline was 90.6 (range 60-133). Patients were evaluated with quantitative rating scales for the efficacy (PANSS score) and extrapyramidal rating scale at week 4 and 8 after starting risperidone treatment. The titrated dose of risperidone was given to the patients with the final dose of 6 mg risperidone throughout the study period. At week 4, the average PANSS score was significantly reduced to 73.4 ($p<0.05$). The average PANSS score at week 8 was further declined to 61.9 which was significantly different ($P<0.05$) from the beseline. Seventy-eight cases (74.3%) were classified as responders (those patients showing more than 20 per cent decrease in PANSS score). Extrapyramidal side effect was occurred in some patients, but usually mild and tolerable. However twenty-four patients (22.9%) required medications for this side effect. Other adverse reactions were insomnia found 15 cases (14.3%), elevated hepatic enzyme 5 cases (4.8%) and weight gained 2 cases (1.9%). Our data suggested that risperidone is effective and well-tolerated in chronic schizophrenic Thai patients.

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Risperidone is the first serotonin-dopamine antagonist antipsychotics that is available for clinical use worldwide. Many clinical studies revealed that risperidone makes a substantial contribution to the treatment of schizophrenia with a greater efficacy against negative symptoms[1,2]. Recent evidence suggests that risperidone was effective for negative and positive symptoms while producing fewer extrapyramidal side effects compared with haloperidol[3,4]. These clinical advantages were apparent when the dose of 6 mg was administered compared with 20 mg of haloperidol daily. However, risperidone also acts as an antagonist at other receptors such as α_1 and α_2 adrenergic receptors, as well as the histamine H_1 receptor. This can lead to orthostatic hypotension, nasal congestion and sedation. Risperidone is also recommended as the first line drug therapy in first-episode schizophrenia[5] and in dementia-related behavioral disturbances[6]. Risperidone was recently launched in Thailand, thus it is interesting to assess the clinical efficacy, optimum dose and side effect profile of this drug in schizophrenic Thai patients.

MATERIAL AND METHOD

Subjects

Chronic schizophrenic patients (based on DSM IV criteria, APA 1994[7]) diagnosed by the treating psychiatrists with a PANSS (the positive and negative symptom scale) score of more than 60 were recruited into the study. Other inclusion criteria were :- age $\geq$15 years ; their relatives had to sign the consent form or give verbal consent in front of a witness.

Exclusion criteria comprised of :-

- patients who were diagnosed as organic or neurological diseases, or psychoactive substance abuse.
- patients who had received depot neuroleptic injection not more than one cycle prior the time of patient selection or received any other experimental drugs 4 weeks prior to selection.
- patients with severe GI, liver, renal and heart disease.
- patients who had clinically abnormal laboratory values.
- female patients of child-bearing age who did not have adequate contraception control.
- female patients who were pregnant or breast-feeding

Study design

The study was conducted as an 8-week multicenter open-label clinical study in six psychiatric hospitals. The protocol was approved by the ethic committee of the Institute of Mental Health, Ministry of Public Health.

After a week of single-blind placebo wash-out period, patients received 8 weeks' treatment with risperidone. Risperidone was titrated from 1 mg bid and increased to a maximum of 6 mg/day within 3 days. Patients were maintained at this dose throughout the period of study. Patients were assessed by a single rater using the PANSS score at week 4 and 8 after starting the treatment to evaluate the efficacy of the drug. ESRS score was also used to evaluate the extrapyramidal side effect. Routine physical and neurological examinations, blood chemistry and hematology were evaluated at week 0 and 8, whereas the vital signs, extrapyramidal symptoms and other adverse events were evaluated weekly until the end of study.

Clinical improvement of risperidone therapy was defined as at least 20 per cent reduction in total PANSS scores for schizophrenia at the end of treatment.

ANOVA statistical analysis was performed to compare baseline, week 4 and week 8 values for the subscale cores of PANSS. Other adverse effects were reported as descriptive statistics.

RESULTS

A total of 120 patients were recruited (20 from each center), and 105 patients completed the study. All met the DSM IV criteria for a diagnosis of schizophrenia. Total PANSS scores of 105 patients decreased significantly from baseline both at week 4 and week 8 (90.6 *vs* 73.4, $p<0.00001$ and 90.6 *vs* 61.9, $p<0.00001$, respectively). Scores on the PANSS positive symptoms subscale also decreased significantly from the baseline as shown in Fig. 1. The reduction in the score of "thought disturbance" was dramatically prominent especially at the end of week 8 as shown in Fig. 2. Similarly, scores on the PANSS negative symptom subscale significantly decreased both at week 4 and week 8 (25.4 *vs* 21.2, $p<0.00001$, and 25.4 *vs* 17.9, $p<0.0001$, respectively). General psychopathological subscale scores also significantly declined particularly at the

