British Journal of Psychiatry (1995), **166**, 712–726

Risperidone in the Treatment of Patients with Chronic Schizophrenia: a Multi-National, Multi-Centre, Double-Blind, Parallel-Group Study versus Haloperidol

J. PEUSKENS, on behalf of the Risperidone Study Group

Background. This study was performed in order to evaluate the short-term efficacy and safety of fixed risperidone doses compared to haloperidol.

Method. In a multi-national, parallel-group, double-blind study, patients with chronic schizophrenia (DSM-III-R) were randomly assigned to risperidone 1, 4, 8, 12 or 16 mg or haloperidol 10 mg daily for 8 weeks. Efficacy was assessed by the Positive and Negative Syndrome Scale for schizophrenia (PANSS) and clinical global impression (CGI), and safety primarily by the Extrapyramidal Symptom Rating Scale (ESRS).

Results. One thousand three hundred and sixty-two patients were evaluated. The optimum risperidone doses were 4 mg and 8 mg, with response rates of 63.4% (56.8%; 69.7%) and 65.8% (59.2%; 71.9%) respectively. Response rate in haloperidol-treated patients was 58.7% (52.0%; 65.3%); the 95% confidence intervals (CI) of the differences between risperidone 4 mg or 8 mg and haloperidol were (−4.3%; 13.7%) and (−1.9%; 16.0%) respectively. There were no significant differences in CGI scores at endpoint between risperidone 4 mg, 8 mg, 12 mg and 16 mg and haloperidol (3.0, 3.0, 3.2, 3.1 and 3.1 respectively); the 95% CI of the differences between risperidone 4 mg or 8 mg and haloperidol were (−0.4; 0.1) and (−0.3; 0.2) respectively. Mean shifts to the maximum total ESRS scores versus baseline (mean (confidence interval)) were significantly greater in haloperidol-treated patients (5.1 (4.0; 6.2)) than in the risperidone 1, 4, 8 and 12 mg groups (1.1 (0.3; 1.9); 1.8 (0.9; 2.7); 2.7 (1.8; 3.6) and 3.2 (2.3; 4.1) respectively ($P<0.05$)).

Conclusion. Risperidone is an effective antipsychotic for the treatment of chronic schizophrenia; doses of 4 and 8 mg seem to be optimal and have a lower incidence of side-effects than haloperidol.

Conventional neuroleptics, which have been the mainstay of treatment for schizophrenia for over 40 years, have two major drawbacks: relative lack of effect on the negative symptoms of chronic schizophrenia (Crow, 1985), and their propensity to induce extrapyramidal side-effects (EPS) (Van Putten, 1974). The search for new antipsychotics has focused on maintained or improved control of positive symptoms and improved efficacy in the control of negative symptoms, while reducing the rate of EPS and general side-effects. One approach, based on the hypothesis that interference with serotonin 5-HT_2 receptors in addition to dopamine-D_2 antagonism may have a role in the treatment of schizophrenia, has led to the development of drugs with potent antagonism of both serotonin 5-HT_2 and dopamine-D_2 receptors – the serotonin–dopamine antagonists (SDAs).

Risperidone, a benzisoxazole derivative, is the first of this new class of centrally acting serotonin–dopamine antagonists (Janssen *et al*, 1988; Leysen *et al*, 1988). It has greatest affinity for serotonin 5-HT_2 receptors, and is also a potent inhibitor of dopamine-D_2 receptors. Risperidone has been found to improve positive, negative, and affective symptoms in chronic psychotic patients in both open, single-blind, placebo-controlled studies (Castelao *et al*, 1989; Gelders, 1989; Meco *et al*, 1989; Mesotten *et al*, 1989; Gelders *et al*, 1990; Bersani *et al*, 1990), and in double-blind studies (Borison *et al*, 1992; Claus *et al*, 1992; Marder & Meibach, 1994) using haloperidol as the standard reference treatment. Marder & Meibach (1994) reported a bell-shaped dose–response curve for risperidone, with the optimal dose at 6 mg daily. At this dose, risperidone had a more rapid therapeutic effect than haloperidol 20 mg, and was significantly more effective in improving positive symptoms, negative symptoms and general psychopathology (including affective symptoms). In addition, the incidence of EPS was not statistically different from placebo.

The aim of the present study was to evaluate the short-term efficacy and safety of five different doses of risperidone compared to a fixed dose of haloperidol in patients with chronic schizophrenia, and thus determine the dose–response relationship for risperidone in this patient population.

Methods

Subjects

Patients with chronic schizophrenia were recruited as possible subjects in 110 centres from 15 countries. Informed consent was obtained in all cases, and the study was approved by local Ethics Committees and conducted in accordance with the Declaration of Helsinki (1964) revised in Tokyo (1975), and the subsequent Venice (1983) and Hong Kong (1989) amendments.

To be eligible for inclusion, patients had to have a diagnosis of chronic schizophrenic disorder according to DSM–III–R (American Psychiatric Association, 1987) with a total score between 60 and 120 on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay *et al*, 1987, 1988). Patients were excluded if they had clinically significant organic or neurological disorders, epilepsy, psychiatric disorders other than chronic schizophrenia, a history of alcohol or drug abuse in the previous 12 months, or had participated in trials of investigational drugs in the preceding 4 weeks. Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded.

Study design

This was a double-blind, randomised, parallel-group study. The primary measure of efficacy was the percentage of patients showing clinical improvement, defined *a priori* as a 20% reduction of the total PANSS score compared with baseline. To detect small differences (15%) in clinical response between effective treatment groups, a total of 200 patients per group were included. All subjects initially underwent a single-blind, placebo wash-out period of 1 week (day −6 to day 0), which could be shortened to a minimum of 3 days in the case of acute psychotic exacerbations. For patients treated with depot neuroleptics, the placebo period started on the day they would otherwise have received their next injection. All psychotropic and antiparkinson medication was withdrawn on the first day of the wash-out period, but other treatments were continued unchanged.

After the placebo period, patients entered the double-blind phase of the study. They were randomly assigned to one of six treatment groups by a random permuted block randomisation procedure with block size 6 (Pocock, 1983). The randomisation list thus developed was transferred to a sequence of sealed envelopes, each containing the allocation for the next patient. Every investigator received one block for each multiple of 6 patients to be included in the trial. No explicit stratification was implemented in the randomisation procedure. The six treatments were risperidone 1 mg, 4 mg, 8 mg, 12 mg, or 16 mg, or haloperidol 10 mg, divided evenly into a morning and an evening administration. These target doses were achieved by dose augmentation, in a double-blind way, within the first week (days 1 to 7). Once attained, the maintenance dose was kept unchanged for the following 7 weeks (day 8 to day 56). Lorazepam, oxazepam or temazepam were permitted if a hypnotic or daytime sedative was required, and biperiden or procyclidine were allowed if EPS emerged.

Efficacy evaluation

Assessment with the PANSS scale (Kay *et al*, 1988) was undertaken at each visit (days −7, 0, 7, 14, 28, 42 and 56). The PANSS includes 30 items which measure both positive and negative symptoms, as well as general psychopathology, by means of a semi-structured interview. Video tapes of patient interviews produced by the authors of the scale were used to train investigators in the use of the PANSS and to assess inter-rater reliability. The primary measure of risperidone efficacy was the percentage of patients showing clinical improvement, defined as a reduction in total PANSS score of at least 20% from baseline. Secondary efficacy parameters were the change in mean total PANSS score and changes in positive, negative and general psychopathology subscale scores. The efficacy of risperidone in various subgroups was evaluated on the basis of previously defined criteria, based on the PANSS baseline scores. Two types of subdivision were applied (Kay *et al*, 1987). In the first system, patients with a composite scale score (the difference between scores from seven symptoms on the positive subscale and seven symptoms on the negative subscale) $\geqslant 0$ were classified as the positive subtype, and those with a score < 0 as the negative subtype. The second system was more stringent: patients were classified as positive subtype if they had three or more scores $\geqslant 4$ on the positive subscale and fewer than three scores $\geqslant 4$ on the negative subscale. The negative subtype exhibited the opposite pattern. Patients with at least three scores $\geqslant 4$ on both subscales were regarded as mixed subtype, while those who

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

reached this criterion for neither scale were considered neither subtype. In addition to the PANSS scores, secondary efficacy measurements included the PANSS-derived Brief Psychiatric Rating Scale (BPRS) total and cluster scores (the PANSS scale includes all 18 BPRS items (Overall & Gorham, 1962)) and the Clinical Global Impression (CGI; Guy, 1976) score of the severity of the illness. The CGI was completed at each visit. At visits 3–7, each patient's present condition was compared to his/her condition at baseline. At the end of the study, the investigator and the patient compared the double-blind treatment with their pre-study neuroleptic therapy on a seven-point scale. It was an ordinal categorical parameter with the following scoring items: much better, better, slightly better, identical, slightly worse, worse and much worse.

Safety evaluation

EPS were evaluated at each visit using the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard *et al*, 1979; 1980), which consists of a questionnaire to evaluate the subjective effects of EPS, a detailed clinical evaluation of parkinsonism, dystonia and dyskinesia, and CGI scales for the severity of parkinsonism and dyskinesia. Investigators also attended training sessions on the use of the ESRS.

