

Long-Term Tolerability and Efficacy of Cabergoline, a New Long-Acting Dopamine Agonist, in Parkinson's Disease

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Summary: Motor fluctuations constitute a severe complication of chronic levodopa therapy. The addition of dopamine agonists may partially alleviate these responses; however, due to the short half-life of these drugs, several daily doses are required. Cabergoline is a new dopamine agonist with a long half-life and can be given in a single daily dose. Seventeen patients with severe fluctuations were treated with cabergoline, seven of them for >1 year (up to 39 months). The motor status ameliorated and the percentage of "off" hours significantly decreased in the first year and did not increase significantly later during long-term follow-up. Cabergoline is a promising treatment for parkinsonian patients with motor fluctuations. **Key Words:** Parkinson's disease—Motor fluctuations—On-off phenomenon—Dyskinesias—Cabergoline—Dopamine agonist.

Severe motor fluctuations complicate chronic levodopa therapy in Parkinson's disease (PD), possibly reflecting the pharmacokinetics and pharmacodynamics of levodopa itself (1). End-of-dose akinesia, early morning and nocturnal immobility, on-off phenomena, and dyskinesias limit the beneficial effect of levodopa in the long term. The addition of synthetic dopamine agonists (DA) such as bromocriptine or lisuride is an efficient therapeutic alternative (2). However, due to their relatively short half-lives, multiple daily doses are required; even pergolide, which has a longer duration of action, has to be given thrice daily (3). Cabergoline (CBG), a new ergot derivative with high affinity for D₂ receptors, has a biological half-life of about 65 h (4). Thus, the drug can be used in a single morning dose and provides continuous dopaminergic stimulation by the oral route. Preliminary reports on the efficacy of CBG were encouraging (5,6), but long-term experience with this compound is limited. When considering prolonged drug use, long follow-up pe-

riods are important in determining their safety. We herein report our experience of prolonged CBG use in patients with PD with severe motor fluctuations.

SUBJECTS AND METHODS

Patients with PD who were 45–80 years of age were recruited to an open-label study. Inclusion criteria were motor fluctuations uncontrolled by available oral treatment including dopamine agonists. Exclusion criteria consisted of evidence of other degenerative central nervous system disorders; severe depression or dementia; cardiac, vascular, hematological, respiratory, or hepatic disease; and a past history of psychosis with DA. Women of child-bearing age not taking contraceptives also were excluded. Patients not available to follow-up or incapable of filling out a self-report diary concerning their motor state were not included. All patients gave written informed consent.

The study design was as follows: Patients were maintained on stable antiparkinsonian therapy for at least 1 month before CBG initiation. Those who had been taking DA had to interrupt this medication at least 1 month before the study. Levodopa dosage was then adjusted and kept stable for at least 2

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weeks before study entry. Twelve patients received DA agonists [$n = 10$ bromocriptine (7.5–40 mg), $n = 2$ lisuride (2.4 and 3.5 mg)]. All patients experienced fluctuations before the interruption of DA. CBG dose was titrated at 0.5 mg increments up to the optimal dose for each individual (4–12 mg). Other antiparkinsonian therapy was kept stable throughout the study or reduced but not increased.

Patients were examined 1 month before the study, at baseline, and at weekly or biweekly intervals during CBG dose titration while consistently in the "on" state. During the stable CBG dose period, they were evaluated at monthly and later at 3-month intervals.

Patients were asked to fill a daily diary of 16 awake hours divided into "on," "intermediate," or "off" states during the week preceding each hospital visit. Dyskinesias were evaluated by item 32 of the Unified Parkinson's Disease Rating Scale (UPDRS) (percentage of awake hours with dyskinesia).

For data analysis we have considered the motor part of the UPDRS and particularly focused on the motor and dyskinesias scores. The bradykinesia score was calculated by arithmetically adding items of hand and leg agility and body bradykinesia (items 23–27 and 31). We also calculated the percentage of hours spent in the off state, among awake hours, in the week preceding each hospital visit. Dyskinesias were evaluated by item 32 of the UPDRS (percentage of awake hours with dyskinesias).

Statistical analysis was performed using the Wilcoxon ranked sign test, comparing the scores at baseline and at the end of the first, second, and third years for the patients who remained on long-term treatment ($n = 7$). For patients who left the study within the second year, the last visit scores were used as equivalent to the second year's. For patients who did not still finish their third year or follow-up, the last visit (December 1992) was used as equivalent to the end of the third year.

