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ORIGINAL COMMUNICATION

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Ropinirole as an adjunct to levodopa in the treatment of Parkinson's disease

A 16-week bromocriptine controlled study

Abstract *Background and objectives* Ropinirole is a non-ergoline, selective dopamine D_2 agonist. The aim of this study was to evaluate the efficacy and safety of ropinirole as an adjunct to levodopa in the treatment of Parkinson's disease (PD) complicated by motor fluctuations. *Methods* A total of 76 patients with PD (Hoehn and Yahr stage II to IV) were included in this trial. Each patient was randomly allocated to receive either ropinirole (n = 37) or bromocriptine (n = 39) as an adjunct to levodopa over a 16-week period. Ropinirole and bromocriptine were titrated for optimal efficacy and tolerability. This optimal dose was then maintained for the rest of the study. Response rate was defined as the percentage of patients who achieved at least a 20 % reduction in levodopa dose. Clinical status was also assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impression (CGI), and reduction in time spent 'off'. *Results* Ropinirole produced a significantly greater response rate than bromocriptine (odds ratio 2.995, 95 % C. I. (1.157, 7.751) $p < 0.05$). There was also a statistically significant difference between the groups in the proportion of patients who were 'improved' on the CGI improvement scale (91.9 % for ropinirole, 74.3 % for bromocriptine, $p = 0.046$). Other measures, including at least a 20 % improvement in the UPDRS motor score (70 % for ropinirole and 63.3 % for bromocriptine), and a 20 % reduction in 'off' duration (81 % for ropinirole and 52.4 % for bromocriptine) showed a trend in favour of ropinirole. There was no significant difference between the two groups in the overall incidence of adverse effects (ropinirole, 59.5 %; bromocriptine, 59 %). In each group, the most common side-effects were dizziness, dyskinesia and nausea/vomiting. No patients were withdrawn from the study because of side-effects. *Conclusion* Ropinirole was found to be safe and well-tolerated. Ropinirole as an adjunct to levodopa in the treatment of PD with motor fluctuation was associated with more significant reduction of levodopa dose and, on one form of analysis, with significantly greater improvement in CGI ratings than bromocriptine. On the other efficacy measures the two drugs were comparable.

Key words ropinirole · bromocriptine · Parkinson's disease · motor fluctuations

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Introduction

Levodopa was first introduced for the treatment of patients with Parkinson's disease (PD) over 30 years ago [3, 4], and it continues to be the most widely prescribed anti-parkinsonian drug. However, long-term levodopa therapy can be complicated by motor fluctuations and dyskinesias, which are some of the most challenging problems in the management of PD [10, 17]. One available option to improve the levodopa induced motor fluctuations is to introduce a dopamine agonist as an adjunct to levodopa [15, 16].

Ropinirole (ReQuip®) is a nonergoline dopamine D_2-

receptor agonist that is effective in the treatment of all stages of PD [1, 2, 11–14, 18–21, 23]. Recent clinical research on ropinirole has focused on its efficacy and safety in patients with early PD [1, 2, 5, 7–9, 11–14, 18–21, 23]. However, its efficacy as an adjunct to levodopa, which is the more classical use of dopamine agonists, has not been studied to the same extent [12, 16, 19–21].

We therefore performed a prospective, bromocriptine-controlled trial of ropinirole as an adjunct to levodopa, to assess its efficacy and safety in patients with PD whose disease was not optimally controlled by levodopa alone, and were experiencing motor fluctuations.

Methods

Patients

Patients were aged over 40 years, had a clinical diagnosis of PD based on the UK brain bank criteria [9], and their disease was at Hoehn and Yahr stages II-IV when assessed in the 'off' state. All patients were receiving treatment with levodopa and either required the addition of a dopamine agonist to alleviate motor fluctuations (with or without dyskinesia), or were already receiving an adjunctive dopamine agonist (other than ropinirole or bromocriptine) and were prepared to switch to study medication. Patients had been receiving a stable dose of levodopa for at least 4 weeks prior to screening. All patients gave written informed consent to take part in the study.

