Yonsei Medical Journal
Vol. 34, No. 2, 1993

Risperidone Versus Haloperidol in the Treatment of Chronic Schizophrenic patients: A parallel Group Double-blind Comparative Trial

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A parallel group double-blind comparative trial was conducted to study the efficacy and safety of risperidone compared with haloperidol. After a one-week wash-out, 35 chronic schizophrenic patients (17 males, 18 females) were randomly assigned to one of two groups for eight weeks of double-blind treatment. The patients' psychopathology was assessed by means of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and the Clinical Global Impression (CGI). Safety assessments included the Extrapyramidal Symptom Rating Scale (ESRS), the UKU Side Effect Rating Scale, vital signs, body weight, ECG and laboratory screening. Thirty-two patients completed the trial: there were 3 drop-outs in the risperidone group. The results on the PANSS and CGI indicate that the mean changes from baseline on the total PANSS score and on the total BPRS score were comparable in both treatment groups. The number of patients where a clinical improvement at least 20% reduction in baseline score was also similar in both treatment groups. Risperidone caused less extrapyramidal symptoms and less side effects in UKU scale than haloperidol. No significant ECG changes were induced, no relevant changes in blood pressure or clinical laboratory parameters were observed. This study has demonstrated that the combined serotonin 5-HT$_2$ and dopamine-D$_2$ antagonist risperidone is an antipsychotic as potent as haloperidol. Risperidone causes less extrapyramidal symptoms, and is better tolerated than haloperidol.

Key Words: Risperidone, haloperidol, schizophrenia

After nearly forty years of clinical experience with neuroleptics there is a broad consensus on the merits and limitations of their use in schizophrenia. It is widely accepted that their ability to block the central dopamine-D$_2$ receptors is highly correlated with their therapeutic potency in the control of positive symptoms of schizophrenia (Creese 1976). This receptor blockade is, however, also held responsible for the occurrence of extrapyramidal symptoms (EPS). Another limitation of classical neuroleptics is the relative lack of effect on negative symptoms in chronic schizophrenia (Crow 1985).

The search for new antipsychotics focuses on the prevention of EPS and improvement of negative symptoms. Two approaches have been opted for: one focuses on the antidopaminergic effect and therefore develops more selective dopamine-D$_2$ antagonists (e.g. pimozide, sulpiride, remoxipride, raclopride); the other investigates more broadly active substances with marked antiserotonergic effects (e.g. clozapine, risperidone). The rationale for the latter is the neurochemical and pharmacotherapeutical evidence that a central 5-HT$_2$ receptor blockade may be effective in diminishing the severity of EPS and improving negative symptoms (Bleich *et al.* 1988).

Received February 22, 1993
Accepted June 9, 1993
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Risperidone is a benzisoxazole derivative with monoaminergic antagonistic properties. It has a high affinity for serotonin 5-HT_2 and dopamine-D_2 receptors: it also binds to al adrenergic receptors and, with lower affinity, to α_2 adrenergic and H_1 histaminergic receptors (Leysen *et al.* 1988; Janssen *et al.* 1988). Risperidone has no affinity for the cholinergic muscarine receptors. It is a potent and selective LSD antagonist, and, unlike other serotonin antagonists, risperidone is devoid of any LSD-agonistic properties (Meert *et al.* 1988). In tests evaluating the effects on spontaneous motor activity in rats, it was demonstrated that with risperidone normal small movements are preserved over a much larger dose interval than with haloperidol. This may be related to its relatively low potency to induce catalepsy and its low propensity to induce EPS (Megens *et al.* 1988, 1989).

In open studies in chronic psychotic patients, risperidone was demonstrated to have a potent antipsychotic effect, to improve negative and affective symptoms of schizophrenia and to reduce pre-existing EPS (Roose *et al.* 1988; Castelo *et al.* 1989; Mesotten *et al.* 1989; Gelders 1989; Meco *et al.* 1989; Bersani *et al.* 1990; Gelders *et al.* 1990; Desseilles *et al.* 1990). The first two double-blind studies (Heylen and Gelders 1988; Claus *et al.* 1992) confirmed these findings from the open trials. In these two trials, as the well as in the present trial, haloperidol was chosen as reference drug since it has been the archetype of all neuroleptic drugs for over 30 years, with a well-known efficacy and safety profile (Kane 1987).