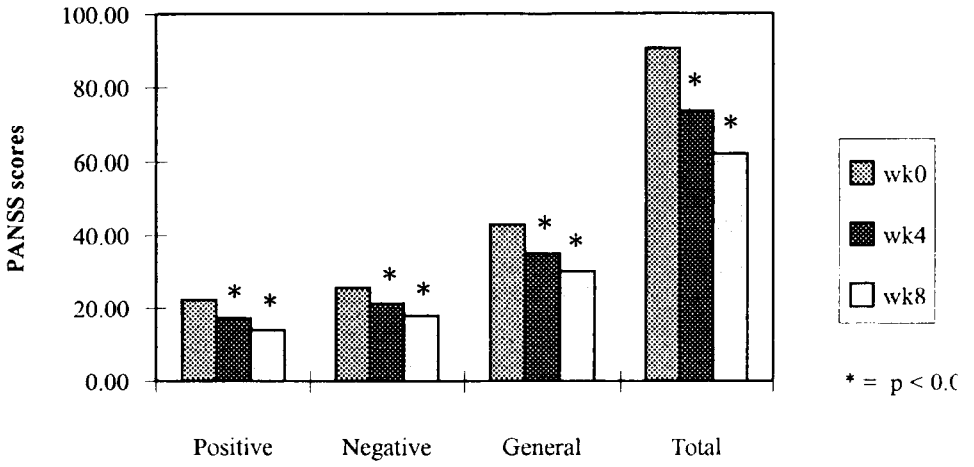

Fig. 1. Reduction of total PANSS and mean subscale score after risperidone treatment.

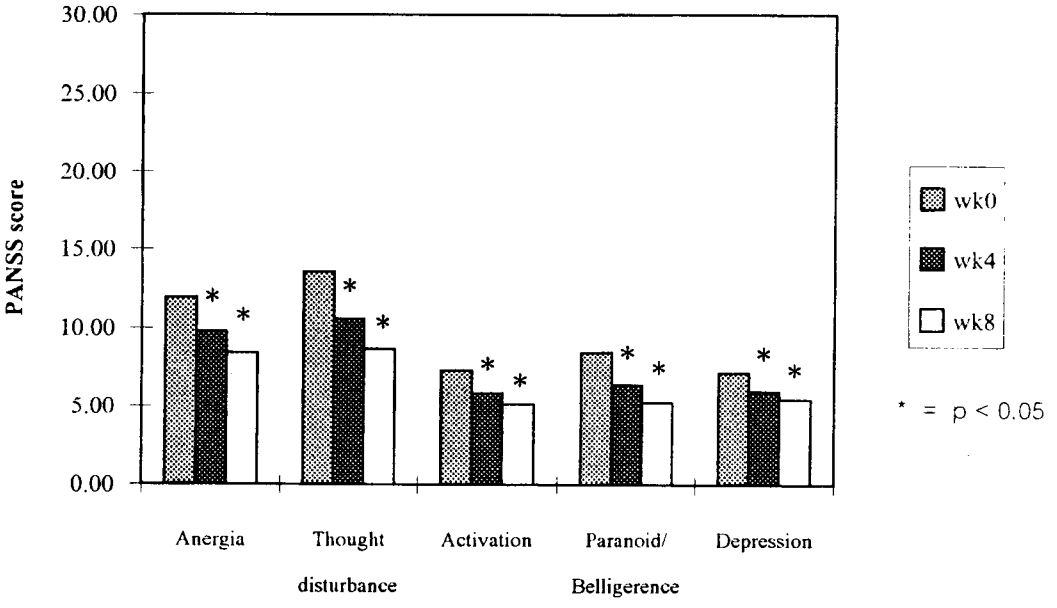

Fig. 2. Some subscale score reduction after risperidone treatment.

end of the study. The reduction of some subscale scores, e.g. anergia and depression are also shown in Fig. 2.

Defining a clinically significant improvement of symptoms as 20 per cent or greater reduction in total PANSS score, 74 per cent of these chronic schizophrenic patients were classified as clinical responsders.

Risperidone was tolerated well in the majority of patients. The maximum shift from baseline on the ESRS total score of + 4.0 was found in only a few patients. The most serious form of EPS, occulogyric crisis, occurred in one case. However, there was a low incidence of EPS during the study. The occurrence of adverse events other than EPS were insomnia, elevated ALT, the level

of increase was in the upper limit and did not present clinically, blurred vision and weight gain. None of the patients demonstrated a change in blood pressure or heart rate.

At the end of the study, the investigator was asked to rate the global evaluation. Move than 40 per cent of the cases were rated as good to excellent for the overall impression.

DISCUSSION

The results of this study suggest that the eight week-treatment with 6 mg risperidone is effective for controlling psychotic symptoms in chronic schizophrenic patients. An improvement in all positive, negative and general psychopathological subscales were seen at the end of week 4 and week 8. This impressive efficacy was in accord with those previously reported[8,9].

