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Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations

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Risperidone (RIS), a new neuroleptic with 5-HT_2- and dopamine D_2 receptor-blocking properties, was compared with perphenazine (PER) in a double-blind, multicentre, parallel-group study in 107 chronic schizophrenics with acute exacerbation. RIS 5–15 mg or PER 16–48 mg daily was given for 8 weeks. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression. Seventy-eight patients completed the trial; there was an equal number of dropouts on both drugs. The mean daily dose at endpoint was 8.5 mg RIS and 28 mg PER. The reduction in total PANSS score to endpoint did not differ significantly, although there was a tendency in favour of RIS. The number of patients with predominantly negative symptoms who showed at least 20% reduction in total PANSS score was significantly larger in the RIS group. Furthermore, the number of patients showing at least 20% reduction in Brief Psychiatric Rating Scale (BPRS) score (BPRS being a subscale of PANSS) was significantly larger in the RIS group. The hostility cluster of BPRS improved more on RIS than on PER in the endpoint analysis. The overall prevalence of side effects was fairly similar in the two groups.

O. J. Høyberg[1], C. Fensbo[2], J. Remvig[3], O. Lingjærde[4], M. Sloth-Nielsen[5], I. Salvesen[6]

[1] Central Hospital, Department of Psychiatry, Aalesund, Norway, [2] Psychiatric Hospital, Aalborg, [3] Glostrup Hospital, Copenhagen, Denmark, [4] Gaustad Hospital, Oslo, Norway, [5] Janssen Pharma, Denmark, [6] Janssen Pharma, Oslo, Norway

Key words: risperidone; perphenazine; serotonin antagonism; schizophrenia; negative symptom; antipsychotic drug

Irene Salvesen, Medical Department, Janssen Pharma, Postboks 143 Holmlia, N-1203 Oslo, Norway

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Neuroleptics are today regarded as a cornerstone in the treatment of schizophrenia. However, conventional neuroleptics are mainly effective against positive symptoms, and it is often difficult to avoid extrapyramidal symptoms when giving effective dosage. There is thus a need to develop new neuroleptics that are more effective against the negative symptoms of schizophrenia, as well as inducing a lower frequency of extrapyramidal symptoms in therapeutic doses.

It is believed that the antischizophrenic effect of neuroleptics is mainly due to their blocking of dopamine D_2-receptors, and one way to search for better neuroleptics is to develop compounds that are more selective against these receptors or perhaps against a subgroup of D_2-receptors. These compounds include sulpiride, remoxipride and raclopride. However, interference with other receptors in the brain may also be of therapeutic value in schizophrenia, and perhaps especially with regard to negative symptoms. This is indicated by the remarkable antischizophrenic effect of clozapine, which has a modest affinity for D_2-receptors, but a rather high affinity to, for example, serotonin 5-HT_2-receptors. However, the relatively high frequency of agranulocytosis limits the use of clozapine.

Risperidone is a benzisoxazole derivative with relatively strong blocking effect on both dopamine D_2 receptors and 5–HT_2 receptors (1, 2). Risperidone binds also to α_1, α_2 and H_1 receptors. It is a potent LSD antagonist, whereas it is practically devoid of anticholinergic effect. Animal experiments have indicated its low potency in inducing extrapyramidal symptoms (3, 4), and all things considered, risperidone thus seems to be a promising drug for use in schizophrenia. Early clinical trials suggest that RIS is effective on both positive and negative symptoms of schizophrenia (5, 6). Subsequent double-blind studies comparing it with haloperidol have confirmed these results (7, 8).

In the present trial, we have compared therapeutic efficacy and side effects of risperidone with that of another potent neuroleptic, perphenazine, in chronic schizophrenic patients suffering from an acute exacerbation.

Material and methods

This was a multicentre double-blind parallel group study that was carried out in 18 centres in Denmark and Norway (see participants in Acknowledgements). The study was approved by the relevant ethics committees and was performed in accordance with the Declaration of Helsinki II.

Inclusion criteria

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

- age between 18 and 65;
- diagnosis according to DSM-III-R of chronic schizophrenic disorder with acute exacerbation (295.14/295.24/295.34/295.94); and
- informed consent from the patients (or their relatives or legal guardians).