The aim of this parallel group double-blind trial was to determine in chronic schizophrenic patients the clinical efficacy and safety of a fixed flexible dosage of risperidone as compared to a similar dosage scheme for haloperidol.

SUBJECTS AND METHODS

This was a double-blind randomised parallel group study comparing risperidone with haloperidol. The study was approved by the Ethics Committee of the centre where the trial was performed. The trial was performed in accordance with the Declaration of Helsinki.

Patient selection

Inclusion criteria: Patients were eligible for this study if they met the following criteria:

① age between 18 and 65, of either sex.

② diagnosis according to DSM-III-R (American Psychiatric Association 1987) of chronic schizophrenic disorder (295.12/295.22/295.32/295.62/295/92),

③ at selection, a total score>60 and <120 on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)(Kay *et al.* 1987. 1988; Kay and Opler 1987),

④ routine physical and neurological examination, laboratory tests and ECG had to be free from clinically relevant abnormalities,

⑤ during the first three weeks of the trial (day-6 till 14), patients had to be hospitalised if possible,

⑥ patients (or their relavtives/legal guardians) had to give their informed consent.

Exclusion criteria: The following patients could not be selected for the trial:

① Patients with mental disorder other than chronic schizophrenic disorder,

② Patients with clinically significant organic or neurologic disorders,

③ Patient with epilepsy,

④ Patients with history of alcohol-or drug abuse within the past 12-month period preceding the study.

⑤ Patients who have been included in trials with investigational drugs during the four weeks preceding the study,

⑥ women of reproductive age without adequate contraception, (sterilisation, IUD, controlled a dministration of oral contraceptives, intramuscular administration of depot progestagens), pregnant or lactating women.

Study design and medication

Study design: The study started with a single-blind placebo wash-out period of one week (day-6 till day 0). For patients treated with depot neuroleptics, the placebo period started from the day they normally should have received their next depot iniection.

In case of acute psychotic exacerbation, the placebo period could be shortened to a minimum of three days.

After this placebo phase, the double-blind medication was administered for 8 weeks (from

day 1 till day 56). During the first two weeks of double blind administration (day 1 till day 14), the dose was 2.5 mg b.i.d. for both the risperidone and haloperidol group. After this period, the dose could be increased to 5 mg b.i.d. in case of insufficient response. Once the dose had been increased to 5 mg b.i.d., it had to be kept unchanged.

Trial medication: From day −6 onwards, all psychotropic and antiparkinson medication was withdrawn. While other medications were continued unchanged. During the single-blind placebo wash-out period, matched placebo tablets were administered, 1 tablet b.i.d. All the study medication was identical in appearance and was labelled with the protocol number, patient number, visit number, batch number and expiry date. All the trial medication was to be taken twice daily, one morning and one evening administration. The double-blind medication consisted of matched tablets with either risperidone or haloperidol. They were dispensed at each trial visit, except at the final visit. The following Lot numbers were used to make the trial medication.

Concomitant medication: All anti-parkinson and psychotropic medication had to be stopped at selection. All concomitant medication which was acceptable for trial inclusion, had to be initiated at least one week prior to visit 1 (day − 7), and the dosing had to be stable and recorded at selection. Any changes in dosage, or new medication added in the course of the trial as a result of an intercurrent illness, had to be recorded in the case report form.

Concomitant administration of benzodiazepines was to be avoided as much as possible. However, lorazepam or oxazepam were allowed if a sleep-inducer or a day-time sedative were required. Benztropine mesylate could be administered if EPS emerged, after completion of the ESRS. Administration of these concomitant medications was done *pro re nata.* according to the individual need of the patient. The use of these drugs had to be recorded in the case report form.

Premature discontinuation: Insufficient response, withdrawal of consent, change of diagnosis, or any severe event were reasons for early discontinuation. The date and reason of discontinuation had to be recorded in the case report form. All the patients who discontinued the study prematurely received a final evaluation (visit 7) if possible.

Assessments

Evaluation of efficacy: As a key efficacy parameter, the Positive And Negative Syndrome Scale for Schizophrenia (PANSS)(Kay *et al.* 1987, 1988; Kay and Opler 1987) was used. This validated rating scale measures positive and negative symptoms as well as general psychopathology by means of a semi-structured patient interview. The 30 items are grouped in three subscales:

the Positive Subscale with seven items: delusions, conceptual disorganisation, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, hostility.

the Negative Subscale with seven items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking:

the General Psychopathology Subscale with 16 items: somatic concern, anxiety, guilt feelings, tension, mannerism and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance.