Other adverse events were assessed by a modified version of the UKU Side-Effect Rating Scale (Lingjaerde *et al*, 1987). As 10 of its original 48 items are duplicated in either the PANSS or ESRS, these were omitted. The remaining 38 items are divided into psychic (seven items), neurological (two items), autonomic (ten items), and others (19 items). Investigators were also asked to report any other symptoms not covered by these items. These adverse events were graded for severity (mild, moderate or severe) and for causal relationship to the study drug (improbable, possible or probable). Both the investigator and patient were asked for a global assessment of the interference caused by each adverse event on daily performance.

Blood pressure and heart rate were measured at each visit. In addition to routine physical examination, ECG and body weight measurement, endocrinological tests, urinalysis, haematology, and blood biochemistry analyses were performed both at the end of the wash-out phase and at the end of the double-blind treatment.

Statistical analysis

For efficacy variables, a two-way ANOVA was used to compare the different treatment schedules for all PANSS-related changes versus baseline, and the 95% confidence intervals were calculated using Fisher's least significance test procedure. To detect possible differences between the treatment groups with respect to categorical variables, the Cochran–Mantel–Haenszel test, stratified by country, was applied and pairwise comparisons were performed using the Mann–Whitney U test. The Chi-square test was applied on the number of patients showing clinical improvement.

In the safety analyses, inter-group comparison of the ESRS was carried out with a two-way ANOVA and pairwise comparisons were performed using Fisher's least significant difference procedure. To avoid possible masking of EPS by the use of antiparkinson medication, the increase between baseline and the maximum score during the double-blind period was calculated (shift to the maximum) for all primary and secondary clusters of the ESRS.

Both safety-related CGIs were used to estimate the time to onset of deterioration of dyskinesia and parkinsonism. The cumulative proportion of patients showing deterioration on the CGIs was estimated by the Kaplan–Meier method. Statistical comparisons (overall as well as pairwise comparisons) were performed by means of the Gehan's generalised Wilcoxon test. For the PANSS, the ESRS and CGI, pairwise comparisons interpreted at the 5% level were only performed if the overall test over the six treatment groups showed a difference significant at the 10% level.

To investigate the dose-relationship between the different risperidone schedules, the Jonckheere-Terpstra test was applied (Lehmann, 1975) on the change between baseline and the maximum score observed.

The incidence of EPS was also evaluated by means of the number of patients who required concomitant use of antiparkinson or any other medication given primarily for EPS. The Chi-square test was used to detect possible inter-group differences for the number of patients; the Gehan's generalised Wilcoxon test was used for assessing the time to first occurrence of only newly reported medications and/or indications during double-blind treatment.

Two-sided P values were used for all analyses; P values $\leqslant 0.05$ were considered significant.

Results

A total of 1362 patients were evaluated, all of whom had a diagnosis of chronic schizophrenia according to DSM–III–R. The median duration of current hospitalisation was about 4 years (Table 1),

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 1
Demographic and baseline characteristics

	Risperidone					Haloperidol
	1 mg (*n* = 229)	4 mg (*n* = 227)	8 mg (*n* = 230)	12 mg (*n* = 226)	16 mg (*n* = 224)	10 mg (*n* = 226)
Male/female	166/63	152/75	144/86	142/83[1]	140/84	150/76
Mean age (years)	38.4	38.1	37.6	37.9	38.5	38.1
Diagnosis of schizophrenia:						
Disorganised	36	49	36	37	31	37
Catatonic	10	9	7	11	7	3
Paranoid	97	82	87	81	90	85
Residual	47	43	58	62	46	50
Undifferentiated	39	43	42	35	49	51
Unspecified		1			1	
Median (25; 75 percentile) age at first onset of psychiatric symptoms (years)	20.5 (18; 25)	21 (17; 27)	21 (18; 25)	21 (18; 26)	22 (19; 27)	22 (18; 28)
Median (25; 75 percentile) age at first hospitalisation (years)	23.5 (20; 28)	23 (19; 29)	23 (20; 29)	23 (20; 28)	24.5 (20; 29)	24 (20; 30)
Median (25; 75 percentile) number of previous hospitalisations	3 (1; 6)	3 (1; 6)	3 (1; 5)	3 (2; 5)	4 (2; 7)	3 (1; 6)
Median (25; 75 percentile) duration of current hospitalisation (months)	7 (0; 78)	4 (0; 62.5)	4 (0; 51)	2 (0; 50)	3 (0; 41)	3.5 0; 62)

1. Sex not recorded in one patient.

demonstrating the chronic nature of the disease. Sixty-three per cent of the patients were receiving oral neuroleptic drugs of diverse categories prior to entry into the trial, 37% had received depot neuroleptics (41%, 37%, 41%, 36%, 34% and 35% in the risperidone 1 mg, 4 mg, 8 mg, 12 mg, 16 mg and haloperidol groups respectively). Phenothiazines and butyrophenones were the most used antipsychotic treatment, in depot (57% and 16% respectively) as well as in oral (62% and 37% respectively) formulation, including haloperidol in 22% of patients. The previous median daily haloperidol dose was 10 mg in the risperidone 1 mg, 8 mg, 16 mg and haloperidol groups, and 9 mg in the risperidone 4 mg and 12 mg groups. Thirty-three per cent of patients were receiving concomitant antiparkinson medication prior to initiation into the study. The mean duration of the placebo wash-out phase was 6.5 days, with no significant differences between the groups; this period was reduced to 6 days or less in 336 patients (25%). Acute deterioration was given as the reason for a shortened wash-out phase in approximately 17% of patients (16%, 15%, 20%, 18%, 18% and 17% in the risperidone 1 mg, 4 mg, 8 mg, 12 mg, 16 mg and haloperidol groups respectively). The eight-week, double-blind phase of the study was completed by 1019 patients (75%), with the most common reasons for drop-out being insufficient response (154 patients) and adverse events (126 patients) (Table 2).

PANSS principal component analysis (PCA)

Inter-rater reliability was demonstrated by the 80% concordance with the score on the training video in 81 of the 96 investigators from whom results were obtained. PCA and equimax rotation performed on the PANSS scores of all investigators at the beginning of the wash out period yielded seven components: negative (six items), positive (six items), depressive (five items) and excited (four items) components plus three components (nine items) which were less distinct. These seven components found indicate, as in the original work of Kay & Sevy (1990), that the PANSS scoring was correctly performed, and suggest that the PANSS psychometric scale has reliability in international cross-cultural settings.

Efficacy

The six treatment groups were comparable at baseline with respect to all efficacy parameters. The key efficacy parameter was the percentage of patients reaching clinical improvement. Clinical improvement, defined as at least 20% reduction of baseline total PANSS score, was achieved by 814 patients (60.2%). Although there were no significant differences between the treatment groups, the highest response rate was seen in the risperidone 4 mg and 8 mg groups (63.4% and 65.8%, confidence intervals (CI) (56.8%; 69.7%) and (59.2%; 71.9%) respectively). These

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 2
Drop-outs during double-blind treatment

Reasons[1]	No. of drop-outs						
	Risperidone					Haloperidol 10 mg	All groups
	1 mg	4 mg	8 mg	12 mg	16 mg		
Adverse experiences	18	15	17	22	31	23	126
Death					1		1
Suicidal attempt/tendency	2	1	1	3		2	9
Insufficient response	40	16	24	32	20	22	154
Intercurrent disease	2			1	1		4
Intercurrent event	2		2	2	2		8
Intercurrent treatment					1	2	3
Lost to follow-up	3	4	4	6	4	5	26
Selection criteria not met	1		1				2
Sufficient response		1		1		1	3
Patient's decision	3	7	9	6	7	15	47
Lack of motivation	3	5	5	5	5	5	28
Uncooperative		5	4	7	8	5	29
Other	1	2	1	1	3	3	11
Unspecified						1	1
Total No. (%) of drop-outs	58 (25%)	45 (20%)	56 (24%)	62 (27%)	59 (26%)	63 (28%)	343 (25%)
Median (25; 75 percentile) no. of days in study	21.5 (8; 39)	24 (13; 41)	20.5 (10.5; 30.5)	22 (12; 34)	20 (13; 29)	21 (7; 34)	21 (11; 35)
Total No. of patients	229	227	230	226	224	226	1362

1. A patient may have more than one reason for prematurely discontinuing the study.

compared with 54.4% (47.7%; 61.0%), 58.2% (51.5%; 64.7%), 60.5% (53.8%; 67.0%) and 58.7% (52.0%; 65.3%) of those treated with risperidone 1 mg, 12 mg, 16 mg and haloperidol respectively. The 95% CI of the difference between risperidone 4 mg and haloperidol were (−4.3%; 13.7%), and between risperidone 8 mg and haloperidol (−1.9%; 16.0%). A similar percentage of patients (62.3%) attained clinical improvement on the total BPRS scale, but there were significantly ($P \leqslant 0.05$) more patients with clinical improvement in the risperidone 4 mg and 8 mg groups (67.0% and 68.4%) than in the risperidone 1 mg group (54.4%).

