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Cabergoline in Parkinson's Disease Complicated by Motor Fluctuations

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Summary: Cabergoline is a long-acting D_2 dopamine (DA) agonist. We conducted an open study to investigate the effectiveness and tolerability of cabergoline, administered once a day orally, in 50 consecutive patients with Parkinson's disease complicated by motor fluctuations and dyskinesias. In 15 patients cabergoline replaced another direct DA agonist. Evaluation after 6 months of treatment (also including patients who dropped out during this period), showed an improvement in off or on hours, or both, in excess of 50% in 27 patients, comprising 20 of the 35 patients (57%) previously untreated with DA agonists and seven of the 15 patients (47%) already on DA agonists when the study began. Of the 22 patients who received the treatment for 1 year, the improvement was maintained up to final evaluation in the patients not on DA agonists at admission (n = 16), whereas a slight deterioration in clinical condition was observed in the patients already on DA agonists at admission (n = 6). Only six patients showed a detectable increase in dyskinesias. The most common side effects were gastric upset (n = 12), orthostatic hypotension (n = 3), and ankle edema (n = 3), all mild; also observed were two cases of pleural effusion/pulmonary fibrosis. Twenty patients (40%) failed to complete the treatment; of these, five (10% of total) dropped out because of adverse effects. It is concluded that once-daily administrations of cabergoline are useful for treating patients with Parkinson's disease with motor fluctuations and may advantageously substitute other DA agonists. The side effects of the drug are generally mild, although two cases involving pleuropulmonary complications did emerge **Key Words:** Parkinson's disease—Motor fluctuations—Dyskinesias—Dopamine agonist—Cabergoline.

Motor fluctuations occur in parkinsonian patients treated chronically with dopamine (DA)-replacing medication (1). Adjustment of the dose or administration schedule often fails to produce satisfactory control of the oscillations from akinesia to dyskinesias. Although the pathogenesis of these motor fluctuations is not entirely clear, results using continuous levodopa infusion (2) indicate that they often reflect discontinuous dopaminergic stimulation. Some therapeutic success has been obtained using continuous subcutaneous infusion of lisuride (3), apomorphine (4), and controlled-release levodopa preparations (5).

Another way to stabilize dopaminergic stimulation is to use inherently long-acting medications. Cabergoline is a new DA agonist derived from ergoline, is active on D_2 receptors, and has a plasma half-life of ~65 h as estimated from renal elimination studies (6). Cabergoline's antiparkinsonian activity and tolerability have been evaluated in a number of clinical studies (7). Two dose response studies have indicated that cabergoline is effective in patients with Parkinson's disease of differing severity (8), whereas other studies have confirmed its effectiveness, both at low (9) and at high dosage levels, in patients with motor fluctuations.

The purpose of the present study was to further explore the effectiveness and tolerability of cabergoline in a fairly large unselected population of parkinsonian patients with motor fluctuations.

PATIENTS AND METHODS

Between November 1988 and October 1990, we enrolled 51 consecutive patients with Parkinson's

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disease complicated by motor fluctuations (wearing-off, on-off) or dyskinesias in an open study. Patients were at stages II–V of the Hoehn and Yahr scale in the off phase of the disease. Each patient gave informed consent for study participation. Exclusion criteria were mental deterioration; cardiovascular, pulmonary, renal, or hepatic disease; and age >80 years.

One patient dropped out for personal reasons after a few days and could not be assessed; efficacy and safety evaluations are accordingly restricted to the remaining 50 patients.

At the time of recruitment, one patient was receiving levodopa without peripheral decarboxylase inhibitor (PDI); the rest were taking levodopa plus PDI. Fifteen patients also were using a direct DA agonist (bromocriptine or lisuride). We therefore divided the patients into two groups: 35 not receiving associated treatment with a direct DA agonist at recruitment (group A) and 15 receiving such treatment (group B). The clinical characteristics of the two groups (Table 1) did not differ significantly. Some patients in each group were taking other antiparkinsonian drugs: eight were on anticholinergics, eight on l-deprenyl, and one on associated treatment with amantadine.