Because all 18 items of the Brief Psychiatric Rating Scale (BPRS)(Overall and Gorham 1962) occur in the PANSS, the BPRS total score and subtotal scores can derived from it.

Every item is rated as 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, or 7=extreme, with each anchor point defined in the PANSS rating manual.

At the final evaluation, a comparison with the previous treatment was made both by the investigator and by the patient.

The Clinical Global Impression (CGI) of the severity of the illness was completed as a global rating (Guy 1976). The overall severity of schizophrenia was rated by the investigator as "not ill, very mild, mild, moderate, marked, severe, or extremely severe".

At visits 3 to 7, the patient's present condition was compared to his/her condition at baseline (visit 2, day 0): very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, very much worse.

Safety Evaluation: Extrapyramidal symptoms

were evaluated by means of the Extrapyramidal Symptom Rating Scale (ESRS)(Chouinard *et al.* 1979, 1980). This scale consists of a questionnaire, evaluating the subjective effects of EPS, a detailed clinical evaluation of parkinsonian, dystonic as well as dyskinetic symptoms, and two global impressions on the severity of EPS.

Other adverse events were assessed by a modified version of the UKU Side Effect Rating Scale (Lingjaerde *et al.* 1987). Of the original 48 items, three items were omitted because they occurred in the PANSS scale (depression, emotional indifference and tension/inner unrest); seven items were removed because they were part of the ESRS (dystonia, rigidity, hypokinesia, hyperkinesia, tremor, akatheisia, and increased salivation).

The events were graded for severity (mild, moderater or severe) and the investigator was asked to assess the causal relationship between the event and the trial drug (improbable, possible, probable). The investigator and the patient were asked for a global assessment of the interference by the existing side effects on the patient's daily performance: 0=no side effects; 1=mild side effects, no interference; 2=side effects with moderate interference, 3=side effects with marked interference.

If the patient had serious or unexpected adverse experiences, or adverse experiences requiring the use of concomitant medication, the following data were to be collected: date of onset, duration, severity, frequency, action taken, relationship to study medication, and patient outcome. If a patient prematurely discontinued the trial because of an adverse experience, the investigator was asked to prepare a statement describing the event.

A routine physical examination was performed at selection and at the end of the double-blind treatment period. At the final physical examination, the investigator was asked to record the changes that had occurred since the examination at selection. Changes resulting in a deterioration of the patient's condition had to be recorded as adverse experience.

Vital signs were registered in a standard way at each visit. Blood pressure (BP) and heart rate (HR) supine were taken when the patient had rested at least five minutes supine on a couch: BP was measured twice on the same supported arm, the second rating was recorded: then the heart rate was recorded. Then the patient stood up and the two BP measurements were repeated as above after one minute standing, followed by a heart rate recording.

A standard ECG was recorded at selection and on the final visit. Body weight was recorded at the same time-points with the patient lightly dressed and without shoes. A blood sample was drawn at selection and at trial completion or discontinuation (after an overnight fast).

Laboratory analyses included the following assessments:

hematology: hemoglobin, RBC count, WBC count with differential count. platelet count. ESR 1h.

blood biochemistry: sodium, potassium, chloride, calcium, phosphorus, total protein, albumin, glucose, total cholesterol, total bilirubin, direct bilirubin, alkaline phosphatase, ASAT, ALAT, CPK, BUN, creatinine, uric acid.

urinalysis: pH, density, protein, glucose, occult blood, urobilinogen, and a microscopic examination of the sediment for RBC, WBC and casts.

Statistics

All randomized patients were included in the main analysis, regardless of their compliance with the protocol. This intention to treat analysis is regarded as the main analysis. To detect differences between the two treatment groups, two-tailed statistical tests were interpreted at the 5% significance level.

Demographic variables and baseline characteristics: The patient's demographic and baseline disease characteristics were compared by means of the Chi-square test or the Fisher's exact probability test for nominal variables (e.g. sex, diagnosis) and the Mann-Whitney U test for ordinal and continuous variables (e.g. baseline scores).