The mean changes in PANSS total score and subscale scores from baseline (start of double-blind treatment phase) to endpoint (time of treatment withdrawal or end of eight-week study period) are shown in Table 3. The total PANSS score showed a significantly ($P \leqslant 0.05$) greater mean change versus baseline in the risperidone 4 mg, 8 mg, and 16 mg groups than in the group receiving risperidone 1 mg. In contrast, the changes in the risperidone 12 mg and haloperidol groups did not differ significantly from those in the risperidone 1 mg group. A similar pattern was observed on the general psychopathology subscale. The effects of both risperidone 4 mg and 8 mg were significantly ($P \leqslant 0.05$) better than those of risperidone 1 mg, while risperidone 4 mg was also significantly ($P \leqslant 0.05$) better than haloperidol.

On the positive subscale of the PANSS, the five other treatment groups showed a better effect than that receiving risperidone 1 mg. On the negative subscale, the changes versus baseline in the six treatment groups were not statistically different at endpoint, but there was a greater magnitude of response in the risperidone 4 mg, 8 mg and 16 mg groups.

The inter-group differences between baseline and endpoint seen in the PANSS total score were mirrored in the PANSS-derived BPRS total score (Table 4). Risperidone doses of 4 mg, 8 mg, and 16 mg were significantly ($P \leqslant 0.05$) better than risperidone 1 mg, while no significant difference was seen between haloperidol and risperidone 1 mg.

In the cluster 'activity', the same three doses of risperidone achieved a significantly ($P \leqslant 0.05$) greater decrease in score than did risperidone 1 mg, while the drop in score with risperidone 4 mg was also significantly ($P \leqslant 0.05$) greater than that seen with haloperidol. The inter-group differences in the clusters 'thought disturbances' and 'hostility' paralleled those of the positive subscale of the

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 3
PANSS total and subscale scores: mean baseline values and changes from baseline to endpoint

	Treatment schedule		Baseline		Endpoint		95% CI of difference with haloperidol[1]	Pairwise intergroup comparison ($P \leqslant 0.05$)
			n	Mean value (s.e.)	*n*	Mean change versus baseline (s.e.)		
Positive subscale	Risperidone	1 mg	229	19.5 (0.44)	226	−2.1 (0.47)	[0.6; 3.0]	
		4 mg	227	19.2 (0.44)	227	−4.2 (0.46)	[−1.6; 0.9]	>1 mg
		8 mg	230	18.9 (0.41)	228	−4.5 (0.45)	[−1.9; 0.6]	>1 mg
		12 mg	226	19.1 (0.44)	225	−3.9 (0.39)	[−1.3; 1.2]	>1 mg
		16 mg	224	19.9 (0.47)	223	−4.9 (0.49)	[−2.3; 0.2]	>1 mg
	Haloperidol	10 mg	226	19.0 (0.43)	223	−3.9 (0.43)		>1 mg
Negative subscale	Risperidone	1 mg	229	26.6 (0.48)	226	−4.5 (0.49)	[−1.0; 1.6]	
		4 mg	227	26.2 (0.50)	227	−5.5 (0.52)	[−2.0; 0.6]	
		8 mg	230	26.8 (0.50)	228	−5.2 (0.48)	[−1.8; 0.9]	
		12 mg	226	26.6 (0.51)	225	−5.0 (0.46)	[−1.5; 1.1]	
		16 mg	224	26.2 (0.50)	223	−5.2 (0.50)	[−1.7; 1.0]	
	Haloperidol	10 mg	226	26.4 (0.48)	223	−4.8 (0.46)		
General psychopathology subscale	Risperidone	1 mg	229	44.0 (0.65)	226	−6.0 (0.78)	[−1.8; 2.5]	
		4 mg	227	44.2 (0.64)	227	−8.9 (0.81)	[−4.7; −0.4]	>1 mg>Hal
		8 mg	230	43.6 (0.67)	228	−8.2 (0.80)	[−4.0; 0.3]	>1 mg
		12 mg	226	44.8 (0.63)	225	−7.7 (0.74)	[−3.5; 0.9]	
		16 mg	224	43.7 (0.64)	223	−6.9 (0.78)	[−2.7; 1.6]	
	Haloperidol	10 mg	226	43.4 (0.62)	223	−6.4 (0.79)		
Total PANSS	Risperidone	1 mg	229	90.1 (1.18)	226	−12.5 (1.55)	[−1.7; 6.6]	
		4 mg	227	89.6 (1.16)	227	−18.6 (1.56)	[−7.7; 0.5]	>1 mg
		8 mg	230	89.2 (1.24)	228	−17.9 (1.55)	[−7.0; 1.2]	>1 mg
		12 mg	226	90.5 (1.20)	225	−16.6 (1.39)	[−5.7; 2.6]	
		16 mg	224	89.8 (1.20)	223	−17.0 (1.54)	[−6.1; 2.1]	>1 mg
	Haloperidol	10 mg	226	88.8 (1.10)	223	−15.0 (1.46)		

>Significantly better than
1. 95% confidence interval of the difference between risperidone and haloperidol in the shift v. baseline at endpoint.

PANSS; the same five treatments were significantly better than risperidone 1 mg. There were no significant inter-group differences in the changes in the 'anergia' and 'anxiety/depression' cluster scores, although the improvement tended to be greater in the risperidone 4 mg and 8 mg groups.

The efficacy of risperidone in the positive, negative and mixed symptom subtypes was found to be similar to that in the total sample.

At study endpoint CGI scores for the severity of schizophrenia were 3.5, 3.0, 3.0, 3.2, 3.1 and 3.1 in the risperidone 1 mg, 4 mg, 8 mg, 12 mg and 16 mg and haloperidol groups respectively, based on scores of 0, 'not ill' and 6, 'extremely severe'. Analysis of these scores revealed a significant difference between risperidone 1 mg and all the other treatment groups ($P \leqslant 0.05$). The 95% CI of the differences between the optimum risperidone doses (4 mg and 8 mg) and haloperidol were (−0.4; 0.1) and (−0.3; 0.2) respectively. When the investigator compared the patients' overall clinical condition at endpoint with baseline CGI scores, treatment with risperidone at a dose of 4 mg or 8 mg resulted in a significantly greater improvement than risperidone 1 mg (mean scores were 3.0, 3.1 and 3.4 ($P \leqslant 0.05$) respectively, where 1 was 'very much improved' and 7 'very much worse'). Also on the investigator's rating, the mean score during double-blind treatment in comparison with previous neuroleptic therapy was significantly better for patients treated with risperidone 4 mg than for the risperidone 1 mg, 12 mg and 16 mg groups.

Safety

The six treatment groups were comparable at baseline with respect to the severity of EPS, as assessed by the ESRS. Inter-group comparison of the six treatments revealed significant ($P \leqslant 0.05$) differences in the shifts to the maximum score during double-blind treatment for the questionnaire, for the items of the 'parkinsonism' cluster, CGI clusters, and all

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 4
The PANSS-derived BPRS total and cluster scores: mean baseline values and changes from baseline to endpoint

Cluster	Treatment schedule		Baseline		Endpoint		95% CI of difference with haloperidol[1]	Pairwise intergroup comparison ($P \leqslant 0.05$)
			n	Mean value (s.e.)	*n*	Mean change versus baseline (s.e.)		
Thought disturbances	Risperidone	1 mg	229	11.9 (0.28)	226	−1.4 (0.27)	(0.2; 1.6)	
		4 mg	227	11.8 (0.30)	227	−2.3 (0.27)	(−0.7; 0.8)	>1 mg
		8 mg	230	11.5 (0.28)	228	−2.6 (0.26)	(−1.0; 0.4)	>1 mg
		12 mg	226	11.8 (0.29)	225	−2.3 (0.22)	(−0.7; 0.7)	>1 mg
		16 mg	224	12.1 (0.31)	223	−2.6 (0.29)	(−1.0; 0.4)	>1 mg
	Haloperidol	10 mg	226	11.8 (0.29)	223	−2.3 (0.26)		>1 mg
Anergia	Risperidone	1 mg	229	12.2 (0.26)	226	−2.1 (0.24)	(−0.9; 0.4)	
		4 mg	227	12.3 (0.24)	227	−2.6 (0.25)	(−1.4; −0.1)	
		8 mg	230	12.6 (0.24)	228	−2.4 (0.23)	(−1.2; 0.1)	
		12 mg	226	12.3 (0.26)	225	−2.1 (0.22)	(−0.8; 0.4)	
		16 mg	224	12.3 (0.25)	223	−2.1 (0.25)	(−0.9; 0.4)	
	Haloperidol	10 mg	226	11.9 (0.24)	223	−1.9 (0.22)		
Anxiety-depression	Risperidone	1 mg	229	9.6 (0.27)	226	−1.7 (0.22)	(−0.8; 0.5)	
		4 mg	227	9.6 (0.25)	227	−2.2 (0.24)	(−1.3; 0.0)	
		8 mg	230	9.4 (0.25)	228	−1.9 (0.24)	(−0.9; 0.4)	
		12 mg	226	9.9 (0.24)	225	−1.8 (0.23)	(−0.8; 0.5)	
		16 mg	224	9.8 (0.27)	223	−1.7 (0.25)	(−0.7; 0.6)	
	Haloperidol	10 mg	226	9.7 (0.27)	223	−1.6 (0.22)		
Activity	Risperidone	1 mg	229	7.8 (0.19)	226	−1.0 (0.20)	(−0.3; 0.8)	
		4 mg	227	7.8 (0.18)	227	−1.8 (0.19)	(−1.1; 0.0)	>1 mg, >Hal
		8 mg	230	7.4 (0.18)	228	−1.6 (0.20)	(−1.0; 0.1)	
		12 mg	226	7.7 (0.19)	225	−1.4 (0.19)	(−0.8; 0.3)	
		16 mg	224	7.9 (0.19)	223	−1.7 (0.21)	(−1.1; 0.0)	>1 mg
	Haloperidol	10 mg	226	7.6 (0.19)	223	−1.2 (0.19)		
Hostility	Risperidone	1 mg	229	7.3 (0.22)	226	−0.5 (0.23)	(0.1; 1.3)	
		4 mg	227	7.1 (0.21)	227	−1.4 (0.23)	(−0.8; 0.4)	>1 mg
		8 mg	230	7.3 (0.19)	228	−1.5 (0.23)	(−0.9; 0.3)	>1 mg
		12 mg	226	7.4 (0.22)	225	−1.4 (0.21)	(−0.9; 0.4)	>1 mg
		16 mg	224	7.4 (0.22)	223	−1.6 (0.24)	(−1.1; 0.2)	>1 mg
	Haloperidol	10 mg	226	7.0 (0.19)	223	−1.2 (0.21)		>1 mg
Total BPRS	Risperidone	1 mg	229	48.9 (0.70)	226	−6.7 (0.87)	(−0.9; 3.7)	
		4 mg	227	48.6 (0.67)	227	−10.2 (0.86)	(−4.4; 0.2)	>1 mg
		8 mg	230	48.1 (0.72)	228	−10.0 (0.89)	(−4.2; 0.5)	>1 mg
		12 mg	226	49.1 (0.67)	225	−9.0 (0.77)	(−3.3;1.4)	
		16 mg	224	49.5 (0.71)	223	−9.7 (0.90)	(−3.9; 0.8)	>1 mg
	Haloperidol	10 mg	226	48.1 (0.68)	223	−8.1 (0.82)		