Patients were excluded from the study if they had severe disabling peak-dose or diphasic dyskinesias and/or complex 'on-off' phenomena. Also excluded were patients with severe systemic or psychiatric disease, a history of alcoholism or drug dependence, severe dementia, severe dizziness or fainting as a result of postural hypotension, or other clinically relevant abnormalities in their history or diagnostic laboratory tests, including electrocardiography. In addition, patients were excluded if they had previously been treated with ropinirole, or had contraindications to bromocriptine or other ergot alkaloids. Women of childbearing age were excluded unless they were postmenopausal, surgically sterilised or had undergone hysterectomy.

Treatment with anticholinergics, amantadine, or selegiline was permitted if the dose was stable for at least 4 weeks before study entry, and the dose was not changed during the study.

Study design

This study was an open, randomised, bromocriptine-controlled, 4-month trial of ropinirole as an adjunct to levodopa, in patients with PD and motor fluctuations. The study was performed at Asan Medical Center in Seoul, South Korea between November 1997 and November 1998. After a 7-day screening period to determine eligibility for study, patients were randomised to receive open treatment with either ropinirole or bromocriptine. Stratified block randomisation method was applied according to the previous exposure to a dopamine agonist.

Drug treatments

In patients who were not already receiving a dopamine agonist, the initial daily doses were 0.75 mg for ropinirole (0.25 mg tid) and 1.25 mg for bromocriptine. Thereafter, the dose of each drug was gradually increased according to a dose-titration schedule with eight dose levels. The minimum daily dose of ropinirole to be reached during titration was 4.5 mg and the maximum daily dose was 9.0 mg (a maximum dose well below the maximum permitted dose for ropinirole of 24 mg). The corresponding doses of bromocriptine in the study were 10 mg/day and 17.5 mg/day, respectively. The dose-titration regimen was followed until an optimal therapeutic dosage was achieved; after that, the same dose could be maintained for the remainder of the study.

Patients who were already receiving a dopamine agonist discontinued this treatment on the day the treatment phase began and followed another more accelerated titration regimen. A dose of 5 mg of pergolide or lisuride was considered equivalent to 40 mg of bromocriptine or 24 mg of ropinirole in calculating the starting dose level for these patients. They started at the closest corresponding dose level to 50 % of their calculated bromocriptine or ropinirole dose at week 1. This could be increased to the dose level closest to 75 % of their calculated bromocriptine dose at week 2 and 100 % at week 3 if required. Patients switching dopamine agonists could receive maximum doses of 9 mg of ropinirole or 17.5 mg of bromocriptine. Alternatively, dose increases after week 1 could follow the main dosing schedule, according to the clinical judgement of investigators.

Once the dopamine agonists had been titrated to optimal doses, investigators tried to reduce the patients' levodopa doses gradually. If PD symptoms increased when the levodopa dose was reduced, the dose of dopamine agonist could be increased. If PD symptoms did not resolve after this increase, the levodopa dose could again be increased. Presciption of domperidone was permitted in patients who developed dopaminergic side-effects such as nausea and vomiting.

Assessments

Patients visited the clinic at baseline, every week for the first month, then every 2 weeks for the next 3 months. The following assessments were made at all visits: the clinical global impression (CGI) global improvement and severity of illness scales, a home diary reflecting hours 'on' and 'off' during the week before the visit, abnormal involuntary movement scale (AIMS), vital signs, levodopa dose, adverse events, any changes in concomitant medication and compliance. In addition, at months 1 and 4 a complete Unified Parkinson's Disease Rating Scale (UPDRS) [5] and standard laboratory analyses were performed.