Analysis of efficacy variables: The PANSS total and subtotal scores and the BPRS and BPRS factor scores were subjected to the Mann-Whitney U test to detect differences on the shift of the endpoint evaluation versus baseline. The number of patients showing clinical improvement (reduction of at least 20% in the total PANSS score as compared to baseline) was analyzed using the Chis-quare test to detect differences between the two treatment groups.

The severity of illness and the global evaluation, both assessed by means of a Clinical Global Impression, were analyzed using the Chi-square test to evaluate differences between the two medications.

Analysis of safety variables: To assess the occurrrence of extrapyramidal symptoms (EPS), a possible masking of these symptoms following the use of antiparkinson treatment had to be taken into account. Therefore, the shift versus baseline of the maximum score observed during treatment on the ESRS, was calculated per patient for each item of the Parkinsonism cluster and for the total Parkinsonism score. The Mann-Whiteny U test was applied to detect differences on the shift to the maximum scores.

To evaluate somatic findings according to the UKU adverse experiences rating scale, the number of patients whose scores for any individual item deteriorated at any time during treatment compared to pre-treatment observations, was calculated for each treatment group.

Kind and incidence of all adverse experiences recorded during trial were reported for all treatment groups: special attention was paid to the incidence of extrapyramidal symptoms.

Intergroup statistics at each time point (by means of the Mann-Whitney U test) and within treatment group comparisons (by means of the Wilcoxon matched-pairs signed-ranks procedure) were reported to evaluate changes versus baseline for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) supine and standing and for body weight.

Summary statistics and intragroup comparisons (by means of the Wilcoxon matched-pairs signed-ranks procedure) were made to evaluate changes versus pre-treatment values for HR, PQ, QRS, QT, QTc and QTm on the ECG.

Study monitoring

Investigator Meeting: All investigators met with representatives from the Janssen Research Foundation (JRF) to review the procedures of the trial before any patients were enrolled. In addition, rating scales were reviewed using videotapes of patient interviews to increase the inter-rater reliability.

Monitoring: A representative of the JRF visited the study sites and met with the investigator and his/her staff prior to the recruitment of the first patient. They reviewed the procedures to be followed in conducting the study and in recording the findings in the case report forms. After enrollment of the first patient, the JRF representative monitored the progress of the trial by visiting the study site as frequently as necessary. The record-keeping and adherence to the protocol were monitored. The JRF representative arranged for the return of the case report forms to the JRF. For each patient a sealed envelope with the randomization was supplied. This envelope was only to be opened in case of a serious event. All envelopes had to be returned to the JRF at the end of the trial.

RESULTS

Patient population

Patient inclusion: A total of 35 Korean chronic schizophrenic patients entered the trial: they were randomized at selection to one of two treatment groups.

Demography and baseline characteristics: The mean age of the patients was 34.1 years (range 18-59): 17 patients (48.7%) were male, 18 (51.3%) were female.

Four patients had a known family history of psychiatric or neurologic disorders. The mean age at first onset of psychiatric symptoms was 23.5 years (range 14~40) and at first psychiatric hospitalisation 25.2 years (range 15~41). The mean number of previous hospitalisations was 3.1 (0~18). The mean duration of the current hospitalisation was 154 days (range 1-554).

The two treatment groups were very similar with respect to demography and baseline characteristics such as sex, weight, height, diagnosis, and other data for the total population and per treatment group.

The data of all the randomized patients were used in the efficacy and safety analysis. The treatment groups were comparable at baseline with respect to the severity scores for all the efficacy parameters and extrapyramidal symptoms.

Single-blind placebo wash-out period: The mean duration of wash-out was 6.8 days (range 5~7) for the total trial population: there was no difference between the treatment groups. The wash-out period was shortened in 2 patients in the risperidone treatment group and in 3 patients in the haloperidol treatment group. The

reason(s) recorded by the investigator to shorten the wash-out period are intercurrent illness, study error or are unknown.

Drop-outs during double-blind treatment: Ninety-one percent of the study population, or 32 patients, completed the trial. There were 3 drop-outs in the risperidone treatment group. The reason for premature discontinuation are decision of patient's relative (1 patient) and intercurrent disease (2 patients).

Medication

Previous medication: Before entering the trial, 34 patients were using drugs of diverse categories. Phenothiazines and butyrophenones were the most widely used antipsychotic treatment, only in oral formulation.

Concomitant medication: During the study all patients used one or more concomitant medications. The consumption of these drugs was evenly distributed in both treatment groups.