Exclusion criteria

The following patients were excluded:

- patients with mental disorders other than chronic schizophrenic disorder;
- patients with clinically significant organic disorders;
- patients with clinically relevant abnormalities in laboratory tests before the start of the trial;
- patients with a history of alcohol or drug abuse as defined in DSM-III-R within the 12-month period preceding the study;
- patients who had received oral neuroleptic treatment less than 72 h or depot neuroleptics less than 3 weeks before the start of treatment;
- patients committed to a mental hospital (Denmark only); and
- women of reproductive age without adequate contraception; pregnant or lactating women.

Medication

Tablets of identical appearance, containing either 2.5 mg RIS or 8 mg PER, were used. The starting dose was one tablet twice daily, that is to say, 5 mg RIS or 16 mg PER daily. During the first 4 weeks the dose was titrated according to the individual needs of the patient, to a maximum dose of 3 tablets twice daily (15 mg RIS, 48 mg PER). During the last 4 weeks of the trial the dose was to be kept unchanged if possible. However, if adverse effects occurred during this fixed-dose period, the dose could be reduced.

Assessment

The key efficacy variable was the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (9). This rating scale consists of 3 subscales: the positive subscale, the negative subscale and the general psychopathology subscale. All 18 items of the Brief Psychiatric Rating Scale (BPRS) (10) occur in the PANSS, so that the BPRS total score and factor scores can be derived from it. The overall severity of illness was also assessed with the 7-point Clinical Global Impressions (CGI) scale, severity version, and the overall improvement since baseline with the CGI, improvement version. All ratings were performed immediately before start of trial medication, and after 1, 2, 4, 6 and 8 weeks.

Parkinsonian symptoms were evaluated by means of the Extrapyramidal Symptom Rating Scale (ESRS) (11). Other adverse events were assessed by the UKU Side Effect Rating Scale (12).

Statistical analysis

In order not to increase the risk of Type 1 error (accepting a difference as "true" when in fact it is only due to chance), only one single improvement variable was chosen for statistical comparisons between the two drug groups: the patients' improvement at endpoint compared with baseline. All patients in whom at least one clinical assessment had been performed after inclusion (50 patients on RIS and 51 on PER) were included in the intention-to-treat or endpoint analysis. The results at other time points are presented but not statistically analysed.

Two-tail parametric significance tests were used, with a level of significance set at 5%, for total and subtotal scores on PANSS, total and factor scores on BPRS and the CGI scores of severity and improvement. The chi-square test was used to compare the number of improved patients at endpoint (with at least 20% reduction in total score on PANSS).

Results

Patient population

A total of 107 patients entered the trial (Norway: 54, Denmark: 53); 55 were allocated to treatment with RIS, 52 to PER. The mean age of the patients was 36 years (range 20–67); 77 patients (72%) were men and 30 women. The two treatment groups were very similar with respect to demography and baseline characteristics such as sex, weight, height, diagnosis and other data (Table 1). For 10 patients (4 RIS, 6 PER) a concomitant disease was recorded at selection.

Premature withdrawal

Seventy-eight patients (73%) completed the 8-week trial period (RIS 41, PER 37). Thus, 14 patients withdrew prematurely in the RIS group and 15 in the

Table 1. Demographic and baseline characteristics of all patients

	Risperidone	Perphenazine
Total no. of patients (M/F)	55 (40/15)	52 (37/15)
Median age in years (range)	38 (21–61)	35 (20–67)
Median weight in kg (range)	75 (50–117)	76 (43–120)
Median height in cm (range)	176 (154–192)	175 (160–190)
Diagnosis according to DSM-III		
Schizophrenia		
Disorganized	11	17
Paranoid	32	23
Catatonic		1
Undifferentiated	12	11
Patients (%) with previous treatments[a]	*51* (93%)[b]	*49* (94%)[c]
Neuroleptics		
Butyrophenones	4	1
Dibenzoxazepines	4	1
Diphenylbutylpiperidines	3	5
Phenothiazines	37	38
Thioxanthenes	14	15
Other neuroleptics		1
Antidepressants		1
Antidyskinetics	3	3
Benzodiazepines	12	11
Antihistamines	4	1
Antiasthmatics	1	
Corticosteroids	2	
Diuretics	1	1
Nonsteroidal anti-inflammatory drugs	2	2
Oral contraceptives		2
Thyroid preparations	2	
Vitamins or minerals	1	

The treatment groups are comparable with respect to demographic and baseline characteristics: $P > 0.05$ (the chi-square test or Fisher's exact probability test for nominal variables, the Cochran-Mantel-Haenszel test stratified by country for ordinal variables, two-way analysis of variance with effects for group, country and interaction for continuous variables).[a] No information available in one risperidone-treated patient. [b] 25 patients received more than one treatment. [c] 22 patients received more than one treatment.