Approximately seventy per cent of these patients achieved a clinical response confirming that risperidone differs profoundly from the classical neuroleptic drugs.

The significant fast onset of action of rispesidone was also observed in this study. Although 74 per cent of the patients showed clinical improvement at the endpoint, after 4 weeks of treatment about 25 per cent of patients already showed clinical improvement. The faster attenuation of these symptoms certainly benefited the well-being of the patient. This may also improve compliance as the patients experienced the fast action of the drug.

Concerning the adverse events of risperidone, despite the α_1 blocking activities of risperidone, no patients complained of dizziness or showed changes in their pulse or blood pressure. Extrapyramidal side effects were usually mild and well tolerated. However, it is rather difficult to count this for risperidone, since most patients had been using conventional antipsychotics prior to trial entry and EPS was still present at the start of the study. If patients are abruptly discontinued from a high potency antipsychotic such as haloperidol and started on risperidone treatment, it is possible that the patients will have temporary worsening side effects, and these effects will be incorrectly attributed to the newer drug[2].

It can be concluded that risperidone is effective in the treatment of chronic schizophrenic patients with well-tolerated adverse event profiles.

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ประสิทธิภาพและความทนต่อยาของยาริสเพอริโดนในการรักษาผู้ป่วยโรคจิตเภทเรื้อรังชาวไทย

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ยาริสเพอริโดนเป็นยารักษาโรคจิตตัวใหม่ที่มีคุณสมบัติปิดกั้นตัวรับซีโรโทนินและโดปาร์มีน จากโครงสร้างทางเคมีจัดอยู่ในกลุ่มอนุพันธ์ของเบนซิซอคซาโซล ซึ่งมีประสิทธิภาพสูงในการลดอาการผิดปกติทางจิตในผู้ป่วยโรคจิตเภท การศึกษานี้เป็นรูปแบบวิจัยแบบไปข้างหน้าและเป็นการศึกษาแบบเปิดซึ่งศึกษาใน 6 โรงพยาบาลที่สังกัดกรมสุขภาพจิต มีผู้ป่วยเข้าร่วมการศึกษา 120 รายและอยู่ร่วมการศึกษาจนสิ้นสุดโครงการวิจัยนาน 8 สัปดาห์ จำนวน 105 ราย เพื่อประเมินประสิทธิภาพของยาผู้ป่วยจะถูกประเมินอาการทางจิตโดยใช้เครื่องวัด PANSS (Positive and Negative syndrome scale) ในการประเมินความรุนแรงของอาการที่สัปดาห์ที่ 0, 4 และ 8 ตามลำดับ และประเมินความทนต่อยาโดยใช้เครื่องวัด ESRS (Extrapyramidal Syndrome Rating Scale) เพื่อประเมินความรุนแรงของอาการเอ็กซ์ตรา-ปิรามิดอลที่อาจเกิดขึ้น ขนาดยาที่ใช้ในการรักษาคือ 6 มิลลิกรัมต่อวัน

คะแนน PANSS เฉลี่ยของผู้ป่วยทั้งกลุ่มที่สัปดาห์ที่ 0 เป็น 90.6 (คะแนนอยู่ในช่วง 60–133) เมื่อสิ้นสุดสัปดาห์ที่ 4 คะแนน PANSS เฉลี่ยลดลงอย่างมีนัยสำคัญทางสถิติเป็น 73.4 ($p < 0.05$) และเมื่อสิ้นสุดการศึกษาที่สัปดาห์ที่ 8 คะแนน PANSS เฉลี่ยลดลงเป็น 61.9 ($p < 0.05$) ซึ่งมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ผู้ป่วย 78 ราย คิดเป็น 74.3 เปอร์เซนต์ของผู้ป่วยทั้งหมด ได้รับการประเมินว่าตอบสนองต่อการรักษา (หลักเกณฑ์การประเมินพิจารณาจากคะแนน PANSS ลดลงมากกว่า 20 เปอร์เซนต์ของคะแนน PANSS ที่สัปดาห์ที่ 0 ของผู้ป่วยแต่ละคน) อาการข้างเคียงที่พบคือ เอ็กซ์ตราปิรามิดอลพบ 24 ราย(22.9%) ซึ่งมีอาการเล็กน้อยถึงปานกลาง อาการข้างเคียงอื่น ๆ ที่พบคือนอนไม่หลับ 15 ราย(14.3%) เอนไซม์ตับเพิ่มขึ้น 5 ราย(4.8%) น้ำหนักขึ้น 2 ราย(1.9%) จากการศึกษาสามารถสรุปได้ว่า ยาริสเพอริโดนเป็นยาที่มีประสิทธิภาพดี และผู้ป่วยทนต่อยาได้ดี ในการรักษาโรคจิตเภทเรื้อรังในผู้ป่วยชาวไทย

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