RESULTS

The study population was composed of 17 patients (12 men, five women) with a mean age of 66 ± 9 years (range 49–75). All were at stages II and III of Hoehn and Yahr (while treated), and the mean disease duration was 9 ± 5 years. L-Dopa dose at study entry was 375–1,200 mg (mean 720.5 ± 242.5 mg). The duration of treatment was 3–17 years (mean 9.7 ± 4.4 years).

Patient Withdrawal

Within the first year of therapy, 10 patients left the study: five within the first 3 months (low compliance, lack of efficacy), four within 6 months (lack of efficacy, side effects), and another after 10 months (side effect). Causes for drop out were lack of efficacy ($n = 4$), low compliance ($n = 2$), dyskinesias ($n = 2$), hallucinations ($n = 1$), and orthostatism ($n = 1$).

Seven patients were followed for >1 year, of whom four remained in follow-up for >2 years (26–39 months). One patient was lost to follow-up after 15 months, another interrupted CBG after 18 months due to acute confusion, and a third died at 19 months due to sepsis after prostatectomy.

Efficacy

In all seven patients who remained on CBG treatment for >1 year, the motor state improved as compared with baseline within the first year and remained stable later (Fig. 1). At the end of follow-up, all patients reported "much improvement" in the clinical global impression scale as compared with baseline. The main improvement was expressed in bradykinesia score in the first year [10 ± 4 at baseline, 6 ± 5 first ($n = 7$), 8 ± 6 second ($n = 7$) and 4 ± 4 third year, ($n = 4$); $p < 0.05$ baseline vs. first year, Fig. 1]. The total UPDRS motor score remained unchanged, and no statistical difference was observed in items of tremor, rigidity, or gait.

The percentage of off hours significantly decreased in the first year ($p < 0.05$) and then continued to improve (31 ± 16 at baseline, 24 ± 17 first, 18 ± 22 second, 14 ± 7 third year; Fig. 1).

Safety and Side Effects

The main side effect was dyskinesias, observed in five of seven patients. The amount of dyskinesias in the whole study group increased within the first and second years (0 ± 1 at baseline, 1 ± 1 first, 2 ± 1 second, 2 ± 2 third year; $p = \text{NS}$; range for scoring 0–4). Two patients had dyskinesias at baseline. One of them reported the same amount in the following years, whereas the other reported a diminution of the dyskinesias during the second year. Dyskinesias appeared de novo during the first study year in three patients, and their amount increased in the second and third years. Two patients remained dyskinesia free throughout.

Other side effects that did not necessitate drug withdrawal were edema ($n = 1$), insomnia ($n = 2$),