>Significantly better than
1. 95% confidence interval of the difference between risperidone and haloperidol in the shift v. baseline at endpoint.

individual and combined clusters, with the exception of the 'dyskinesia' cluster (Table 5).

The mean shift to the maximum for the total score of parkinsonism, dystonia and dyskinesia is shown in Fig. 1. On all the primary and secondary parameters of the ESRS, except dyskinesia, CGI dyskinesia and CGI parkinsonism, the shift to the maximum was significantly ($P \leqslant 0.05$) larger in the haloperidol group than in the risperidone 1 mg, 4 mg, 8 mg and 12 mg groups. For the 'dystonia' cluster and the item akathisia in the 'parkinsonism' cluster, the shift was significantly higher with haloperidol than with any dose of risperidone, moreover there were no significant differences between the risperidone groups (Fig. 2). Tests revealed a significant dose–response relationship between the five risperidone treatment groups, again for the ESRS clusters and ESRS total score (with the

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 5
Extrapyramidal Symptom Rating Scale (ESRS) cluster and total scores: mean values at baseline and mean shifts to maximum score over the double-blind period v. baseline, by treatment schedule

Cluster		Treatment schedule		Baseline		Double-blind period			
				n	Mean value (s.e.)	*n*	Mean shift of maximum total score v. baseline (s.e.)	95% CI of difference with haloperidol[3]	Pairwise intergroup comparison ($P \leqslant 0.05$)
I	Questionnaire total score	Risperidone	1 mg	229	2.8 (0.22)	226	0.8 (0.19)	(−2.6; −1.2)	
			4 mg	227	2.9 (0.26)	227	0.9 (0.25)	(−2.5; −1.1)	
			8 mg	230	2.7 (0.24)	228	1.6 (0.26)	(−1.8; −0.4)	>1 mg, >4 mg
			12 mg	226	2.7 (0.21)	225	1.9 (0.25)	(−1.5; −0.1)	>1 mg, >4 mg
			16 mg	224	2.9 (0.22)	224	2.6 (0.29)	(−0.8; 0.6)	>1 mg, >4 mg
		Haloperidol	10 mg	226	2.7 (0.21)	223	2.7 (0.27)		>1 mg, >4 mg, >8 mg, >12 mg
II	Parkinsonism total score[1]	Risperidone	1 mg	229	5.3 (0.34)	226	0.6 (0.25)	(−4.7; −2.7)	
			4 mg	227	5.2 (0.38)	227	1.7 (0.34)	(−3.5; −1.5)	>1 mg
			8 mg	230	5.5 (0.38)	228	2.4 (0.36)	(−2.8; −0.8)	>1 mg
			12 mg	226	5.2 (0.34)	225	2.9 (0.36)	(−2.4; −0.4)	>1 mg, >4 mg, >8 mg, >12 mg
			16 mg	224	5.4 (0.38)	224	4.1 (0.43)	(−1.1; 0.9)	>1 mg, >4 mg, >8 mg, >12 mg
		Haloperidol	10 mg	226	5.0 (0.34)	223	4.2 (0.42)		>1 mg, >4 mg, >8 mg, >12 mg
IIa	Hypokinesia symptoms factor	Risperidone	1 mg	229	3.7 (0.25)	226	0.3 (0.17)	(−3.2; −1.7)	
			4 mg	227	3.6 (0.26)	227	1.2 (0.24)	(−2.3; −0.8)	>1 mg
			8 mg	230	3.9 (0.28)	228	1.9 (0.27)	(−1.7; −0.2)	>1 mg
			12 mg	226	3.6 (0.23)	225	2.1 (0.27)	(−1.5; −0.0)	>1 mg, >4 mg
			16 mg	224	3.6 (0.27)	224	3.0 (0.32)	(−0.5; 1.0)	>1 mg, >4 mg, >8 mg, >12 mg
		Haloperidol	10 mg	226	3.5 (0.24)	223	2.8 (0.31)		>1 mg, >4 mg, >8 mg, >12 mg
IIb	Hyperkinesia symptoms factor	Risperidone	1 mg	229	1.2 (0.12)	226	0.5 (0.10)	(−1.4; −0.7)	
			4 mg	227	1.3 (0.13)	227	0.6 (0.12)	(−1.3; −0.6)	
			8 mg	230	1.3 (0.12)	228	0.7 (0.13)	(−1.2; −0.5)	
			12 mg	226	1.2 (0.12)	225	0.8 (0.12)	(−1.0; −0.3)	>1 mg
			16 mg	224	1.4 (0.13)	224	1.0 (0.13)	(−0.8; −0.1)	>1 mg, >4 mg, >8 mg
		Haloperidol	10 mg	226	1.2 (0.12)	223	1.5 (0.15)		>1 mg, >4 mg, >8 mg, >12 mg, >16 mg
III	Dystonia total score	Risperidone	1 mg	229	0.4 (0.07)	226	0.1 (0.06)	(−0.5; −0.1)	
			4 mg	227	0.4 (0.07)	227	0.2 (0.06)	(−0.4; −0.1)	
			8 mg	230	0.3 (0.06)	228	0.1 (0.05)	(−0.5; −0.1)	
			12 mg	226	0.3 (0.06)	225	0.1 (0.05)	(−0.5; −0.1)	
			16 mg	224	0.4 (0.06)	224	0.2 (0.06)	(−0.4; −0.0)	
		Haloperidol	10 mg	226	0.3 (0.05)	223	0.4 (0.09)		>1 mg, >4 mg, >8 mg, >12 mg, >16 mg
IV	Dyskinesia total score[2]	Risperidone	1 mg	229	2.1 (0.26)	226	0.8 (0.21)	(−0.7; 0.4)	
			4 mg	227	2.0 (0.28)	227	0.3 (0.17)	(−1.1; −0.1)	
			8 mg	230	1.4 (0.21)	228	0.5 (0.14)	(−1.0; 0.0)	
			12 mg	226	1.5 (0.20)	225	0.6 (0.19)	(−0.9; 0.2)	
			16 mg	224	2.0 (0.26)	224	0.9 (0.22)	(−0.6; 0.5)	
		Haloperidol	10 mg	226	1.7 (0.25)	223	1.0 (0.23)		

(continued)