Trial medication: A final dose of 5 mg trial medication was administered to 8 risperidone treated patients and 4 haloperidol treated patients, whereas a final dose of 10 mg was given to 8 risperidone and 15 haloperidol patients respectively.

Clinical results: efficacy

PANSS: The comparative efficacy on the changes in mean score on the PANSS total score and subscale scores is summarized in Tablel. The mean changes from baseline on the total PANSS score and on the total BPRS score were comparable in both treatment groups and no statistically significant differences could be detected (Table 1). On the subscales of the PANSS and on the clusters of the BPRS. the decrease in score was also similar with both trial drugs.

Of the 35 patients, 24 or 68.6% reached clinical improvement (at least 20% reduction from

Table 1. PANSS and PANSS derived BPRS: mean scores at basline and mean changes from baseline after 8 weeks and at endpoint

	Item	Treatment group	Baseline(a) N	Baseline(a) Mean (extremes)	8 Weeks N	8 Weeks Mean change versus baseline (extremes)	Endpoint N	Endpoint Mean change versus baseline (extremes)	MWU two-tailed probability
PANSS scale	Positive subscale	risperidone	16	19.8(8; 29)	13	−4.7(−10; 3)	16	−4.3(−10; 3)	0.47
		haloperidol	19	18.2 (12; 31)	19	−3.3(−14; 8)	19	−3.3(−14; 8)	
	Negative subscale	risperidone	16	24.3 (16; 34)	13	−6.1(−21; 2)	16	−4.5(−21; 7)	0.09
		haloperidol	19	23.7 (15; 33)	19	−7.4(−15; 5)	19	−7.4(−15; 5)	
	General psychopathology subscale	risperidone	16	47.9(35; 61)	13	−10.4(−30; 9)	16	−8.3(−30; 9)	0.53
		haloperidol	19	46.3 (32; 64)	19	−11.3(−31; −2)	19	−11.3(−31; −2)	
	Total PANSS core	risperidone	16	92.0(62; 103)	13	−21.2(−58; 6)	16	−17.1(−58; 12)	0.41
		haloperidol	19	88.2 (60; 126)	19	−21.9(−57; −1)	19	−21.9(−57; −1)	
PANSS derived BPRS scale	Activity	risperidone	16	8.6(5; 14)	13	−1.8(−5; 3)	16	−1.7(−5; 3)	0.45
		haloperidol	19	7.6(4; 11)	19	−1.3(−7; 5)	19	−1.3(−7; 5)	
	Anergia	risperidone	16	12.9(8; 18)	13	−3.8(−10; 2)	16	−2.8(−10; 7)	0.71
		haloperidol	19	11.7(5; 19)	19	−3.3(−10; 4)	19	−3.3(−10; 4)	
	Anxiety/depression	risperidone	16	12.0(7; 20)	13	−3.2(−9; 4)	16	−2.8(−9; 4)	0.88
		haloperidol	19	10.8(6; 16)	19	−2.8(−8; 1)	19	−2.8(−8; 1)	
	Hostility	risperidone	16	7.9(4; 11)	13	−2.1(−5; 1)	16	−1.6(−5; 3)	0.47
		haloperidol	19	7.4(4; 11)	19	−2.1(−5; 1)	19	−2.1(−5; 1)	
	Thought disturbanoes	risperidone	16	11.9(6; 24)	13	−2.5(−6; 1)	16	−2.4(−6; 1)	0.85
		haloperidol	19	11.4(7; 23)	19	−2.6(−11; 8)	19	−2.6(−11; 8)	
	Total BPRS score	risperidone	16	53.4(35; 70)	13	−13.5(−31; 2)	16	−11.2(−31; 6)	0.96
		haloperidol	19	48.8(34; 71)	19	−11.9(−35; 0)	19	−11.9(−35; 0)	

(a) baseline=start double-blind treatment; no significant intergroup differences (MWU)
MWU=Mann-Whitney U

Table 2. Clinical improvement, defined as a reduction of the total PANSS score and PANSS derived BPRS score by 20% or more, by treatment schedule

A. Clinical improvement on the total PANSS score

Treatment schedule	Baseline		8 weeks		Endpoint		Chi-square test two-tailed probability
	N	Mean total PANSS score	N	No. of responders(%) (a)	N	No. of responders (%)(a)	
risperidone	16	92.0(62; 103)	13	10(76.9)	16	10(62.5)	n.s.
haloperidol	19	88.2(60; 126)	19	14(72.7)	19	14(73.7)	