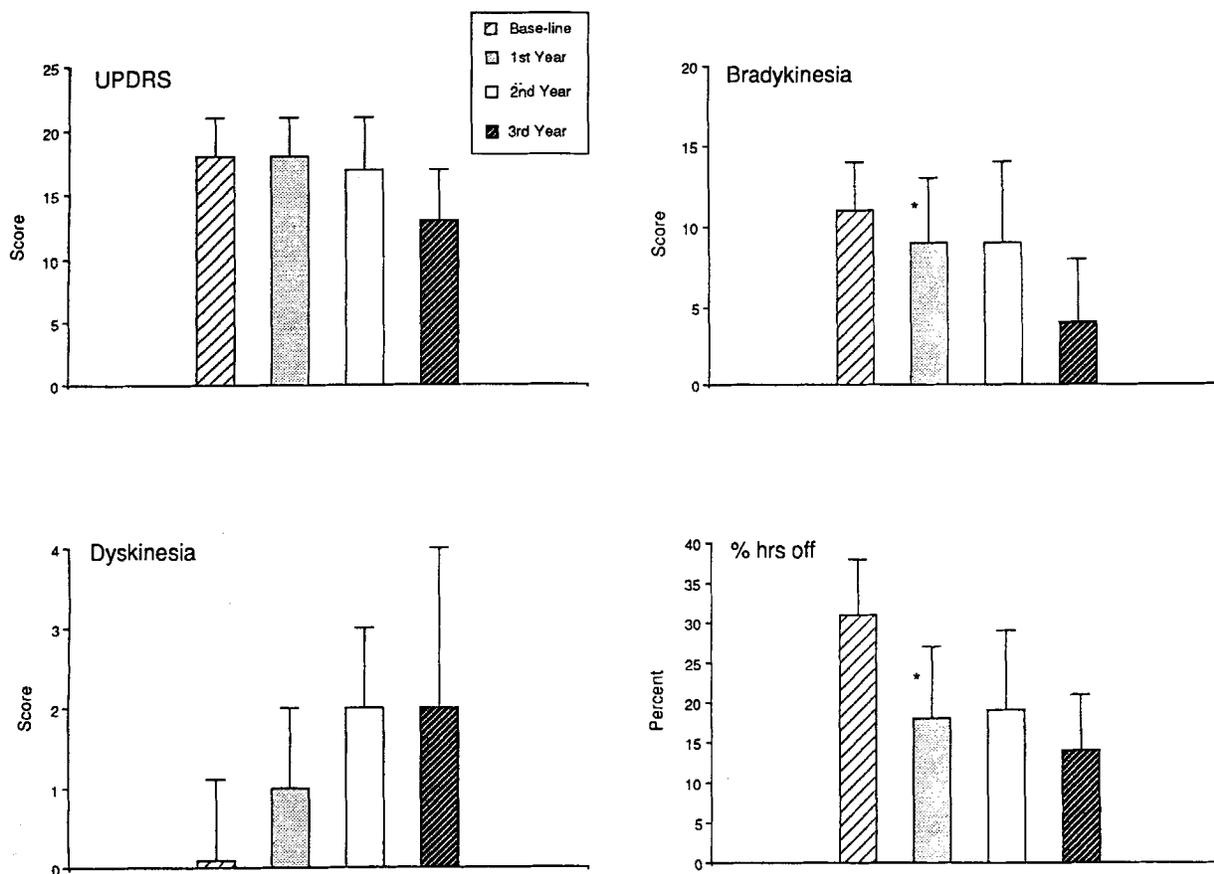


FIG. 1. Schematic representations of bradykinesia, total UPDRS motor scores, percentage of hours spent in the off state, and dyskinesia scores. The heights of the bars represent the mean values and standard errors at baseline, after 1 ($n = 7$), 2 ($n = 7$), and 3 ($n = 4$) years of treatment, respectively. Upper panels: The bradykinesia scores decreased significantly during the first year and remained stable in the second and third years (right). Total UPDRS motor scores remained stable (left). Lower panels: The percentage of off hours significantly decreased during the first year and did not increase later (right). Note the increasing amount of dyskinesias during the first and second years (left). The differences are not statistically significant. *, significantly different from baseline.

and erythromelalgia ($n = 1$). During the treatment period levodopa dosage was reduced in three patients due to dyskinesias and was not increased thereafter. This reduction was possible without causing motor deterioration and was not statistically significant.

Among patients who were dropped out within the first year due to side effects ($n = 4$), a beneficial effect was also recorded; however, disability from unwanted symptoms outweighed. The percentage of off hours decreased in all four, although the total UPDRS and separate UPDRS items remained unchanged.

Severe complications of therapy were not observed in any of the 17 patients. Results of laboratory tests and electrocardiogram remained normal in all patients.

DISCUSSION

Our results suggest that CBG is efficacious in reducing motor fluctuations, mainly off phenomena, in PD. The main side effects were dyskinesias and hallucinations, as also observed with other dopamine agonists in patients with a long-standing disease.

Fluctuations complicate long-term treatment in PD and seriously disable patients. The short plasma half-life of levodopa determines response duration (7). In early stages of the disease, the striatum still provides a sufficient buffer store of dopamine to last several hours between consecutive L-dopa doses. However, at later stages this capacity is lost, and the "efficacy half time" becomes even shorter than the half-life of the drug (8). Fluctuations then occur

and their severity increases gradually, leaving the dose-response curve steeper. In managing motor fluctuations, the addition of DA provides an efficacious alternative. However the relatively short half-life of the available compounds still requires several daily administrations. CBG, with a half-life of 65 h, provides a greater duration of dopaminergic effect (4). The long half-life of the compound probably explains the significant reduction in off hours. This finding is in agreement with previous reports of shorter follow-up duration with CBG (5,9).

The main side effect among our patients was the increasing amount of dyskinesias, which were even more accentuated in the second treatment year, although antiparkinsonian treatment was stable or reduced. This increase is not paradoxical because an association between the production of dyskinesias and duration of dopaminergic therapy has been reported (1), as well as a progressively lower threshold for levodopa to induce dyskinesias during chronic use (10).

In the present study a high percentage of patients dropped out within the early stages of treatment. However, there was a selection bias in the study population consisting of severely disabled patients who were resistant to other antiparkinsonian drugs.

This study was designed as an open study; therefore, some placebo effects might have existed, although the selective improvement of certain motor parameters reinforces the possibility of a nonplacebo effect.

CBG has side effects similar to those of other

DAs. The long half-life and therefore the possibility of using a single daily dose is an advantage. Double-blind comparative studies with other DAs will establish the relative efficacy of CBG.

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