Table 5 *(continued)*

Cluster		Treatment schedule		Baseline		Double-blind period			
				n	Mean value (s.e.)	*n*	Mean shift of maximum total score v. baseline (s.e.)	95% CI of difference with haloperidol[3]	Pairwise intergroup comparison ($P \leqslant 0.05$)
IVa	Bucco-linguo-masticatory factor	Risperidone	1 mg	229	1.2 (0.16)	226	0.6 (0.12)	(−0.1; 0.5)	
			4 mg	227	1.0 (0.17)	227	0.2 (0.10)	(−0.5; 0.1)	
			8 mg	230	0.7 (0.11)	228	0.2 (0.07)	(−0.5; 0.2)	
			12 mg	226	0.8 (0.13)	225	0.3 (0.11)	(−0.4; 0.2)	
			16 mg	224	1.1 (0.15)	224	0.5 (0.14)	(−0.2; 0.4)	
		Haloperidol	10 mg	226	0.9 (0.14)	223	0.4 (0.10)		
IVb	Choreoathetoid movements limbs	Risperidone	1 mg	229	0.5 (0.09)	226	0.2 (0.09)	(−0.4; 0.1)	
			4 mg	227	0.5 (0.09)	227	0.2 (0.07)	(−0.4; 0.1)	
			8 mg	230	0.4 (0.08)	228	0.2 (0.07)	(−0.4; 0.1)	
			12 mg	226	0.3 (0.06)	225	0.3 (0.07)	(−0.3; 0.2)	
			16 mg	224	0.4 (0.08)	224	0.4 (0.09)	(−0.2; 0.3)	
		Haloperidol	10 mg	226	0.5 (0.09)	223	0.3 (0.10)		
II + III + IV	Parkinsonism/ dystonia/ dyskinesia	Risperidone	1 mg	229	7.7 (0.56)	226	1.1 (0.39)	(−5.4; −2.7)	
			4 mg	227	7.6 (0.62)	227	1.8 (0.44)	(−4.6; −2.0)	
			8 mg	230	7.3 (0.53)	228	2.7 (0.45)	(−3.8; −1.1)	>1 mg
			12 mg	226	7.0 (0.50)	225	3.2 (0.48)	(−3.3; −0.6)	>1 mg, >4 mg
			16 mg	224	7.8 (0.58)	224	4.7 (0.56)	(−1.8; 0.9)	>1 mg, >4 mg, >8 mg, >12 mg
		Haloperidol	10 mg	226	7.0 (0.51)	223	5.1 (0.57)		>1 mg, >4 mg, >8 mg, >12 mg
V	CGI of severity of dyskinesia	Risperidone	1 mg	228	0.9 (0.10)	226	0.2 (0.07)	(−0.5; −0.1)	
			4 mg	226	0.8 (0.09)	226	0.2 (0.07)	(−0.5; −0.1)	
			8 mg	230	0.6 (0.08)	227	0.3 (0.07)	(−0.4; 0.0)	
			12 mg	226	0.7 (0.08)	225	0.4 (0.08)	(−0.3; 0.1)	
			16 mg	224	0.9 (0.09)	224	0.4 (0.08)	(−0.3; 0.2)	>1 mg, >4 mg
		Haloperidol	10 mg	226	0.7 (0.09)	222	0.5 (0.08)		>1 mg, >4 mg
VI	CGI of severity of parkinsonism	Risperidone	1 mg	228	1.1 (0.09)	226	0.2 (0.07)	(−1.2; −0.7)	
			4 mg	226	1.2 (0.10)	226	0.5 (0.09)	(−0.9; −0.4)	>1 mg
			8 mg	230	1.2 (0.10)	227	0.7 (0.10)	(−0.8; −0.2)	>1 mg
			12 mg	226	1.1 (0.09)	225	1.0 (0.11)	(−0.5; 0.1)	>1 mg, >4 mg, >8 mg
			16 mg	224	1.1 (0.10)	224	1.2 (0.11)	(−0.3; 0.3)	>1 mg, >4 mg, >8 mg
		Haloperidol	10 mg	226	1.1 (0.10)	222	1.2 (0.12)		>1 mg, >4 mg, >8 mg

> = Significantly higher change v. baseline.

1. Parkinsonian factors formed by summing individual items scores: (a) Hypokinesia factor (expressive automatic movement, body kinesia, rigidity, gait and posture and sialorrhea; (b) Hyperkinesia factor (akathisia and tremor).

2. Dyskinetic factors formed by summing individual items scores: (a) Bucco-linguo-masticatory (lingual, jaw and bucco-labial movements); (b) Choreoathetoid (upper and lower extremities).

3. 95% confidence interval of the difference between risperidone and haloperidol in the shift v. baseline at endpoint.

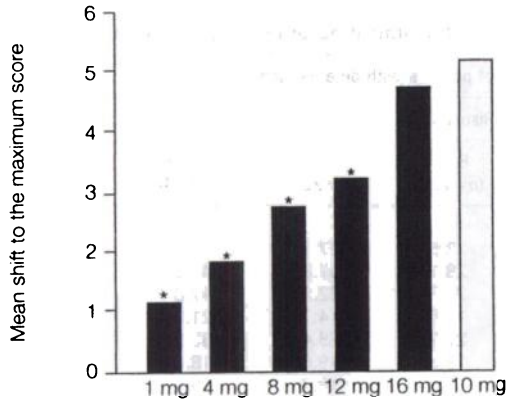

FIG. 1 Mean shift to the maximum in the extrapyramidal symptom rating scale: total score for parkinsonism, dystonia and dyskinesia. ■, Risperidone; □, Haloperidol; *$P<0.05$ versus haloperidol.

exception of dyskinesia), and for all the items (except akathisia) in the parkinsonism cluster.

Similar findings arose when the number of patients requiring concomitant antiparkinson drugs was assessed (Fig. 3). The highest percentage was in the haloperidol group (29.6%), significantly higher than in either the risperidone 1 mg, 4 mg or 8 mg groups (9.6%, 17.1% and 19.5%, respectively) ($P\leqslant 0.05$). Logistic regression analysis performed on the five risperidone doses revealed a significant positive slope ($P<0.0001$) indicating a dose proportional to intake

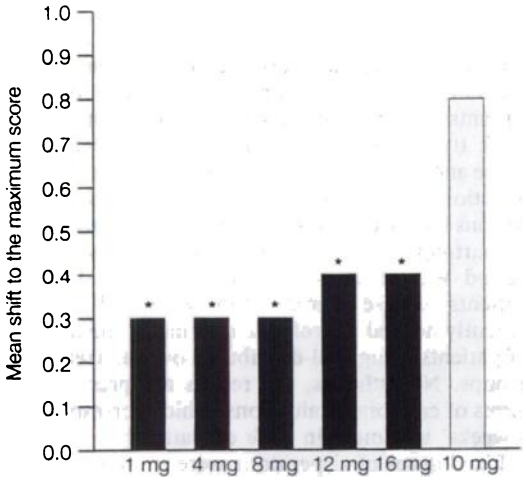

FIG. 2 Mean shift to the maximum for the item akathisia. ■, Risperidone; □, Haloperidol; *$P<0.05$ versus haloperidol.

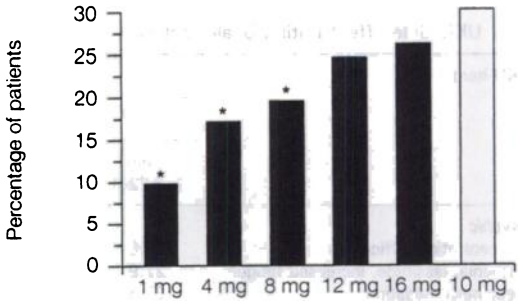

FIG. 3 Use of antiparkinson medication. ■, Risperidone; □, Haloperidol; * $P<0.05$ versus haloperidol.

of antiparkinson medication. Additionally, the need for concomitant antiparkinson medication occurred significantly earlier in the haloperidol and risperidone 16 mg groups than in the low-dose risperidone groups.

On the UKU Side-Effect Rating Scale, psychic symptoms were the most prevalent. The percentage of patients reporting an increase in severity during double-blind treatment in some items of the UKU Side-Effect Rating Scale is shown in Table 6. Generally, this effect was lower in risperidone 4 mg and 8 mg groups than in the haloperidol group. UKU global assessment of the interference caused by adverse events on patients' daily functioning revealed that, in the opinion of both the investigators and the patients, the score at endpoint was directly proportional to the dose (lowest for risperidone 1 mg). The score in the haloperidol-treated patients was similar to that of the risperidone 12 mg group.

The percentage of patients who discontinued treatment due to adverse events varied between 7% (risperidone 4 mg and 8 mg) and 14% (risperidone 16 mg). In the haloperidol group, adverse events resulted in discontinuation in 10% of patients.

Body weight significantly increased in all risperidone groups, the mean increase varying between 0.3 kg in the risperidone 1 mg and 1.6 kg in the risperidone 8 mg group. The weight increase in the 8 mg, 12 mg, and 16 mg groups was significantly higher than in the haloperidol group. Only small fluctuations were seen in heart rate, blood pressure, and ECG; none of these were clinically significant and they were all comparable across all groups. No relevant changes occurred in clinical laboratory parameters, except for a dose-proportional increase in serum prolactin concentration in risperidone-treated patients.

https://doi.org/10.1192/bjp.166.6.712 Published online by Cambridge University Press

Table 6
UKU Side-Effect Rating Scale: deterioration during double-blind treatment occurring in ⩾10% of patients