Efficacy

The primary efficacy variable was the number of responders (defined as the patients who achieved at least a 20 % reduction in levodopa dose). The secondary efficacy variables were the number of patients who showed at least a 20 % improvement in the motor score of the UPDRS (section III), at least a 20 % reduction in time spent 'off', and improvement in the CGI score between the baseline and final visits.

Safety

All adverse experiences, reported spontaneously in response to non-leading questions or when observed directly by the investigators, were recorded at each visit. Safety was also measured using vital signs and standard laboratory tests.

Statistics

All analyses were performed on an intention-to-treat basis and included all randomised patients who had at least one assessment after receiving study medication. The percentages of responders, in terms of levodopa dose, reduction in 'off' time and UPDRS motor score were all analysed by logistic regression and presented in terms of odds ratios with 95 % confidence intervals. The difference in the proportion of patients showing improvement on the CGI between the two treatment groups was analysed by Wilcoxon's rank sum test. This

method of analysis of CGI improvement was determined before the study. The incidences of adverse effects in treatment groups were evaluated using Fisher's exact test. Abnormal results of laboratory studies, changes in vital signs and AIMS were also compared between groups.

Results

Of the 81 patients who were enrolled into the trial, 76 patients (37 taking ropinirole and 39 bromocriptine) were randomized to treatment. Of these, 65 patients completed the trial. The reasons for withdrawal were protocol violations (1/37 [2.7%] in the ropinirole group; 2/39 [5.1%] in the bromocriptine group), requests to withdraw (3/37 [8.1%] in the ropinirole group; 1/39 [2.6%] in the bromocriptine group), lack of treatment compliance (2/39 [5.1%] in the bromocriptine group), and incomplete follow-up (1/37 [2.7%] in the ropinirole group; 1/39 [2.6%] in the bromocriptine group). The treatment groups were well matched in terms of their demographic characteristics, disease and treatment (Table 1).

Assessment of efficacy

At the time of the final assessments, the average dose of ropinirole was 7.9 ± 2.2 mg/day, and the average bromocriptine dose was 15.4 ± 4.3 mg/day (Table 2). The proportion of patients whose levodopa dose was reduced by at least 20%, which was the primary assessment criterion, was 54.1% in the ropinirole group and 28.2% in the bromocriptine group. Thus, on this measure, patients taking ropinirole showed a significantly greater response rate than those taking bromocriptine (odds ratio 2.995, C. I. (1.157, 7.757) $p < 0.05$) (Table 3). At the start of the study, there was no significant difference in levodopa dose between the two treatment groups. Over the 4-month study, levodopa dose reduced from 711.1 ± 239.2 mg/day to 548.0 ± 216.3 mg/day in the ropinirole group ($p < 0.05$), compared with a reduction from 681.7 ± 256.5 mg/day to 636.2 ± 274.0 mg/day (not significant) in the bromocriptine group. The proportion of patients in whom the UPDRS motor score was reduced by at least 20% was 70% in the ropinirole group and 63.3% in the bromocriptine group; there was no significant difference between the two groups on this measure. There was also no significant difference between the groups in terms of mean UPDRS motor scores before and after treatment (Tables 2 and 3).

The proportion of patients in whom 'off' time was reduced by at least 20% was 81% in the ropinirole group and 52.4% in the bromocriptine group; this difference did not reach statistical significance (Table 3). The mean daily time spent 'off' decreased by a mean of 1.65 hours in the ropinirole group and 0.69 hours for the bromocriptine group (no significant difference) (Tables 2 and 3).

There were no differences between the total CGI scores in the two groups at the end of the trial on two-by-seven chi-square test. However, the proportion of patients defined as 'very much improved' on the CGI improvement scale was greater in the ropinirole group (51.4%) than in the bromocriptine group (25.6%). When the assessment results for each category were classified into 'improvement' (between 1 and 3 points) and 'no improvement' (between 4 and 7 points) and analysed, there was a significant difference between the ropinirole group (91.9%) and the bromocriptine group (74.3%) (chi-square test, $p = 0.046$) (Table 3).