Antecedent antiparkinsonian therapies were continued without change for at least 1 month before baseline examination, which included administration of the Unified Parkinson's Disease Rating Scale (UPDRS) and assessment of the weekly hours in the on, intermediate, and off phases as determined from a weekly diary compiled by the patient. Standard blood tests (hematological and chemical) were performed, and an electrocardiographic (ECG) trace and chest radiograph obtained.

TABLE 1. *Demography and Parkinson's disease history in patients on treatment (group B) or not (group A) with other DA agonists at admission*

		Group A	Group B
No. of patients		35	15
Age (yr)		56.0 ± 9.6	56.7 ± 9.7
Parkinson's disease duration (yr)		11.6 ± 5.8	10.9 ± 4.2
	on	17.3 ± 11.0 (n = 29)	18.6 ± 8.2 (n = 14)
UPDRS (factor III)			
	off	36.0 ± 12.6 (n = 18)	47.4 ± 22.4 (n = 7)
Stage of disease in off (Hoehn & Yahr stage)		3.3 ± 1.1	3.7 ± 0.9
Levodopa dose (mg/day)		764.3 ± 321.8	915.0 ± 159.5
Direct DA agonists at admission		None	4 Lisuride (0.5–2 mg/day, mean 1.5 mg/day)
			11 Bromocriptine (10–50 mg/day, mean 24.6 mg/day)

Values are means ± SD.

Direct DA agonists were discontinued after the baseline evaluation and cabergoline started 1 or 2 days later. The levodopa plus PDI dose was reduced only when the UPDRS showed worsened dyskinesias. Other associated antiparkinsonian drugs were administered unchanged throughout the study period.

Cabergoline was started at 1 mg daily, taken as a single morning dose. In the first 25 patients recruited, the dosage was usually increased by 0.5 mg every 2 weeks; in later patients the dose was increased every week. Increases continued until the optimal dose level was reached, as identified by the following criteria:

1. Dose that increased the number of on hours or reduced the number of off hours by at least 20%.
2. Dose immediately below that associated with notable side effects or a substantial increase in dyskinesias that could not be reduced by lowering levodopa dosage (substantial increase in dyskinesia defined as increase by two or more points in the UPDRS items assessing duration and severity of dyskinesias).
3. Maximum daily dose of cabergoline 10 mg.

Patients were examined clinically, including administration of the UPDRS and evaluation of the weekly diary, before each increase in cabergoline dosage. Blood tests and ECG were performed approximately monthly. After a stable dose had been reached, blood tests and ECG were monitored at 3-month intervals, and chest radiographs were obtained every 6 months. At time of dropout, baseline evaluations were repeated. The study concluded between March and May 1991, by which time all patients still on cabergoline had reached stable dosage.

The efficacy of cabergoline was assessed at each checkup from hours in on, intermediate, and off phases, as entered in the patient's diary the week preceding the checkup, and from the UPDRS items concerned with the duration and severity of dyskinetic phenomena in the week preceding checkup. The choice of these parameters was based on the consideration that patients' clinical status at the checkups might not accurately reflect the overall clinical course of the disease. Moreover, the number of on hours and the magnitude of dyskinetic

phenomena are the fundamental targets of dosage adjustments in Parkinson's disease with motor fluctuations.

Statistical comparisons between groups used the pooled Student's *t* test and within-group comparisons used the paired Student's *t* test.

RESULTS

Thirty of the initial 50 patients were still on cabergoline at study completion, after 103–652 days (mean 352 ± 152 days) of treatment. Of the 20 who dropped out, seven were in group A (cabergoline replaced another direct DA agonist), and 13 were in group B (not receiving direct DA agonists at baseline). The clinical characteristics of dropout patients did not differ from those of patients who completed the study (Table 2): mean age and clinical stage at admission were closely similar in the two groups, whereas duration of Parkinson's disease was lower in the dropout patients (9.9 ± 4.6 years) than in those continuing cabergoline treatment up to the end of the study (12.4 ± 5.6 years), but not significantly so.