PER group. Of these, 8 patients on RIS and 6 on PER were withdrawn because of adverse events. Two patients on RIS were withdrawn due to lack of therapeutic effect (after 15 and 28 days); 3 patients on PER were withdrawn for the same reason (after 13, 31, and 41 days). Four patients on RIS and 6 on PER were withdrawn because they stopped coming to the control visits.

All prematurely withdrawn patients are included in the side effect analysis, whereas endpoint analysis of therapeutic effect comprises only patients who were assessed at least once after initiation of trial medication (50 on RIS, 51 on PER). Hence, 9 of the 14 prematurely withdrawn patients on RIS and 14 of the 15 on PER are included in the endpoint analysis.

Medication

Previous medication. Before entering the wash-out phase of the trial, 93% of the patients had been using drugs of diverse categories. Phenothiazines and thioxanthenes were the most commonly used antipsychotics. Twenty-two patients (21%) had used benzodiazepines. The two groups were comparable regarding previous medication (Table 1).

Trial medication. The mean daily dose of trial medication at endpoint was 8.5 mg for risperidone and 28 mg for perphenazine.

Concomitant medication. During the entire treatment period, 42 patients (76%) in the risperidone group and 38 patients (73%) in the perphenazine group used one or more concomitant medicines. Benzodiazepines and orphenadrine were the most frequently used concomitant drugs. There were no significant differences in the use of concomitant drugs between the two treatment groups.

Clinical results: efficacy

The total treatment groups. Table 2 shows the total and subtotal PANSS scores and the total and cluster scores for BPRS for the treatment groups at baseline, after 8 weeks and at endpoint. There is only one significant difference in the endpoint analysis: the hostility cluster of BPRS is improved more on RIS than on PER ($P < 0.005$). There is a nonsignificant tendency for RIS to be better than PER also on the positive subscale of PANSS.

The reduction in mean total PANSS score at the various time points is shown in Fig. 1. There is a tendency for greater improvement in the RIS than in the PER group at weeks 2, 4, en 6. Corresponding results were recorded for the 3 PANSS subscales (not shown).

Clinical improvement, defined as at least 20% reduction in total PANSS score at endpoint, was seen in 74% on RIS and 59% on PER (NS). If clinical improvement is instead defined as at least 20% reduction in total BPRS score, then improvement occurred in 78% on RIS and 59% on PER ($P < 0.05$) (Table 3). The CGI severity scores were comparable between the 2 treatment groups at every time point during the treatment period. The mean CGI improvement scores, on the other hand, showed a (nonsignificant) tendency for more favourable results in the RIS group: the number of patients showing any degree of improvement at endpoint was 80% in the RIS group and 67% in the PER group.

Negative and positive subtypes according to PANSS. At baseline, 76 patients had a higher score on the negative than on the positive PANSS subscale, whereas the opposite was the case for 31 patients.

In the positive subgroup, there was no significant difference in improvement at endpoint between those

Table 2. PANSS and PANSS-derived BPRS: mean scores at baseline and mean changes from baseline after 8 weeks and at endpoint, by treatment group