UKU-item	% of patients with deterioration[1]					
	Risperidone					Haloperidol
	1 mg (*n* = 226)	4 mg (*n* = 227)	8 mg (*n* = 228)	12 mg (*n* = 225)	16 mg (*n* = 224)	10 mg (*n* = 225)
Psychic						
Concentration difficulties	28.8	25.6	28.5	27.1	26.3	31.6
Asthenia, lassitude, increased fatigue	27.9	34.4	28.1	37.8	42.0	38.7
Sleepiness, sedation	23.5	31.7	33.3	32.9	47.8	39.6
Failing memory	19.0	15.4	13.6	14.7	21.9	22.7
Sleep duration increased	20.4	24.2	27.2	28.4	33.9	28.4
reduced	27.4	19.8	15.8	19.6	18.8	21.8
Increased dream activity	15.0	13.2	18.0	18.7	16.5	17.3
Autonomic						
Accommodation disturbances	8.9	8.8	14.0	13.3	17.0	17.3
Reduced salivation	12.8	10.1	11.0	11.1	16.5	13.8
Nausea/vomiting	15.0	10.6	12.7	14.2	15.6	18.2
Constipation	13.7	15.4	15.4	14.2	14.7	15.6
Polyuria/polydipsia	10.6	13.2	13.2	13.3	16.5	16.4
Orthostatic dizziness	15.0	20.7	18.4	29.3	30.4	23.1
Palpitations, tachycardia	17.7	14.6	16.7	19.6	28.1	12.0
Increased sweating	11.1	7.9	8.8	11.6	13.4	15.1
Other						
Weight change gain	26.1	31.3	33.8	30.2	38.8	24.9
loss	14.2	15.4	15.4	17.3	13.4	16.9
Amenorrhoea[2]	9.8	5.3	8.1	8.4	13.1	10.5
Sexual desire increased	7.5	10.6	5.7	8.0	7.1	7.6
decreased	9.3	10.1	10.1	14.2	11.6	11.6
Erectile dysfunction[2]	4.2	10.5	8.5	17.7	10.7	12.8
Ejaculatory dysfunction[2]	3.6	7.9	9.2	17.7	11.4	6.7
Tension headache	10.6	4.4	10.1	10.7	10.3	11.1

1. Increase in severity of a symptom by at least one score compared with baseline.
2. Percentage calculated in male or female patients only.

Discussion

As this was a short-term trial, the rationale for the 8-week duration of double-blind treatment was based on the guidelines of the Third Consensus Conference on the Methodology of Clinical Trials of Antipsychotic Drugs (1990) which state that the optimal duration of a short-term trial is 4 to 8 weeks. In clinical practice neuroleptic therapy is evaluated every 6 weeks, further supporting short-term assessment over this period.

However, since all patients were on oral or depot neuroleptic treatment before entry to the trial, and since the wash-out period was only one week, there was a possibility of an unknown continuing effect of previous neuroleptic medication during the trial, especially for those patients previously receiving depot preparations. It is not easy to overcome this. However, the percentage of patients who had previously received depot neuroleptics was well-distributed over the treatment groups, and for these patients the endpoint evaluation represents the 8 week treatment phase, plus the 1-week wash-out phase and the duration of the cycle from the previous injection to the start of the wash-out. For ethical reasons longer wash-out periods were not permissible in participating countries. Indeed, the wash-out period was shortened in approximately 17% of patients because their condition worsened and they urgently needed neuroleptic treatment, the number of patients being well-distributed over all treatment groups. Nevertheless, the results are presented in terms of endpoint evaluations, which correspond to 8 weeks' treatment in 75% of patients.

Fixed doses of risperidone were employed as the dose eliciting a certain response should preferably be determined by measuring the responses observed in separate groups of patients randomly allocated to

different fixed doses rather than by treating every patient with increasing (or decreasing) doses of the drug until a therapeutic and/or unwanted effect is observed (or is no longer observed) (Turri & Stein, 1986). A single dose of haloperidol (10 mg) was used as active control in this trial. The question can be raised whether lower or higher doses would have been more effective. At a dose of 10 mg, blockade of dopamine-D_2 receptors by haloperidol has been shown to be high enough for an optimal therapeutic effect (Farde & Hall, 1992; Nordström *et al*, 1992). Van Putten *et al* (1990) compared the antipsychotic effectiveness of haloperidol 5 mg, 10 mg and 20 mg daily and found no significant differences, although the 20 mg dose tended to have a slight advantage. In previous trials of risperidone, mean haloperidol doses of 18 mg (Borison *et al*, 1992) and 20 mg (Marder & Meibach, 1994) gave variable response rates (25% and 44% respectively), a response being defined as a 20% improvement in Brief Psychiatric Rating Scale (BPRS) scores. These response rates are lower than that found in the present study utilising the haloperidol 10 mg dose (58.7%). In addition, Baldessarini *et al* (1988) suggested that doses of 10 to 12 mg of haloperidol are usually adequate and that higher doses may not only be associated with increased risk of side-effects, but possibly also with inferior clinical responses. All these findings suggest that the use of haloperidol 10 mg in the current study provided a fair balance between good antipsychotic efficacy and limited side-effects.

The results of this study have shown that, in patients with chronic schizophrenia, the optimal antipsychotic effects of risperidone are seen at doses of 4 mg or 8 mg daily. In the higher-dose groups of 12 and 16 mg, the therapeutic effect was lower than the effects of 4 and 8 mg, so that a bell-shaped response emerges for the therapeutic effect as a function of dose. Pairwise comparisons of the change versus baseline on the PANSS, and BPRS total score at endpoint showed no significant differences between risperidone 1 mg and haloperidol, while risperidone doses of 4 mg, 8 mg, and 16 mg had a significantly greater beneficial effect than risperidone 1 mg. Similarly, only risperidone, 4 mg and 8 mg resulted in significantly more patients having a 20% decrease in BPRS total score than was the case with risperidone 1 mg. The superiority of haloperidol and the four other risperidone groups over risperidone 1 mg is shown in the CGI, in the positive subscale of the PANSS, and in the 'thought disturbances' and 'hostility' cluster of the BPRS.

The results in the risperidone 4 mg and 8 mg groups were better than those observed in the haloperidol group on all primary and secondary efficacy parameters, similarly, the shifts versus baseline on the PANSS, BPRS, and CGI were larger and there were more responders on these scales. In addition, risperidone 4 mg was significantly superior to haloperidol in the 'general psychopathology' cluster of the PANSS and 'activity' cluster of the BPRS. These dose-related effects of risperidone confirmed the findings of early dose-titration studies, in which the mean daily dose at endpoint varied between 3 mg and 9 mg (Castelao *et al*, 1989; Gelders, 1989; Meco *et al*, 1989; Mesotten *et al*, 1989; Bersani *et al*, 1990; Gelders *et al*, 1990). These results are consistent with the results of Chouinard *et al* (1993), where a similar bell-shaped dose–response was observed, with risperidone 6 mg the optimal dose. At this level, risperidone was shown to be effective on positive, negative, and affective symptoms.

The finding that the optimal antipsychotic effects of risperidone were seen at doses of 4 mg and 8 mg is especially interesting in view of the safety profile of the drug. The most striking inter-group differences were in fact found in the evaluations of EPS. There was a remarkable consistency in the results on the ESRS and the use of antiparkinson medication. On these measures, a linear dose relationship was seen for the five doses of risperidone, with haloperidol at the upper end of the curve. Moreover, this dose relationship was reported both by investigators and by patients. Such a relative lack of EPS seen with risperidone might be expected to have major implications in the improvement of patient compliance, with consequent reduction in the risk of relapse due to psychotic symptoms (Van Putten, 1974).

A clinically relevant advantage of risperidone over haloperidol is its low propensity to induce dystonic symptoms: the scores in the 16 mg and 1 mg groups were not significantly different, while haloperidol induced significantly more dystonic symptoms than any of the five risperidone treatment groups. Since dystonia is extremely disturbing for the patient, this side-effect is one of the major drawbacks in conventional neuroleptic treatment and reasons for non-compliance (Van Putten, 1974).

Similarly, with akathisia, the shift to the maximum score was higher under haloperidol than under all risperidone regimens; additionally, no significant differences occurred between the risperidone groups. A relative lack of akathisia may also help the patient in accepting antipsychotic treatment, since this symptom has been reported as being more difficult to endure than any of the symptoms for which the patient was originally treated, is very resistant to treatment (Kalinowski, 1958), and is strongly associated with depression and dysphoric responses

to neuroleptics (Shear *et al*, 1983; Van Putten, 1984; Drake & Ehrlich, 1985; Barnes, 1987; Van Putten & Marder, 1987).

Since risperidone has no inherent anticholinergic activity, the low profile of inducing EPS is most probably related to its potent serotonin 5-HT_2 antagonistic properties. Other serotonin 5-HT_2 receptor antagonists, such as ritanserin and setoperone, have also been associated with a favourable effect on EPS (Ceulemans *et al*, 1985; Reyntjens *et al*, 1986).

From the extensive evaluations in this large trial, risperidone emerges as a safe drug, while the tolerability of both 4 mg and 8 mg is better than that of haloperidol. Indeed, there were fewer adverse experiences reported, and the incidence and increase in severity of many of the items of the UKU Side-Effect Rating Scale were lower with the optimal doses of risperidone than with haloperidol.

No clinically significant fluctuations were seen in heart rate or blood pressure with either risperidone or haloperidol. No relevant changes occurred in ECG parameters or clinical laboratory parameters, except for a dose-proportional increase in serum prolactin concentration in risperidone-treated patients, a common effect with dopamine antagonists. Nevertheless, the adverse events expected as a consequence of this increase, such as galactorrhoea, amenorrhoea and menorrhagia were reported in only a small percentage of patients.

The results from this study have demonstrated that the optimal dose of risperidone for maximal efficacy and minimal occurrence of EPS appears to be in the range of 4 to 8 mg daily. At these doses, risperidone was effective in producing beneficial effects on negative, positive and affective symptoms, as well as being more effective overall than haloperidol in the management of chronic schizophrenia. After placebo wash-out the occurrence of dystonia, akathisia and parkinsonism was lower with risperidone than with haloperidol. This was reflected in the fact that significantly fewer patients required antiparkinson therapy with risperidone 4 mg and 8 mg.