Nine patients dropped out for poor compliance. Six others requested release from the study because they considered the treatment ineffective in controlling motor fluctuations and dyskinesias: they retired after 2–12 months on cabergoline at 2.5–6 mg daily. The remaining five patients dropped out because of notable side effects. In two pleural effusion/pulmonary fibrosis was evident after 10–11 months (cabergoline administered at 3.5 and 5.5 mg daily, respectively). In one patient the pleural effusion disappeared 3 months after cabergoline administration had ceased. The other patient with pleural effusion and pulmonary fibrosis presented modest lung alterations at baseline radiography, attributed to past treatment with bromocriptine; 6 months after stopping cabergoline the radiological picture had improved. In one patient, severe edema in both legs after 3 months on cabergoline (3 mg daily) necessitated withdrawal of therapy. Another patient was withdrawn after developing delirium and hallucinations at 79 days of treatment (4 mg daily). Another patient, later rediagnosed with multiple system atrophy, developed severe orthostatic hypotension after 13 days of treatment (1.5 mg daily); after 98 days the treatment was stopped when the dose had reached 4.5 mg/day.

Side effects other than dyskinesias occurred in 18 patients and were relatively mild except in the five dropout patients mentioned above. There were 12 cases of gastrointestinal side effects (nausea, vomiting, dyspepsia, or gastritis), three of orthostatic hypotension, three of lower limb edema, three of dyspnea, one of psychosis with hallucinations, two of increased sex drive, two of pleural effusion/pulmonary fibrosis, and two of transient confusional state. No meaningful changes were detected in blood parameters or ECG traces.

The results of the assessment after 6 months of treatment (including the last assessment of patients who dropped out during this period) are shown in Table 3. Motor fluctuations are shown for only 49 patients because one patient in group A had dyskinesia only. As evident from Table 3, daily on hours in the whole series increased after cabergoline treatment, from 6.1 ± 3.3 at baseline to 8.4 ± 3.6 at last checkup in the 6-month period ($p < 0.01$, Student's *t* test for paired data). Similarly, the daily off hours decreased from 5.0 ± 3.0 to 2.8 ± 2.9 ($p < 0.01$),

TABLE 2. *Demography and Parkinson's disease history in patients who dropped out from the study and patients under long-term treatment*

	Drop out	Long term
No. of patients	20	30
Age (yr)	55.6 ± 8.6	56.6 ± 10.3
Parkinson's disease duration (yr)	9.9 ± 4.6	12.4 ± 5.6
Stage of disease in off (Hoehn & Yahr stage)	3.5 ± 1.0	3.3 ± 1.0
Levodopa dose (mg/day)	783.1 ± 274.0	829.3 ± 302.2

Values are means ± SD.

TABLE 3. *Motor fluctuations and dyskinesias at baseline and at last assessment within the first 6 months of treatment (all patients)*

Motor fluctuations	Time	Total (n = 49)	Group A[a] (n = 34)	Group B[b] (n = 15)
"On" hours	Baseline	6.1 ± 3.3	5.9 ± 3.2	6.6 ± 3.5
	Within 6 mo	8.4 ± 3.6[c]	8.5 ± 3.8	8.0 ± 3.1
"Intermediate" hours	Baseline	4.7 ± 3.1	4.6 ± 3.1	5.0 ± 3.2
	Within 6 mo	4.2 ± 2.7	4.1 ± 2.5	4.4 ± 3.1
"Off" hours	Baseline	5.0 ± 3.0	5.3 ± 3.3	4.3 ± 2.3
	Within 6 mo	2.8 ± 2.9[c]	2.7 ± 3.2	2.8 ± 2.4
Dyskinesias	**Time**	**Total (n = 50)**	**Group A[a] (n = 35)**	**Group B[b] (n = 15)**
Duration score (0–4)	Baseline	1.3 ± 0.7	1.2 ± 0.8	1.4 ± 0.5
	Within 6 mo	1.5 ± 0.9	1.4 ± 1.0	1.5 ± 0.8
Disability score (0–4)	Baseline	1.5 ± 1.2	1.4 ± 1.2	1.7 ± 1.0
	Within 6 mo	1.4 ± 1.2	1.3 ± 1.2	1.7 ± 1.2

Values are means ± SD.
[a] Not on treatment with DA agonists.
[b] On treatment with DA agonists.
[c] $p < 0.01$ versus baseline.

whereas intermediate hours remained unchanged (initial 4.7 ± 3.1, final 4.2 ± 2.7).