B. Clinical improvement on the PANSS derived BPRS score

Treatment schedule	Baseline		8 weeks		Endpoint		Chi-square test two-tailed probability
	N	Mean total PANSS score	N	No. of responders(%) (a)	N	No. of responders (%)(a)	
risperidone	16	53.4(35; 70)	13	10(76.9)	16	11(68.4)	n.s.
haloperidol	19	48.8(34; 71)	19	14(68.8)	19	13(68.4)	

(a) Responders = patients showing clinical improvement, defined as at least 20% reduction from baseline

Table 3. Clinical Global Impression: severity of illness(a)

Time in study	Treatment group	N	NR	Very mildly ill	mildly ill	moderately ill	markedly ill	severely ill	mean score(b)	MWU two-tailed probability
start wash -out	risperidone	16			2	9	5		3.2	0.14
	haloperidol	19			6	10	3		2.8	
start DB	risperidone	16			1	6	8	1	3.6	0.52
	haloperidol	19			2	9	6	2	3.4	
Week1	risperidone	16			3	6	5	2	3.4	0.15
	haloperidol	19			4	12	3		2.9	
Week2	risperidone	14	1		4	6	3	1	3.1	0.27
	haloperidol	19		1	6	10	2		2.7	
Week4	risperidone	13		1	6	3	2	1	2.7	0.88
	haloperidol	19		1	8	9	1		2.5	
Week6	risperidone	13		1	6	4	1	1	2.6	0.90
	haloperidol	19		3	6	8	2		2.5	
Week8	risperidone	13			9	2	1	1	2.5	0.84
	haloperidol	19		1	10	6	2		2.5	
Endpoint	risperidone	16			10	2	2	2	2.8	0.71
	haloperidol	19		1	10	6	2		2.5	

N = number of patients

NR = missing values

MWU = Mann-Whitney U

(a) None of the patients scored not ill or extremely severely ill

(b) not ill = 0; extremely severely ill patients = 6

Table 4. Clinical Global Impression: improvement as compared to baseline(a)

Time in study	Treatment group	N	NR	Much improved	minimally improved	unchanged	minimally worse	much worse	mean score(b)	MWU two-tailed probability
Week1	risperidone	16		1	6	5	3	1	3.8	0.27
	haloperidol	19		4	7	5	2	1	3.4	
Week2	risperidone	14	1	2	6	4	2		3.4	0.18
	haloperidol	19		4	11	4			3.0	
Week4	risperidone	13		3	5	4	1		3.2	0.67
	haloperidol	19		3	12	3		1	3.2	
Week6	risperidone	13		5	3	4	1		3.1	0.55
	haloperidol	19		7	9	2		1	2.9	
Week8	risperidone	13		5	3	4	1		3.1	0.46
	haloperidol	19		8	7	4			2.8	
Endpoint	risperidone	16		5	4	5	1	1	3.3	0.19
	haloperidol	19		8	7	4			2.8	

N=numberofpatients

NR=missingvalues

MWU=Mann-Whitney U test

(a) None of the patients scored very much improved or very much worse

(b) very much improved=1; very much worse=7

baseline score) on the total PANSS score at endpoint (Table 2A). This percentage was 62.5% in the risperidone group, and 73.7% in the haloperidol group. Intergroup comparison (Chi-square test) indicated that the difference between the treatment groups was not statistically significant ($p=0.477$).

A similar percentage of patients reached clinical improvement on the BPRS (Table 2B). There was no statistically significantly different response in the two treatment groups.

CGI: The results on the CGI of the severity of illness are given in Table 3. Intergroup comparison of the mean scores showed the severity of schizophrenia to be comparable in both treatment groups at every timepoint of the study (Table 3).

From visit 3 onwards, the investigator was asked to compare the overall clinical condition of the patient at that timepont with his/her condition at baseline. Statistical analysis revealed the improvement to be similar with the two trial drugs (Table 4). A total of 24 patients were considered "improved" to a more or lesser degree. This percentage was 56% and 79% in the risperidone and haloperidol group resectively.

Global evaluation: At the end of the study, the investigator and the patient compared the double-blind treatment with previous neuroleptic treatment on a seven-point scale. In the investigator's rating, the mean scores were comparable in both treatment groups. A total of 32 patients compared the treatment they had received with their previous neuroleptic treatment. There were no significant intergroup differences.