Table 1 Demographic, disease and treatment characteristics of patients enrolled in the trial

	Ropinirole	Bromocriptine	P value
Number	37	39	
Sex (male:female)	21:16 (57%:43%)	20:19 (51%:49%)	NS[a]
Mean age ± SD (years)	63.5 ± 10.8	60.0 ± 8.3	NS[b]
Mean weight ± SD (kg)	58.0 ± 7.9	58.9 ± 8.7	NS[b]
Mean height ± SD (cm)	162.3 ± 9.6	160.1 ± 9.8	NS[b]
Hoehn and Yahr stage;			
II	16 (43%)	17 (44%)	
II.5	10 (27%)	12 (31%)	
III	10 (27%)	9 (23%)	
IV	1 (3%)	1 (3%)	
Mean duration of disease ± SD (months)	81.3 ± 45.3	77.2 ± 38.2	NS[b]
Mean dose of levodopa ± SD (mg/day)	711.1 ± 239.2	681.7 ± 256.5	NS[b]
Mean duration of treatment with levodopa ± SD (months)	47.5 ± 44.7	43.1 ± 27.9	NS[b]
Previous medication with dopamine agonists			
Pergolide	12 (32%)	10 (26%)	NS[c]
Lisuride	3 (4%)	7 (18%)	

NS not significant; *SD* standard deviation.
[a] Chi-squared test; [b] Unpaired t-test; [c] Fisher's exact test.

Assessment of safety

Side-effects were experienced by 59.5% of patients in the ropinirole group and 59% of patients in the bromocriptine group. No patients dropped out during the course of the study due to side-effects. In both groups, the most common side-effect was dizziness (ropinirole group 29.7%, bromocriptine group 25.6%) and in each group one patient had dizziness resulting from orthostatic hypotension. Other common side-effects were, in the ropinirole group, dyskinesia (21.6%), nausea/vomiting (8.1%), headache (8.1%) and vivid dreams (5.4%) and, in the bromocriptine group, nau-

Table 2 Drug doses and absolute efficacy ratings for patients at baseline and at the end of the trial

	Ropinirole		Bromocriptine		P value
	Baseline	Final visit	Baseline	Final visit	
Dosage of test drug (mg/day)	–	7.9±2.2	–	15.4±4.3	
Daily dose of levodopa (mg/day)	711.1±239.2	548±216.3	681.7±256.5	636.2±274.0	0.002[a]
UPDRS motor score	19.0±10.5	13.1±10.5	21.8±9.5	17.3±11.6	NS[a]
Duration of 'off' time (hours/day)	4.39±3.13	2.74±2.95	5.36±3.12	4.68±4.52	NS[a]
Clinical global impression: severity of illness	3.5±0.6	2.9±1.0	3.6±0.5	3.2±0.8	NS[a]

All values are means ± standard deviations
UPDRS: Unified Parkinson's Disease Rating Scale.
[a] Wilcoxon's rank sum test