Dyskinetic manifestations did not change markedly over this period. At the baseline rating, the mean score for duration of dyskinesias was 1.3 ± 0.7 and the disability score was 1.5 ± 1.2; at 6 months, duration was 1.5 ± 0.9 and disability was 1.4 ± 1.2.

At baseline, peak-dose dyskinesias were present in 38 patients and biphasic dyskinesias in 12, and off-phase dystonia and dyskinesias were present in six patients; five patients were free of prominent dyskinesias. The pattern at 6 months was substantially similar, except that three of the five patients without dyskinesia at baseline now presented modest peak-dose dyskinesias, whereas two patients with mild peak-dose dyskinesias at baseline were essentially free of dyskinesias after 6 months on cabergoline.

Statistical comparisons between groups A and B were not performed because of the size difference between them. It is apparent from Table 3, however, that the treatment produced similar results in both, the only apparent difference being the lower number of off hours at baseline in group B compared with group A.

A >50% improvement in off or on hours (or both) was observed in 20 of the 35 group A patients (57%) and in seven of the 15 group B patients (47%), with improvements of 20–50% in on or off hours or both in six of 35 group A patients (17%) and in six of 15 group B patients (40%). No change was observed in four of 35 group A and one of 15 group B patients, whereas worsening was observed in four of 35 group A and one of 15 group B patients.

Although there were no significant differences between baseline dyskinesias and those observed at 6 months in either group, some patients did obtain notable reductions in dyskinesias. Six patients (four of group A and two of group B) achieved a reduction of at least two in the scores for either duration or disability of dyskinesias. Conversely, however, six other patients (four of group A and two of group B) experienced a notable increase (at least 2 points) in dyskinetic phenomena for at least one of the two items.

As noted, 22 patients (16 group A and six group B) received cabergoline for 1 year. Dyskinesia data, as well as on, off, and intermediate hours for these patients at baseline, 6 months, and 12 months, are given in Table 4 according to group. Results at 6 months are similar to those noted for the total population. Considering all 22 patients, the beneficial effect of cabergoline on and off times was maintained for the whole year compared with baseline. Thus, mean off hours decreased from 4.4 ± 2.7 at baseline to 2.3 ± 2.4 at 6 months but increased to 3.1 ± 2.6 at 1 year (1 year vs. baseline, $p < 0.05$). Mean on hours increased from 5.9 ± 3.6 at baseline to 8.5 ± 4.1 at 6 months but had decreased to 7.7 ± 4.2 after a year (1 year vs. baseline, $p < 0.05$).

TABLE 4. *Motor fluctuations and dyskinesias at baseline, after 6 months, and after 1 year of treatment in 22 patients completing 1 year*

Motor fluctuations	Time	Total (n = 22)	Group A[a] (n = 16)	Group B[b] (n = 6)
"On" hours	Baseline	5.9 ± 3.6	5.4 ± 3.2	7.3 ± 4.4
	6 mo	8.5 ± 4.1	8.7 ± 4.0	8.2 ± 4.6
	1 yr	7.7 ± 4.2[c]	8.0 ± 4.2	6.7 ± 4.6
"Intermediate" hours	Baseline	5.5 ± 3.8	5.6 ± 3.7	5.2 ± 4.4
	6 mo	4.9 ± 2.7	4.8 ± 2.6	5.2 ± 3.2
	1 yr	5.4 ± 3.2	5.6 ± 3.2	4.7 ± 3.4
"Off" hours	Baseline	4.4 ± 2.7	4.9 ± 3.0	3.4 ± 1.6
	6 mo	2.3 ± 2.4	2.2 ± 2.6	2.7 ± 2.0
	1 yr	3.1 ± 2.6[c]	2.6 ± 2.6	4.4 ± 2.0
Dyskinesias	**Time**	**Total (n = 22)**	**Group A[a] (n = 16)**	**Group B[b] (n = 6)**
Duration score (0–4)	Baseline	1.3 ± 1.6	1.2 ± 0.6	1.3 ± 0.5
	6 mo	1.6 ± 1.1	1.5 ± 1.1	1.7 ± 0.8
	1 yr	1.6 ± 0.9	1.5 ± 1.0	1.7 ± 0.8
Disability score (0–4)	Baseline	1.4 ± 1.1	1.4 ± 1.2	1.3 ± 0.8
	6 mo	1.6 ± 1.1	1.6 ± 1.2	1.7 ± 1.0
	1 yr	1.7 ± 1.2	1.7 ± 1.3	1.7 ± 0.8

[a] Not on treatment with DA agonists.
[b] On treatment with DA agonists.
[c] $p < 0.05$ versus baseline.