	Item	Treatment schedule	Baseline n	Baseline Mean values (range)	8 weeks n	8 weeks Mean change versus baseline (range)	Endpoint n	Endpoint Mean change versus baseline (range)	ANOVA[a]
PANNS scale	Positive subscale	Risperidone	55	22 (9–36)	41	−8 (−23–3)	50	−7 (23–7)	NS
		Perphenazine	52	21 (12–36)	37	−7 (−26–3)	51	−5 (−26–6)	
	Negative subscale	Risperidone	55	26 (11–42)	41	−7 (−24–6)	50	−6 (−24–6)	NS
		Perphenazine	52	26 (8–43)	37	−7 (−33–4)	51	−5 (−33–6)	
	General psychopathology subscale	Risperidone	55	47 (29–67)	41	−12 (−34–11)	50	−11 (−34–11)	NS
		Perphenazine	52	46 (30–74)	37	−12 (−43–4)	51	−9 (−43–16)	
	Total PANSS score	Risperidone	55	96 (58–136)	41	−27 (−80–13)	50	−24 (−80–14)	NS
		Perphenazine	52	93 (50–151)	37	−26 (−102–8)	51	−20 (−102–26)	
PANSS-derived scales	Activity	Risperidone	55	8 (3–15)	41	−2 (−9–2)	50	−2 (−9–2)	NS
		Perphenazine	52	8 (3–15)	37	−3 (−9–2)	51	−2 (−9–4)	
	Anergia	Risperidone	55	12 (5–23)	41	−3 (−14–2)	50	−2 (−14–2)	NS
		Perphenzaine	52	12 (5–20)	37	−3 (−12–3)	51	−3 (−12–6)	
	Anxiety or depression	Risperidone	55	12 (5–19)	41	−3 (−9–5)	50	−3 (−9–5)	NS
		Perphenazine	52	11 (5–20)	37	−4 (−11–5)	51	−3 (−11–5)	
	Hostility	Risperidone	55	8 (3–18)	41	−3 (−11–2)	50	−3 (−11–4)	$P<0.01$
		Perphenazine	52	7 (3–14)	37	−2 (−7–2)	51	−1 (−7–4)	
	Thought disturbances	Risperidone	55	13 (4–24)	41	−4 (−13–1)	50	−4 (−13–5)	NS
		Perphenazine	52	13 (4–24)	37	−5 (−20–1)	51	−3 (−20–4)	
	Total BPRS score	Risperidone	55	54 (33–77)	41	−15 (−39–11)	50	−14 (−39–11)	NS
		Perphenazine	52	52 (30–82)	37	−15 (−51–5)	51	−12 (−51–11)	

[a] Variables being treatment schedule and country; significance levels for the variable treatment schedule are given; no significant differences for the variable country.

treated with RIS and those treated with PER. This applied to total or subtotal PANSS scores, BPRS total or cluster scores and the number of patients showing at least 20% reduction in PANSS or BPRS total scores at endpoint.

In the negative subgroup, there was also no significant difference between the two treatment groups in improvement at endpoint according to total or subtotal PANSS scores or in BPRS total score. But there was a significantly greater improvement on RIS than on PER in the BPRS hostility score ($P<0.01$).

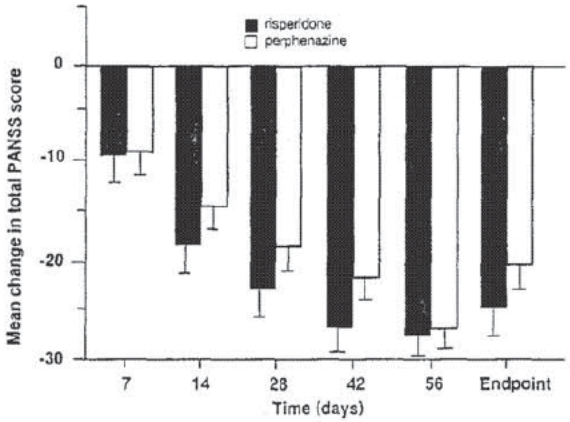

Fig. 1. Mean (± SEM) changes in total PANSS score (analysis includes all patients).

Also the number of patients improved was significantly larger in the RIS than in the PER group (76% *vs* 53%, $P<0.05$, according to total PANSS score, and 78% *vs* 53%, $P<0.05$, according to total BPRS score (Table 4)).

Table 3. Clinical improvement, defined as a reduction of the total PANSS score and PANSS-derived BPRS score by 20% or more, by treatment group

	Clinical improvement on the total PANSS score				
	8 weeks		Endpoint		
Treatment group	n	No. of responders[a] (%)	n	No. of responders[a] (%)	Chi-square two-tailed probability
Risperidone	41	33 (81)	50	37 (74)	NS
Perphenazine	37	28 (76)	51	30 (59)	

	Clinical improvement on the PANSS-derived BPRS score				
	8 weeks		Endpoint		
Treatment group	n	No. of responders[a] (%)	n	No. of responders[a] (%)	Chi-square two-tailed probability
Risperidone	41	34 (83)	50	39 (78)	$P<0.05$
Perphenazine	37	28 (76)	51	30 (59)	

[a] Responders = patient showing clinical improvement, defined as at least 20% reduction from baseline.