Clinical results: Safety

Extrapyramidal symptom rating scale: The two treatment groups were comparable at the start of the trial. The mean scores at baseline and the shift to the maximum during the double-blind treatment are given in Table 5 (questionnaire, clusters and CGIs).

The main shifts to the maximum score were larger in the haloperidol group than in the risperidone group regarding the hyperkinetic symptoms factor, the dystonia total score and the parkinsonism/dystonia/dyskinesia score.

Table 5. Extrapyramidal symptom rating scale (ESRS): mean values at baseline and mean shifts of maximum score over the double-blind period versus baseline, by treatment schedule

Cluster	Treatment	Baseline(a)		Double-blind period		MWU two-tailed probability
		N	Mean value (extremes)	N	Mean shift to maximum total score versus baseline(extremes)	
I. QUESTIONNAIRE TOTAL SCORE	risperidone	16	2.7(0; 8)	16	3.3(−2; 15)	0.37
	haloperidol	19	1.9(0; 8)	19	6.6(−4; 34)	
II. PARKINSONISM TOTAL SCORE	risperidone	16	5.4(1; 15)	16	4.5(−2; 11)	0.13
	haloperidol	19	4.2(0; 12)	19	8.0(−9; 29)	
IIa. Hypokinetic symptoms factor	risperidone	16	4.4(1; 10)	16	2.4(−2; 7)	0.50
	haloperidol	19	3.3(0; 10)	19	3.8(−8; 17)	
IIb. Hyperkinetic symptoms factor	risperidone	16	0.8(0; 4)	16	2.1(0; 5)	0.07
	haloperidol	19	0.6(0; 5)	19	4.1(0; 13)	
III. DYSTONIA TOTAL SCORE	risperidone	16	0(0; 0)	16	0.3(0; 3)	0.56
	haloperidol	19	0.1(0; 1)	19	0.4(−1; 2)	
RARKINSONISM+DYSTONIA+ TOTAL SCORE (II+III)	risperidone	16	5.4(1; 15)	16	4.6(−2; 11)	0.11
	haloperidol	19	4.2(0; 12)	19	8.4(−10; 30)	
IV. DYSKINESIA TOTALSCORE	risperidone	16	0.4(0; 2)	16	0.6(−2; 6)	0.09
	haloperidol	19	0.8(0; 6)	19	1.5(−5; 8)	
IVa. Bucco-linguo-masticatory factor	risperidone	16	0.4(0; 2)	16	0.5(−2; 6)	0.27
	haloperidol	19	0.7(0; 4)	19	0.6(−4; 5)	
IVb. Choreoathetoid movement limbs	risperidone	16	0(0; 0)	16	0.4(0; 3)	0.85
	haloperidol	19	0.1(0; 2)	19	0.5(−1; 4)	
PARKINSONISM/DYSTONIA/ DYSKINESIA TOTAL SCORE (II+III+IV)	risperidone	16	5.8(1; 15)	16	5.1(−2; 16)	0.09
	haloperidol	19	5.1(0; 18)	19	9.3(−15; 31)	
V. CGI OF SEVERITY OF DYSKINESIA	risperidone	16	0.8(0; 3)	16	0.3(−3; 3)	0.67
	haloperidol	19	0.8(0; 4)	19	0.4(−1; 2)	
VI. CGI OF SEVERITY OF PARKINSONISM	risperidone	16	1.1(0; 3)	16	1.7(0; 4)	0.21
	haloperidol	19	0.9(0; 5)	19	2.8(0; 11)	

(a) Baseline=start of double-blind treatment; no significant differences between the two groups (Mann-Whitney U, two tailed probability)

MWU=Mann-Whitney U test

However, statistical significance was not reached, except for hyperkinetic symptoms factor (P=0.07) and the item tremor of the parkinsonism cluster (p=0.03)(not seen in table 5). where the shift to the maximum score was significantly higher in the haloperidol treated pa-

tients.

UKU side effect rating scale: The percentage of patients who reported an increase in severity is comparable in both treatment groups for most of the treatment and after 2 weeks of risperidone treatment. The systolic blood pressure (standing) was significantly decreased after 1 week and 8 weeks of haloperidol treatment and at endpoint. There were no significant intragroup or intergroup changes in diastolic blood pressure or in heart rate.