The maintenance of improvement was strongly evident in group A considered alone, whereas in the six group B patients (on treatment with DA agonists at admission) there was a slight deterioration in on/off times compared with baseline (Table 4).

Dyskinesias at 1 year were similar to those in the total population at 6 months, both in group A and group B. Increases of two or more points in disability and/or duration of dyskinesias occurred in three patients of group A and one patient of group B, whereas in two group A patients dyskinesias improved to similar extents.

The mean dose of cabergoline at 6 months was 4.1 ± 1.7 mg/day (group A 3.6 ± 1.4, group B 5.3 ± 1.9). The dosage difference between the groups was significant ($p < 0.01$). After 1 year a similar difference was still apparent among the 22 patients still on cabergoline: 4.6 ± 1.6 mg/day in group A, 6.5 ± 3.1 in group B.

When the cabergoline dose at the end of titration was compared with the bromocriptine dose being taken on admission in 10 of 11 group B patients (excluding a patient who dropped out during dose titration because of an adverse event), a significant positive correlation ($r = 0.73$, $p < 0.001$) emerged.

Levodopa dosages decreased from 794.2 ± 308.1 mg/day at baseline to 719.5 ± 327.7 mg/day at 6 months, the difference being highly significant by the paired t test ($p < 0.005$). The dosage reduction was significant ($p < 0.005$) in group A (from 742.5 ± 451 to 663.6 ± 429.5 mg/day), but not in group B (from 915.0 ± 159.5 to 850.0 ± 242.8 mg/day). After 1 year, levodopa dose was still lower than at baseline in group A (735 ± 416.9 mg/day; 1 year vs. baseline $p < 0.01$) but not in group B, possibly related to the fact that there were only six patients in group B after 1 year (785.4 ± 27.9 mg/day). Levodopa dosage did not differ significantly between the two groups either at baseline or after cabergoline treatment.

DISCUSSION

Changes over time in the clinical condition of parkinsonian patients with motor fluctuations render controlled long-term clinical trials with such patients difficult. For this reason we conducted an open trial with an unselected (consecutive) series of patients. The ample size of the series, the protracted follow-up period, and the relative homogeneity of the results indicate that placebo effects played a small role in determining the observed clinical benefits.

A large number of patients (40%) dropped out, indicative of the difficulties of prolonged follow-up in parkinsonian patients with motor fluctuations and dyskinesias. This in part reflects the well-known difficulty in maintaining steady therapeutic benefit in parkinsonian patients but was aggravated in the present study by the slow increase in drug dosage (and hence slow attainment of therapeutic effect) dictated by the long half-life of cabergoline. Although slow titration afforded good tolerability during the titration period and allowed attainment of optimal clinical effect with minimum drug dosage, some patients became impatient with the lack of immediate benefit, prompting them to demand release from the trial. It is noteworthy that the dropout patients had a shorter mean duration of illness than did those who completed the study (difference 2.5 years), although their illness severity was similar or greater (Table 2), suggesting that dropouts had a more quickly progressing disease form.