Acknowledgements

We wish to thank Harry Goyvaert Lic. Math. for carrying out the statistical analyses for this trial.

Appendix

The Risperidone Study Group comprises: Dr VF Donnoli, Dr ME Portnoy, Dr NR Stingo, Hospital Neuropsiquiátrico "José T. Borda", Buenos Aires, Argentina; Dr A Duarte, Hospital Nacional "José T. Borda", Buenos Aires, Argentina; Dr MS Richards, Hospital "Alejandro Korn", Buenos Aires, Argentina; Dr C Geretsegger, Landes-Nervenklinik Salzburg, Salzburg, Austria; Prof GF Hebenstreit, Niederösterreichische Landesnervenklinik, Amstetten/Mauer, Austria; Prof H Hinterhuber, Universitätsklinik für Psychiatrie, Innsbruck, Austria; Prof P König, Landes-Nervenkrankenhaus Valduna, Rankweil, Austria; Dr T Platz, Psychiatrische Abteilung, Landeskrankenhaus, Klagenfurt, Austria; Dr W Pühringer, Prof W Schöny, Wagner-Jauregg-Krankenhaus des Landes Oberösterreich, Linz, Austria; Prof H Schubert, Landes-Nervenkrankenhaus Hall in Tirol, Hall in Tirol, Austria; Dr E De Bleeker, Psychiatrisch Ziekenhuis, Sint Niklaas, Belgium; Dr J De Wilde, Dr M Dierick, Kliniek St Camillus, Sint Denijs-Westrem, Belgium; Dr P Kindts, Dr G Touquet, Psychiatrisch Centrum H Hart, Ieper, Belgium; Dr C Mertens, Psychiatrisch Centrum Sleidinge, Sleidinge-Evergem, Belgium; Dr F Mesotten, Psychiatrisch Centrum, Munsterbilzen, Belgium; Prof J Peuskens, Universitair Centrum St Jozef, Kortenberg, Belgium; Prof A Acioli, Faculdade de Medicina de Teresópolis, Niteroi, Brazil; Prof LP Bechelli, Faculdade de Medicina de Teresópolis, Ribeirão Preto, Brazil; Prof D Caetano, State University of Campinas, Campinas, Brazil; Prof J Mari, Rua Botucatú 740—3° andar, São Paulo, Brazil; Dr R Moreno, Faculdade Medicinia-Universidade de São Paulo, São Paulo, Brazil; Prof M Versiani, Universidade Federal do Rio de Janeiro, A Copacabana, Brazil; Prof J Andersen, Psychiatric Hospital, Vordingborg, Denmark; Prof P Kragh-Sorensen, Odense University Hospital, Odense C, Denmark; Prof A Bourguignon, Hôpital Albert Chenevier, Créteil, France; Dr G Clerc, Centre Hospitalier Spécialisé, Pontorson, France; Prof G Darcourt, Centre Hospitalier Régional et Universitaire de Nice, Nice, France; Dr G Ferrey, Centre Hospitalier Emile Roux, Eaubonne, France; Dr C Gaussares, Centre Hospitalier Spécialisé, Cadillac, France; Prof D Ginestet, Université de Paris XI, Villejuif, France; Dr M Guibert, Centre Hospitalier Spécialisé du Bon Sauveur, Saint-Lo, France; Prof T Lemperiere, Université de Paris VII, Colombes, France; Prof H Loo, Centre Hospitalier Sainte-Anne, Paris, France; Prof P Moron, Hôpital de la Grave, Toulouse, France; Dr R Pagot, Centre Hospitalier Spécialisé de St Ave, Saint-Ave, France; Prof JG Pascalis, Centre Hospitalier Régional et Universitaire de Reims, Reims, France; Prof M Petit, Centre Hospitalier Spécialisé de Rouvray, Sotteville les Rouen, France; Dr R Ropert, Centre Hospitalier Sainte Anne, Paris, France; Dr H Sauret, Centre Hospitalier Spécialisé, Saint-Cyr-au-Mont-d' Or, France; Prof H Scharbach, Centre Hospitalier Régional et Universitaire de Nantes, Nantes, France; Dr AP Van Amerongen, Centre Hospitalier de Saint-Germain-en-Laye, Saint-Germain-en-Laye, France; Prof K Diebold, University of Heidelberg, Heidelberg, Germany; Prof H Dilling, Medizinische Universität zu Lübeck, Lübeck, Germany; Prof H Hippius, University of Munich, München, Germany; Prof H Lauter, Technical University of Munich, München, Germany; Prof H-J Möller, Universitäts-Nervenklinik Bonn, Bonn, Germany; Dr E Aguglia, University of Trieste, Trieste, Italy; Dr A Bosio,

S Anna Clinic, Brescia, Italy; Prof N Ciani, Clinica Pio XI—ambulatorio de Psychiatrica, Roma, Italy; Prof C Faravelli, Clinica Psichiatrica, Firenze, Italy; Prof P Giordano, Università degli Studi di Palermo, Palermo, Italy; Prof D Kemali, University of Naples, Naples, Italy; Prof G Meco, Viale dell' Università 30, Roma, Italy; Prof G Muscettola, University of Naples, Naples, Italy; Prof P Pancheri, Università degli Studi di Roma "La Sapienza", Roma, Italy; Prof V Rapisarda, Istituto di Clinica Psichiatrica Università di Catania, Catania, Italy; Prof L Ravizza, Istituto di Clinica Psichiatrica dell' Università di Torino, Torino, Italy; Prof A Rizzoli, Hospital of Treviso, Treviso, Italy; Prof E Sacchetti, Ospedale San Paolo, Milano, Italy; Prof PL Scapicchio, Ospedale Psichiatrico "S M Immacolata", Guidonia, Roma, Italy; Dr G Baquedano-López, Hospital Psiquiátrico "Yucatán", Yucatán, Mexico; Dr M Camelo-Marinez, Fundación de Beneficencia Socia Camelo Martinez, Nuevo León, Mexico; Prof FG Sandoval, Sanatorio Psiquiátrico "Nuestra Señora de Guadalupe", Puebla, Mexico; Prof SG Gutiérrez, Clinica "San Rafael", Delegación Tlalpan, Mexico; Dr G Heinze, Instito Mexicano de Psiquiatria, Col San Lorenzo Huipulco, Mexico; Dr CP Salcedo, Hospital Psiquiátrico Del Carmen, Calzado Tulyehualco, Mexico; Dr LER Almanzor, Hospital Psiquiátrico San Juan de Dios, Jalisco, Mexico; Dr JF Torres-Plank, "Centro Comunitario de Salud Mental, IMSS", Jalisco, Mexico; Dr JL Vargas Elias, Hospital Psiquiátrico "San Fernando" IMSS, Toriello Guera, Mexico; Dr AJ Boom, Streekziekenhuis Walcheren, Vlissingen, The Netherlands; Dr TW Bos, Provinciaal Ziekenhuis te Santpoort, Santpoort Zuid, The Netherlands; Dr L Brok, Psychiatrisch Centrum St Willibrord, Heiloo, The Netherlands; Dr JA Den Boer, University Hospital, Utrecht, The Netherlands; Dr MJ Hoogschagen, Provinciaal Ziekenhuis te Santpoort, Santpoort Zuid, The Netherlands; Dr J Rijpkema, Psychiatrisch Ziekenhuis "Groot Bronswijk", Wagenborgen, The Netherlands; Dr AJMP Rutgers, Psychiatrisch Ziekenhuis "Vogelenzang", Bennebroek, The Netherlands; Dr HC Staverman, Psychiatrisch Ziekenhuis Franeker, The Netherlands; Dr W Bodemer, University of Pretoria, South Africa; Dr F Daubenton, Valkenberg Hospital, Cape Town, South Africa; Dr RA Emsley, University of Stellenbosch, Stikland Hospital, Bellville, South Africa; Dr CA Gagiano, Oranje Hospital, Bloemfontein, South Africa; Dr GAD Hart, Sterkfontein Hospital, Krugersdorp, South Africa; Dr WH Wessels, King George V Hospital, Dormerton, South Africa; Dr E Alvarez, H Santa Cruz y San Pablo, Barcelona, Spain: Prof JL Ayuso, H Clinico San Carlos, Madrid, Spain; Prof J Guimón, Instituto de Psicoterapia de Bilbao, Bilbao, Spain; Prof M Gutierrez, H Santiago Apóstol, Vitoria, Spain; Prof JJ Lopez-Ibor, H Ramón y Cajal, Madrid, Spain; Dr B Andrée Frösö Clinics, Frösön, Sweden; Dr S Bäck, Västervik Hospital, Västervik, Sweden: Dr G Eberhard, Malmö General Hospital, Malmö, Sweden; Dr A Edsbagge, Uddevalla Hospital, Uddevalle, Sweden; Dr E Eftring, KSS, Major Medical Center, Skövde, Sweden; Dr J Eriksson, Central Hospital of Eskilstuna, Eskilstuna, Sweden; Dr N Guldberg, St Lars Hospital, Lund, Sweden; Dr C Kollind, Lillhagen Hospital, Hisings Backa, Sweden; Dr J Lachman, Prof L Von Knorring, Akademiska Hospital, Uppsala, Sweden; Dr KA Larsson, Central Hospital, Kristianstad, Sweden; Dr R Lindlelius, Söder Hospital, Stockholm, Sweden; Dr P Nilsson, Sundsvall County Hospital, Sundsvall, Sweden; Dr R Persson, Klingbergsgarden, Norrköping, Sweden; Dr J Sin, Hospital of Pitea, Pitea, Sweden; Dr B Smith, Northern Älvsborg Hospital, Trollhättan, Sweden; Dr M Swartz Central Hospital, Karlstad, Sweden; Dr IM Wieselgren, Ulleraker Hospital, Uppsala, Sweden; Dr F Ferrero, Clinique Psychiatrique Universitaire, Chêne-Bourg, Switzerland; Dr GP Bray, Winterton Hospital, Stockton on Tees, UK; Dr JC Cookson, The Royal London Hospital - St Clements, London, UK; Dr JMR Damas-Mora, North Tyneside General Hospital, North Shields, UK; Dr JM Dingwall, Dykebar Hospital, Paisley, UK; Dr C Hyde, Withington Hospital, Manchester, UK; Dr P Jauhar, Dr G Crocket, Parkhead Hospital, Glasgow, UK; Dr AS Lee, University Hospital, Nottingham, UK; Dr MG Livingston, Gartnavel General Hospital, Glasgow, UK; Dr RG McCreadie, Crichton Royal Hospital, Dumfries, UK; Dr AM Mortimer, St Luke's Hospital, Huddersfield, UK; Dr M Peet, Northern General Hospital, Sheffield, UK; Dr SC Rastogi, St Ann's Hospital, Poole, UK; Dr KL Shrestha, Ryhope, UK; Dr S Soni, Hope Hospital, Salford, UK; Dr E Stonehill, Central Middlesex Hospital, London, UK; Dr SW Turner, St Luke's-Woodside Hospital, London, UK.