Table 4. Clinical improvement group, defined as a reduction of the total PANSS score and PANSS-derived total BPRS score by 20% or more, by treatment group and clinical subtype

		Total PANSS score			Total BPRS score		
		Endpoint			Endpoint		
Subtype	Treatment group	*n*	No. of responders[a] %	Chi-square two-tailed probability	*n*	No. of responders[a] (%)	Chi-square two-tailed probability
Positive	Risperidone	13	9 (69)	NS	13	10 (77)	NS
	Perphenazine	15	11 (73)		15	11 (73)	
Negative	Risperidone	37	28 (76)	$P<0.05$	37	29 (78)	$P<0.05$
	Perphenazine	36	19 (53)		36	19 (53)	

[a] Responders = patients showing clinical improvement, defined as at least 20% reduction from baseline.

Clinical results: side effects

Extrapyramidal symptoms. Parkinsonian symptoms were assessed with the parkinsonism subscale of the ESRS (11). This scale comprises a number of single symptoms arranged in 2 clusters: hypokinetic symptoms (expressive automatic movements, bradykinesia, rigidity, gait and posture and sialorrhoea) and hyperkinetic symptoms (tremor and akathisia); the first cluster can range from a total score of 0 (absent) to an extreme of 48, the second from 0 to 54. A parkinsonism total score combines both clusters plus postural stability.

Table 5 shows the mean of these scores at baseline and the mean shift from baseline to maximum score during treatment. There is a somewhat larger increase in hypokinetic symptoms and parkinsonism total score in the RIS group than in the PER group, but the differences are far from significant.

During the trial period, use of antiparkinson drugs was required by 15 patients (27%) in the RIS and 17 (33%) in the PER group.

UKU Side Effect Rating Scale. On this scale (12), the single symptoms are rated on a scale ranging from 0 (absent) to 3 (maximal), regardless of cause; in addition, a judgement is given on how likely the symptom in question is drug-induced. Table 6 shows the most important results from use of the UKU scale during the trial: (a) The percentage of patients showing (any degree) of the various symptoms at baseline and after 1 and 8 weeks (for brevity, the results after 2, 4 and 6 weeks are not shown), and (b) the percentage of patients who at least once during the trial were given a higher score on the symptom in question than at baseline.

As is usually seen in a drug trial, the picture is complex: the overall frequency of many symptoms (such as depression) is markedly reduced during the treatment period, but there are always some patients who at some time show deterioration. In general, the percentage of patients who reported an increase in severity of symptoms in this study was similar in both treatment groups for most items, with some exceptions. An increase in severity of asthenia was more frequently observed in the RIS group (44%) than in the PER group (28%). This effect was also seen in the item sleepiness or sedation (40% with RIS, 24% with PER). Other items with at least 10% more patients reporting a deterioration in the ris-

Table 5. Rating of extrapyramidal symptoms at baseline and during the trial period. See text for further explanation

Item		Mean score of baseline				Shift of maximum score versus baseline score			
Cluster	Treatment group	*n*	Mean	Range	ANOVA[a]	*n*	Mean	Range	ANOVA[a]
Hyperkinetic symptoms factor[b]	Risperidone	55	1.7	0–7	NS	50	0.9	−4–5	NS
	Perphenazine	52	1.2	0–8		51	1.0	−1–9	
Hypokinetic symptoms factor[c]	Risperidone	55	3.4	0–14	NS	50	1.9	−2–12	NS
	Perphenazine	52	3.6	0–12		51	1.2	−3–7	
Parkinsonism total score	Risperidone	55	5.5	0–20	NS	50	2.6	−5–18	NS
	Perphenazine	52	5.2	0–22		51	2.0	−4–11	

[a] Variable being treatment schedule and country; significance levels for the variable treatment schedule are given; for the variable country, $P<0.05$ for expressive automatic measurements. [b] Hyperkinetic symptoms factor includes the items tremor and akathisia. [c] Hypokinetic symptoms factor includes the items expressive automatic movements, bradykinesia, rigidity, gait and posture and sialorrhoea.

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