The results of this study indicate that once-daily administration of cabergoline to patients with Parkinson's disease with motor fluctuations produces a significant increase in on hours and a significant reduction in off hours. Similar results have been obtained in other studies on parkinsonian patients with motor fluctuations, with high and low doses of cabergoline. Lera et al. (3) administered high doses of cabergoline (12 mg daily on average) to parkinsonian patients with motor fluctuations and followed them for over a year. Their results were only slightly superior to our own, although the high cabergoline dose permitted considerable reduction in the levodopa dose. On the other hand, the incidence of psychiatric side effects (five of 36 cases) was higher than in the present study. Further increase in cabergoline in our patients may have produced greater benefits on motor fluctuations and also afforded the opportunity for greater reduction of levodopa dosages. The multicentre study of Lieberman et al. on patients with motor fluctuations (9) showed that cabergoline also was beneficial at the much lower average dosage level of 2.8 mg daily. A study by Hutton et al. (8) explored the efficacy of cabergoline administered at 2–2.5 mg daily in a series of patients that, in addition to those with motor fluctuations, also included patients at Hoehn and Yahr stage I. Furthermore, these patients were followed for the relatively short time of 8 weeks. Such dosages may be lower than those needed for effective treatment of parkinsonian patients, as indicated by the fact that the investigators found no dose-response effect at this low dose range.

The titration protocol used in our study showed that the mean dose compatible with good benefit and good tolerability was the region of 5 mg daily. Although some patients obtained more benefit from higher dosages, advantages diminished sharply above 5 mg, probably related to the concomitant reduction in levodopa. On the other hand, some patients obtained substantial benefit from very low dose cabergoline, probably because of milder disease, low dosages of concomitant antiparkinsonian therapy, and the absence of treatment with direct DA agonists at baseline.

In patients who received cabergoline in substitution for another direct DA agonist, the drug resulted in increased on hours and reduced off hours compared with baseline, although the absolute differences were smaller than in patients who had not

previously received direct DA agonists (statistical comparison not performed), probably because of the better baseline status of the former group (Table 3). Furthermore, observations of individual case behavior show that this group benefited from the substitution of classical DA agonists with cabergoline. This study did not set out to compare the effectiveness of cabergoline with that of established direct DA agonists. However, our patients in group B were taking dosages of direct DA agonists that were probably effective in reducing parkinsonian symptoms. Because cabergoline replaced such drugs completely and produced a slight improvement of motor fluctuations (average 35% in off hours) at end titration, it seems legitimate to suggest that the effectiveness of cabergoline is at least as good as that of the established DA agonists. In this context it is noteworthy that in these patients there was a positive correlation ($r = 0.73$) between the dosages of bromocriptine taken at baseline and dosages of cabergoline taken at end titration. This supposition is further supported by the observation that concomitant dosages of levodopa had to be reduced in those patients to reduce worsening dyskinesias.

In this study cabergoline had no overall influence on dyskinesias. This contrasts with the increase in dyskinesias in the on phase noted in the study of Lera et al. (3), albeit with larger cabergoline dosages. The low-dosage study of Hutton et al. (8) noted one case of increased dyskinesias. The increased on hours obtained with cabergoline would also be expected to produce increased dyskinesias, or at least increased dyskinesia duration at peak dose; that this did not happen may be attributed to concomitant levodopa reduction. The steady plasma levels characteristic of the drug also may have played a role.

Although in some patients cabergoline resulted in aggravated dyskinesias, others enjoyed considerable diminution of this symptom. These findings point to dyskinetic symptoms in Parkinson's disease being a complex phenomenon and do not simply reflect plasma levels of dopaminergic drugs.

The tolerability of cabergoline was satisfactory overall; in the early phase of treatment, only mild side effects were observed: the most common were mild gastrointestinal disturbances. Orthostatic hypotension was infrequent, contrary to the report of Lieberman et al. (9). However, during chronic treatment lower limb edema was relatively frequent (three cases), and we noted also the development of pleural effusion/pulmonary fibrosis (two cases). In comparison, bromocriptine has been associated with lung alterations in 5.7% of cases (10), whereas the incidence of symptomatic cases has been estimated in the range of 0.5–2% (11). The rather high incidence of minor side effects reported by Hutton et al. (8) may reflect the fact that their series included patients with mild forms of the disease who presumably were not habituated to the action of dopaminergic drugs.

In conclusion, in full accord with all previous studies, the present study indicates that once-daily administration of cabergoline is effective in ameliorating the parkinsonian symptomatology complicated by motor fluctuations. Further studies, however, particularly controlled long-term clinical trials, clearly are required to confirm these results, to establish optimum doses for different disease stages, and to compare cabergoline with established DA agonists.

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