References

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.

Baldessarini, R. J., Cohen, B. M., Teicher, M. H. (1988) Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Archives of General Psychiatry*, **45**, 79-91.

Barnes, T. R. E. (1987) The present status of tardive dyskinesia and akathisia in the treatment of schizophrenia. *Psychiatric Developments*, **4**, 301-319.

Bersani, G., Bressa, G. M., Meco, G., *et al* (1990) Combined serotonin 5-HT_2 and dopamine-D_2 antagonism in schizophrenia: clinical, extrapyramidal and neuroendocrine response in a preliminary study with risperidone (R64766). *Human Psychopharmacology*, **5**, 225-231.

Borison, R. L., Pathiraja, A. P., Diamond, B. I., *et al* (1992) Risperidone: Clinical safety and efficacy in schizophrenia. *Psychopharmacology Bulletin* **28**(2), 213-218.

Castelao, J. F., Ferreira, L., Gelders, Y. G., *et al* (1989) The efficacy of the D_2 and 5-HT_2 antagonist risperidone (R64766) in the treatment of chronic psychosis: an open dose-finding study. *Schizophrenia Bulletin*, **2**, 411-415.

Ceulemans, D. L. S., Gelders, Y. G., Hoppenbrouwers, M-L. J. A., *et al* (1985) Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone. *Psychopharmacology*, **85**, 329-332.

Chouinard, G., Annable, L., Ross-Chouinard, A., *et al* (1979) Ethopropazine and benztropine in neuroleptic-induced Parkinsonism. *Journal of Clinical Psychiatry*, **40**, 147-152.

———, Jones, B., Remington, G., *et al* (1993) A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *Journal of Clinical Psychopharmacology*, **13**, 25-40.

———, Ross-Chouinard, A., Annable, L., *et al* (1980) The Extrapyramidal Symptom Rating Scale. *Canadian Journal of Neurological Sciences*, **7**, 233.

CLAUS, A., BOLLEN, J., DE CUYPER, H., *et al* (1992) Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicenter double-blind comparative study. *Acta Psychiatrica Scandinavica*, **85**, 295–305.

CROW, T. J. (1985) The two-syndrome concept: origins and status. *Schizophrenia Bulletin*, **11**, 471–486.

DRAKE, R. E. & EHRLICH, J. (1985) Suicide attempts associated with akathisia. *American Journal of Psychiatry*, **142**, 499–501.

FARDE, L., HALL, H. (1992) Positron emission tomography. Examination of chemical transmission in the living human brain. *Arzneim-Forsch/Drug Research*, **42**, 260–264.

GELDERS, Y. G. (1989) Thymosthenic agents, a novel approach in the treatment of schizophrenia. *British Journal of Psychiatry*, **155**(suppl 5), 33–36.

———, HEYLEN, S. L. E., VANDEN BUSSCHE, G., *et al* (1990) Pilot clinical investigations of risperidone in the treatment of psychotic patients. *Pharmacopsychiatry*, **23**, 206–211.

GUY, W. (1976) ECDEU Assessment Manual for Psychopharmacology (revised). Published by DHEW, No (ADM) 76–338, Rockville, MD: *National Institute of Mental Health*.

JANSSEN, P. A. J., NIEMEGEERS, C. J. E., AWOUTERS, F., *et al* (1988) Pharmacology of risperidone (R64766), a new antipsychotic with serotonin-S_2 and dopamine-D_2 antagonistic properties. *Journal of Pharmacological Experimental Therapeutics*, **244**, 685–693.

KALINOWSKI, L. B. (1958) Appraisal of the "tranquillisers" and their influences on other somatic treatment in psychiatry. *American Journal of Psychiatry*, **115**, 94–300.

KAY, S. R., FISZBEIN, A. & OPLER, L. A. (1987) The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin*, **13**, 261–276.

———, OPLER, L. A. & LINDENMAYER, J. P. (1988) Reliability and validity of the Positive and Negative Syndrome Scale for Schizophrenics. *Psychiatric Research*, **23**, 99–110.

KAY S. R. & SEVY, S. (1990) Pyramidical model of schizophrenia. *Schizophrenia Bulletin*, **16**, 537–545.

LEHMANN, E. L. (1975) Nonparametric Statistical Methods, Statistical Methods based on Ranks. San Francisco: Holden-Day.

LEYSEN, J. E., GOMMEREN, W., EENS, A., *et al* (1988) The biochemical profile of risperidone, a new antipsychotic. *Journal of Pharmacological Experimental Therapeutics*, **247**, 661–670.

LINGJAERDE, O., AHLFORS, U. G., BECH, P., *et al* (1987) The UKU Side-Effect Rating Scale. *Acta Psychiatrica Scandinavica*, **76**(suppl 334), 81–94.

MARDER, S. R., MEIBACH, R. C. (1994) Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry*, **151**, 1825–1835.

MECO, G., BEDINI, L., BONIFATI, V., *et al* (1989) Risperidone in the treatment of chronic schizophrenia with tardive dyskinesia: a single-blind crossover study versus placebo. *Current Therapeutic Research*, **46**, 876–883.

MESOTTEN, F., SUY, E., PIETQUIN, M., *et al* (1989) Therapeutic effect and safety of increasing doses of risperidone (R64766) in psychotic patients. *Psychopharmacology*, **99**, 445–449.

NORDSTRÖM, A. L., FARDE, L., HALLDIN, C. (1992) Time course of D_2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol. *Psychopharmacology*, **106**, 433–438.

OVERALL, J. F. & GORHAM, D. R. (1962) The Brief Psychiatric Rating Scale. *Psychological Reports*, **10**, 799–812.

POCOCK, S. J. (1983) Methods of randomisation: Preparing the randomisation list. In *Clinical Trials. A Practical Approach*, pp 73–80. Chichester: John Wiley & Sons.

REYNTJENS, A. J. M., GELDERS, Y. G., HOPPENBROUWERS, M.-L. J. A., *et al* (1986) Thymosthenic effects of ritanserin (R55667), a centrally acting serotonin-S_2 receptor blocker. *Drug Development and Research*, **8**, 205–211.

SHEAR, K., FRANCES, A. & WEIDEN, P. (1983) Suicide associated with akathisia and depot fluphenazine treatment. *Journal of Clinical Psychopharmacology*, **3**, 235–236.

TURRI, M., STEIN, G. (1986) The determination of practically useful doses of new drugs: some methodological considerations. *Statistics in Medicine*, **5**, 449–457.

VAN PUTTEN, T. (1974) Why do schizophrenic patients refuse to take their drugs? *Archives of General Psychiatry*, **31**, 67–72.

——— (1984) Akathisia with haloperidol and thiothixene. *Archives of General Psychiatry*, **41**, 1036–1039.

——— & MARDER, S. R. (1987) Behavioral toxicity of antipsychotic drugs. *Journal of Clinical Psychiatry*, **48**(suppl 9), 13–19.

———, MARDER, S. R. & MINTZ, J. (1990) A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. *Archives of General Psychiatry*, **47**, 754–758.

Correspondence: Professor J. Peuskens, Universitair Centrum St Jozef, Leuvense Steenweg 517, 3070 Kortenberg, Belgium.

(First received 17 November 1993, final revision 4 July 1994, accepted 10 November 1994)