Table 3 Response rates on different parameters for patients during the trial

	Ropinirole	Bromocriptine	Statistics	
			Odds ratio (C. I.)	P value
Number (%) of patients whose levodopa dose was reduced by:			2.995 (1.157, 7.757)	< 0.05
> 20%	20 (54.1%)	11 (28.2%)		
< 20%	17 (45.9%)	28 (71.8%)		
Mean (± SD) reduction in levodopa dose (mg/day)	163.2±159.9	61.9±109.9		0.002[a]
Number (%) of patients whose UPDRS motor score was reduced by:			1.351 (0.460, 3.968)	
> 20%	21 (70%)	19 (63.3%)		
< 20%	9 (30%)	11 (36.7%)		
Mean (± SD) reduction in UPDRS motor score	5.9±5.9	4.6±9.1		NS[a]
Number (%) of patients for whom the duration of 'off' time (hours/day) was reduced by:			3.864 (0.967, 15.443)	
> 20%	17 (81%)	11 (52.4%)		
< 20%	4 (19%)	10 (47.6%)		
Mean (± SD) reduction in the duration of 'off' time (hours/day)	1.65±1.60	0.69±4.08		NS[a]
Clinical global impression				
Mean (± SD) change of severity of illness	–0.6±0.7	–0.4±0.8		NS[a]
Number of patients for whom the global improvement was:				0.046[b]
Not assessed	1 (2.7%)	0 (0%)		
Very much improved	19 (51.4%)	10 (25.6%)		
Much improved	8 (21.6%)	9 (23.1%)		
Minimally improved	7 (18.9%)	10 (25.6%)		
No change	2 (5.4%)	10 (25.6%)		
Minimally worse	0 (0%)	0 (0%)		
Much worse	0 (0%)	0 (0%)		
Very much worse	0 (0%)	0 (0%)		

C. I. confidence interval; *SD* standard deviation; *UPDRS* Unified Parkinson's Disease Rating Scale.
[a] Wilcoxon's rank sum test; [b] Chi-square test

sea/vomiting (17.9%), dyskinesia (10.3%), headache (7.7%), dry mouth (7.7%) and abdominal pain (7.7%) (Table 4). Apart from the two patients with orthostatic hypotension, there were no clinically relevant changes in vital signs or laboratory tests in either treatment group.

Discussion

This open study compared the efficacy and safety of ropinirole, a new dopamine agonist, with those of bromocriptine, a familiar drug with a similar mechanism of action. Ideally, the trial would have been blinded, but importation of matched tablets of these drugs is difficult in Korea. Thus the present study was designed as an open comparative one, but with patients randomly assigned to the treatment groups. Bromocriptine was selected for comparison because it is a commonly used dopamine agonist in Korea, and it was judged to be appropriately comparable in terms of its tolerability, safety and efficacy. In this study, significantly more patients on adjunctive ropinirole than on adjunctive bromocriptine were able to reduce their levodopa intake by at least 20%. This finding was supported by the effects of the drugs on time spent 'off': ropinirole produced numerically (but not statistically) greater effects on these measures than bromocriptine. Furthermore, the proportions of patients 'improved' on the CGI-global improvement scale (defined as a score of 1–3 points) was also greater in the ropinirole group than the bromocriptine group, again indicating an overall improvement with ropinirole treatment. As expected, there was little difference in the UPDRS score following adjunctive therapy, as this was assessed during 'on' periods, and the main effects of both dopamine agonists was in reducing the duration of 'off' periods.

Table 4 The most common adverse events experienced by patients during the trial

	Ropinirole (n = 37)	Bromocriptine (n = 39)
Number of patients experiencing adverse events	22 (59.5%)	23 (59%)
Number of adverse events	42	48
Common dopaminergic adverse events		
Dizziness	11 (29.7%)	10 (25.6%)
Dyskinesia	8 (21.6%)	4 (10.3%)
Nausea/vomiting	3 (8.1%)	7 (17.9%)
Vivid dreams	2 (5.4%)	2 (5.1%)
Orthostatic hypotension	1 (2.7%)	1 (2.6%)
Confusion	1 (2.7%)	0
Hallucination	1 (2.7%)	0
Other adverse events		
Headache	3 (8.1%)	3 (7.7%)
Dry mouth	2 (5.4%)	3 (7.7%)
General malaise	2 (5.4%)	1 (2.6%)
Insomnia	3 (8.1%)	2 (5.1%)
Constipation	1 (2.7%)	2 (5.1%)
Visual disturbance	1 (2.7%)	2 (5.1%)
Palpitation	1 (2.7%)	1 (2.6%)
Light-headedness	1 (2.7%)	0
Rash	1 (2.7%)	0
Abdominal pain	0	3 (7.7%)
Chest pain	0	1 (2.6%)
Facial oedema	0	1 (2.6%)
Sweating	0	1 (2.6%)
Facial flushing	0	1 (2.6%)
Itching sense	0	1 (2.6%)
Tinnitus	0	1 (2.6%)
Abnormal sense of taste	0	1 (2.6%)

