

RISPERIDONE FOR THE TREATMENT OF SCHIZOPHRENIA

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SUMMARY

Results of an open-label trial of risperidone in the treatment of schizophrenia involving 30 subjects are reported. During the 8-week long trial, the overall improvement rate was 87 %. Risperidone treatment improved both positive and negative symptoms while its side-effects were generally mild and tolerable. Our findings also suggest that risperidone can be used as a first line treatment for schizophrenia.

Key words : risperidone, schizophrenia, effectiveness, Chinese

INTRODUCTION

Risperidone, a new, atypical antipsychotic drug, was developed by Janssen Pharmaceutica (Belgium) in 1984. It has a strong antagonistic effect on 5-HT₂ receptors and moderate antagonistic action on D₂ receptors in the central nervous system. Risperidone has been used in clinical practice since 1993 and proved to be efficacious for both negative and positive symptoms of schizophrenia. It has only mild extrapyramidal side effects (EPS) hence a wider safety margin than most traditional antipsychotic drugs. Here we report the results of an open label clinical trial of risperidone in the treatment of schizophrenia.

METHODS

All 30 patients entering the study met both ICD-10 and DSM-IV diagnostic criteria for schizophrenia. Patients with medical and neurological conditions and/or a history of alcohol or drug abuse were excluded from the study.

All subjects were male with a mean age of 29.1±8.9 years (range : 16-59 years) ; 83% of the subjects were between 19 and 35 years of age. The duration of illness ranged from 2 months to 25 years (mean : 5.97±6.03 years). According to ICD-10 diagnostic criteria, subtype diagnoses of schizophrenia were as follows : 11 paranoid type, 8 undifferentiated type, 4 hebephrenic type, 2 residual type, 1 simple type and 4 other, ie. not identifiable, subtype. Only 12 patients had received antipsychotic medication prior to the study. Of these 12 subjects, 8 responded to previous neuroleptic treatment.

Xian-Janssen Pharmaceutica provided risperidone tablets of 1 mg strength and identical-looking placebo tablets. The initial dose of risperidone was set at 1mg/day. Thereafter, the dose was increased according to the patients' clinical condition. The maximum dose was 10 mg/day. Among the 12 patients who had received previous antipsychotic treatment, 10 underwent a single-blind, one-week wash-out period using 1 placebo tablet twice a day. The whole trial lasted eight weeks. During the trial the administration of anti-parkinson drugs or benzodiazepines was permitted.

Assessment was made at baseline and at the 1st, 2nd, 4th, 6th and 8th weeks of treatment by using the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) and the

Treatment Emergent Side Effects Scale (TESS). We also used our traditional clinical evaluation to obtain an estimation of global improvement at the end of the trial.

Laboratory investigations included full blood picture, liver and renal function tests, serum electrolytes and urinalysis. ECG and EEG were evaluated at baseline and at the 4th and 8th weeks of treatment.

For statistical analysis, paired t-test, group t-test and chi-square-test were used. Statistical significance was predetermined at the $p < 0.05$ level.

RESULTS

EFFECTIVENESS OF RISPERIDONE TREATMENT

29 patients completed the study; 1 subject dropped out at the 5th week because of cerebral thrombosis unrelated to risperidone therapy. According to our traditional clinical evaluation, 13 subjects (43.3%) was judged as completely free of symptoms, 9 (30 %) remarkably improved, 4 improved and 4 remained unchanged. Overall improvement rate was 87 %.

BPRS total score showed a significant decrease throughout the trial period (Table 1)

Changes in BPRS factor scores during risperidone treatment are shown in Table 2. The majority of factors decreased significantly except for factor 1 in the first week. The items "slowness", "inability in emotional communication" and "apathy" in BPRS were grouped together as negative symptoms, while others as positive symptoms. There was a significant decrease in both negative and positive symptom clusters during risperidone treatment (paired t-test).

Table 1. Changes in BPRS total score of (paired t-test)

Time	No of cases	Mean ± sd	t	p
Pre-treatment	30	43.30±8.27		
week 1	30	39.57±7.89	6.13	$p < 0.001$
week 2	30	34.53±6.53	8.26	$p < 0.001$
week 4	30	29.36±5.74	9.59	$p < 0.001$
week 6	29	26.21±6.54	9.27	$p < 0.001$
week 8	29	24.31±7.14	8.88	$p < 0.001$