Electrocardiograms; At start of the double-blind treatment, 35 patients had an ECG recording taken, and 31 at endpoint. The two treatment groups were comparable at start of the double-blind period for all parameters. Intragroup comparisons between baseline and endpoint revealed a statistically significant increased QTc (15 msec) in the risperidone group.

Body weight; The mean body weight slightly decreased in both groups, the mean decrease from baseline varied between 0.2 kg in the risperidone group and 0.8 kg in the haloperidol group. The weight change was not significantly different between the two treatment groups.

Laboratory safety: Thirty-one sets of paired blood samples were collected in the course of the trial, 13 in the riperidone group and 18 in the haloperidol group. No abnormal trends were observed in any of the laboratory parameters.

DISCUSSION

The results of this study confirm that risperidone, like haloperidol, is a potent antipsychotic. In the comparisons on the efficacy evaluations, the shifts versus baseline at endpoint on the total PANSS and BPRS score were more favourable with haloperidol. The percentage of patients reaching clinical improvement on the total PANSS score was considerable in both treatment groups, but was slightly higher under haloperidol, Yet, the differences in the PANSS evaluations between the two treatment groups failed to reach statistical significances. In items. Increase in severity of concentration difficulties was more frequently observed in the haloperidol group (53%) than in the risperidone group (25%). This effect was also observed for the item asthenia (25% with risperidone, 47% with haloperidol) and for the item palpitations/tachycardia (25% with risperidone, 47% with haloperidol). Other items with at least 10% more patients reporting a deterioration in the haloperidol group were: failing memory, reduced duration of sleep, parasesthesias, accomodation disturbances, increased tendency to sweating, weight gain/loss, diminished/increased sexual desire and erectile dysfunction. Increase in severity of sleepiness/sedation was more frequently observed in the risperidone group (44%) than in the haloperidol group (26%). This effect was also observed in the items amenorrhoea, dry vagina and orgastic dysfunction.

Adverse events

Of the 35 patients in the intention-to-treat analysis, 20(57%) reported adverse experiences after the placebo wash-out period.

During the double-blind treatment, 33 patients (94%) reported adverse experiences. The percentage was lowest in the risperidone group (87.5%), while 100% of the haloperidol patients reported adverse experiences. The most frequently mentioned adverse effects were neurologic and psychiatric symptoms; they were equally distributed in both treatment groups.

Extrapyramidal symptoms were reported as an adverse experience in 6 risperidone (37.5%) and 13 haloperidol (68.4%) patients (akathisia, extrapyramidal disorder, hypertonia and tremor).

Vital signs

Blood pressure and heart rate: Intergroup comparison indicates that the systolic blood pressure (standing) decreased significantly more in the haloperidol-treated patients after 1 week of treatment ($p=0.02$). Intragroup comparison of changes versus baseline revealed that the systolic blood pressure (supine) was significantly decreased after 2 weeks of haloperidol addition, the evaluations on the CGI were improved to a greater extent after haloperidol medication, although no statistical significance was obtained.

In the comparisons on the safety evaluations, the shifts of the maximal score versus baseline on the ESRS total score, the hyperkinetic symptoms factor and the dyskinesia total score were higher under haloperidol, indicating that

there was a tendency for a more favourable outcome under risperidone. However, the power of the trial was too small to demonstrate statisticalcy significant differences between the two treatment groups, except for the item tremor, where risperidone was statistically superior to haloperidol. Moreover, the number of patients reporting extrapyramidal symptoms as an adverse event was significntly higher under haloperidol than under risperidone. Since risperidone has no inherent anticholinergic activity, the low EPS-inducing profile of risperidone is most probably related to its 5 HT_2-antagonistic properties. This relative lack of EPS could contribute to a better patient compliance and consequently to a reduction of psychotic symptoms (Van Putten 1974).

The tolerability of both drugs was comparable for most of the items on the UKU side effect rating scale. However, concentration difficulties, asthenia and palpitations/tachycardia were more frequently observed in the haloperidol group as compared to the risperidone group. These results, together with the fact that more haloperidol-treated patients reported adverse experiences during medication as compared to risperidone, indicate that risperidone is better tolerated than haloperidol. Vital signs show only minor flucturations in both treatment groups. The clinical laboratory and ECG evaluations give further evidence that risperidone is well tolerated.

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