No significant differences between groups on Fisher's exact test

The average daily dose of ropinirole as an adjunct to levodopa was 7.9 mg, which is a dose similar to that used in the studies performed outside Korea [19, 20]. This is smaller than the average dose when this drug was used as a monotherapy in long-term studies of patients in the early stages of Parkinson's disease in which the average daily dose of ropinirole was between 15 and 19 mg [14, 18], with a maximum permissible dose of 24 mg. This difference in doses is to be expected, as patients receiving adjunct therapy are, by definition, also receiving a therapeutic effect from their levodopa therapy.

In terms of safety, there was no evidence of any significant effect of either study drug on factors such as blood pressure, pulse rate and laboratory test values in either group. One patient in each group experienced orthostatic hypotension but they did not complain of any subjective symptoms and, on the contrary, appeared to be satisfied with the improvement in motor functions produced by treatment. The common side-effects in the study were dopaminergic side-effects, including dizziness, nausea and vomiting, but these could be effectively controlled by the administration of the peripheral dopamine antagonist, domperidone (2 in the ropinirole group; 6 in the bromocriptine group). Compared with the bromocriptine group, the ropinirole group exhibited a somewhat higher frequency of dyskinesia, but this difference was not significant, and may be due to more potent dopaminergic stimulation by this drug. In all patients who experienced this side-effect, it comprised a small increase in existing dyskinesia (associated with long-term levodopa therapy) after administration of the drug, rather than the emergence of new symptoms. In the ropinirole group, one patient experienced confusion and one hallucination, although these were mild in severity. The confusion occurred intermittently, whereas the hallucinations resolved spontaneously or with continued treatment. Sudden-onset sleep, which has recently been reported for the major dopaminergic agents including levodopa, was not found in the present study [6–8, 22]. Overall, there were no significant differences in the incidences of side-effects between the two treatment groups. In addition, in most cases, side-effects were transient and tended to improve spontaneously,

and no patients dropped out of the study because of side-effects.

Most previous trials of ropinirole have concentrated on its use as monotherapy for treating the early stages of PD. In this indication, ropinirole was significantly more effective than placebo [1, 2,11, 13, 14, 23]. When ropinirole was administered over a period of 5 years, it was associated with a significantly lower incidence of dyskinesias (levodopa group 45 %, ropinirole group 20 %), while the activities of daily living scores were similar [18]. In a 3-year comparison with bromocriptine as monotherapy in early disease, ropinirole appeared to produce greater beneficial effects on patients' overall functioning (UPDRS activities of daily living score) than bromocriptine [13]. These and other studies of the early use of dopamine agonists, have led to a change in the strategy for early therapy of Parkinson's disease. Agonists are now widely used as an initial therapy, to delay the initiation of levodopa therapy, and therefore the onset of its associated motor complications.

Until now there has been only one published study comparing ropinirole and bromocriptine in adjunct therapy, and that study was designed primarily to assess safety [21]. Thus, the present study has a different emphasis, in that it compared the efficacy of these two drugs.

In conclusion, the authors consider that ropinirole can be safely used as an adjunctive treatment for patients with PD who cannot be properly controlled by levodopa preparations because of motor fluctuations. Significantly more patients receiving adjunct therapy with ropinirole than with bromocriptine achieved at least a 20 % reduction in levodopa dose. On one form of analysis, but not on another, improvement in CGI ratings was significantly better ($p = 0.046$) than on bromocriptine. There is now a need for continuing clinical research in order to determine factors such as the appropriate dose of ropinirole as a monotherapy for Korean patients and to confirm the effects and side-effects of ropinirole when it is administered to Korean patients over a longer period of time.

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