Table 2. Changes in BPRS factor scores (paired t-test)

	pre-treatment	week 1	week 2	week 4	Week 6	week 8
factor 1	6.8(3.6)	6.4(3.4)	5.6(2.1**)	4.3(1.4**)	4.6(1.0***)	4.3(2.7*)
factor 2	11.0(3.3)	10.2(3.2*)	9.5(3.6**)	8.3(3.6**)	7.3(3.8**)	7.2(3.8**)
factor 3	11.9(4.4)	11.1(4.9*)	9.5(3.9***)	7.6(2.9***)	6.5(2.6***)	5.9(2.8***)
factor 4	5.1(2.8)	4.4(2.2*)	3.9(1.6**)	3.5(1.1**)	3.4(0.9**)	3.4(1.3***)
factor 5	0.4(3.1)	7.1(2.7**)	6.1(2.6***)	5.1(2.0***)	4.3(1.5***)	3.6(1.3**)

(P>0.05 *P<0.05 **P<0.01 ***P<0.001)

The mean decrease of BPRS total score in patients who were completely symptom-free, remarkably improved or improved were 23.6 ± 7.1 , 23.3 ± 9.1 and 19.5 ± 9.6 respectively; in percentage the corresponding figures were 52.8 ± 8.0 , 51.8 ± 8.3 and 25.7 ± 3.8 %. On the CGI, 12 patients remarkably, 9 moderately and 4 slightly improved, 2 remained unchanged, 3 were difficult to evaluate. The patients above the level of the "slightly improved" category accounted for 83% of the total sample.

DOSE RANGE

The dose range for the whole sample was 4 - 10 mg. The mean daily dose for symptom-free patients was 7.09 ± 1.38 mg. Time patients start to improve ranged from 14 to 49 days with a mean of 20.08 ± 8.78 days. The length of time from the initial dose up to maximum improvement was 39.66 ± 11.05 days.

SIDE EFFECT PROFILE AND SAFETY

Side effects were evaluated by the TESS. Common side-effects included dizziness (36.7%), dry mouth (30%), nausea and vomiting (20%), insomnia (20%), anxiety (13%), fatigue (13%), constipation (13%), tremor (10%), depression (10%), palpitation (10%), rigidity (3%) and akathisia (3%). 13 patients (43.3%) needed the addition of a benzodiazepine and only 1 subject needed trihexyphenidyl.

Risperidone had no effect on full blood count, serum levels of BUN and electrolytes, urinalysis, ECG and EEG. 3 patients had a transient increase in the level of serum GPT and GOT while 2 patients had higher level of serum triglyceride.

DISCUSSION

Since the introduction of chlorpromazine in the early 1950s, traditional (typical) antipsychotic drugs have been used effectively in the treatment of major psychoses. These neuroleptics have been particularly efficient in suppressing positive symptoms but they have less or minimal effect on negative symptoms. In addition, typical antipsychotic drugs frequently cause crippling extrapyramidal side effects. For these reasons the development of new, atypical antipsychotics remains an important task for psychopharmacology.

In the present study the overall rate of improvement was in the range of 73 - 87% according to the treating clinicians' global impression. This result is quite satisfactory since most of the subjects suffered from chronic, treatment-refractory

schizophrenic illness. Previous antipsychotic drug treatment or its effectiveness did not seem to influence the outcome of risperidone treatment.

There was a marked decrease in both negative and positive symptom scores of BPRS suggesting that risperidone had significant effect on negative as well as positive symptoms. Since the negative symptom profile of BPRS is narrower than that of PANSS, further research is warranted as to the effect of risperidone on the whole spectrum of negative symptoms.

With the exception of Factor 1, all factors of BPRS showed a significant reduction from week 1 of the trial while Factor 1 started decreasing only from week 2. Thirteen subjects (43.3%) reported anxiety symptoms during treatment and received benzodiazepine medication. Further research is needed concerning risperidone's antianxiety and antidepressant effects.

No patient dropped out of the trial because of side effects. EPS infrequently occurred and only to a mild/moderate degree. Risperidone had transient effect on serum levels of GOT and GPT while the cardiovascular system, blood picture, renal function and EEG were not affected. Risperidone proved to be an easily tolerable and safe antipsychotic drug.

In our sample the dose range of risperidone was 5.0 - 10.0 mg/day, the optimal dose was 7.09 ± 1.38 mg/day. Our results are comparable to those reported in the literature although recent reports suggest that significantly lower doses (2 - 4 mg/day) may suffice for the majority of schizophrenic patients.

In our study most subjects showed marked clinical improvement after the second week of the trial. There was a trend for the BPRS total score to go down from the 6th to 8th weeks. Since the majority of our patients suffered from chronic schizophrenia, no further improvement was expected after 8 weeks of risperidone treatment.

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