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Clinical Experience with Cabergoline in Patients with Advanced Parkinson's Disease Treated with Levodopa

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Summary

The clinical efficacy of the long-acting dopamine agonist cabergoline as an adjunct to levodopa has been investigated in controlled and uncontrolled studies in >1500 patients with advanced Parkinson's disease and motor complications. Four of these studies (including 2 comparisons with placebo and 2 with bromocriptine), which used similar methodology (including study design, blindness, selection criteria, treatment modalities and duration) and measurements of efficacy and safety, are reviewed.

Compared with placebo, cabergoline 2 to 10 mg/day (median 5 mg/day) induced a significantly higher percentage decrease in the number of 'off' hours (18 *vs* 45%) in a preliminary phase II study that included 37 patients with severe motor fluctuations. This was not associated with an increase in dyskinesia in either treatment group. In a subsequent phase III placebo-controlled study (n = 188 patients with motor fluctuations), treatment with cabergoline 0.5 to 5 mg/day (median 3.5 mg/day) achieved a statistically significant decrease in levodopa dosage compared with placebo (18 *vs* 3%) and improved the Unified Parkinson's Disease Rating Scale scores for activities of daily living in a greater number of patients (23 *vs* 4%).

Comparisons of cabergoline with bromocriptine have been conducted in 750 patients stabilised on levodopa therapy; one study was conducted in patients without, and the other in patients with, previous exposure to dopamine agonists. Cabergoline was administered once daily at doses ranging from 0.5 to 6mg, and bromocriptine was given at a dosage of 5 to 40 mg/day divided into 3 administrations. A combined analysis of the response rates obtained in the 2 studies found cabergoline to be at least as effective and well tolerated as bromocriptine, with a trend in favour of cabergoline in terms of response rate and number of 'off' hours.

The majority of adverse events in this patient population were those associated with levodopa therapy, as shown by the high frequency of adverse events in the placebo group (68%). Both cabergoline and bromocriptine showed a comparable incidence of adverse events, with CNS and gastrointestinal events being the most common.

Thus, the potential advantages of cabergoline include improved patient compliance as a result of its once-daily administration, and an increased threshold for the development of dyskinesia as a result of the levodopa sparing effect of cabergoline.

Symptoms of Parkinson's disease result from a deficiency of the neurotransmitter dopamine. This is caused by progressive degeneration of pigment-containing cells of the substantia nigra. Current therapy for Parkinson's disease aims to restore dopaminergic neurotransmission in the nigrostriatal pathway by use of the dopamine precursor levodopa, dopamine agonists or centrally acting anticholinergic agents. Other treatments include selegiline, a selective inhibitor of type B monoamine oxidase, anticholinergic drugs and amantadine.

Levodopa (the amino acid precursor of dopamine) in combination with a peripheral dopadecarboxylase inhibitor (benserazide or carbidopa) is the most widely used treatment for this disease. However, its use is limited in the long term by a loss of efficacy and the development of response fluctuations ('wearing-off' and 'on-off' phenomena). The 'long term levodopa syndrome' is characterised by a decrease in the control of parkinsonian symptoms, the appearance of abnormal involuntary movements (dyskinesias), alterations in mentation, and increased fatigue and neurasthenia. Continuous infusion with levodopa or apomorphine has been found to markedly reduce the number of hours 'off' in patients with severe fluctuations and also to reduce the intensity of 'peak dose' dyskinesia; however, this method of drug delivery is not suitable for routine outpatient therapy.

Dopamine agonists such as cabergoline exert their antiparkinsonian activity through acting directly on the postsynaptic dopamine D_2 receptor. Dopamine agonists have been used as adjuvants to long term levodopa therapy, allowing a reduction in levodopa dosage in patients experiencing motor fluctuations.

The efficacy of a new dopamine agonist, cabergoline, has been investigated in a total of approximately 4000 patients in Europe, the Americas and Japan. Most of these patients were experiencing motor fluctuations during long term levodopa therapy (table I). This review will focus on the results of 4 pivotal studies that form the core of clinical trial experience in patients with advanced Parkinson's disease in Westernised countries.[1-4]

Table I. Clinical experience with cabergoline in patients with advanced Parkinson's disease

Europe, USA, Latin America, Australia, Israel
Trial details:
23 phase II-III trials
11 double-blind trials
2870 patients included
1800 patients treated with cabergoline
Japan
Trial details:
9 phase II-III trials
4 double-blind trials
1100 patients included
720 patients treated with cabergoline

1. Clinical Studies

1.1 Clinical Efficacy

The 4 studies of cabergoline to be reviewed include 2 placebo-controlled studies and 2 double-blind comparisons with bromocriptine (table II). Demographic and baseline Parkinson's disease characteristics were similar and well matched within each study with regard to age (61 to 63 years), sex distribution (prevalence of males), onset of Parkinson's disease (at age 47 to 53 years), duration of disease (9 to 14 years), and presence of motor fluctuations at baseline. The daily dosage of levodopa ranged from 650 to 1000mg, being higher in the largest placebo-controlled study[2] than in the 2 comparisons with bromocriptine.

In all studies, treatment was started with a dose titration phase of 10 to 22 weeks' duration: the initial dose of cabergoline 0.5mg once daily was increased at 1- to 2-week intervals to the optimal dose. This optimal dose was then administered for a minimum 3-month treatment period.

Patients were examined at weekly or bi-weekly intervals during titration, and monthly thereafter. Efficacy assessments included the following:

- rating of clinical improvement in motor disability according to the Clinical Global Impression

(CGI) scale (this was the primary end-point in the 2 comparative studies with bromocriptine)
- quantification of 'off' hours from the patients' diaries, which were started 1 week prior to treatment and completed before each visit (the number of 'off hours' was the primary end-point in the study by Steiger et al.[3])
- changes in daily levodopa dosage (the primary end-point in the study by Hutton et al.[2]).

In all studies, signs and symptoms of Parkinson's disease were evaluated according to the Unified Parkinson's Disease Rating Scale.[5] Tolerability assessment included monitoring of adverse events, chest x-ray, ECG and laboratory tests.

The results of these studies are summarised in table II and figure 1.

1.1.1 Placebo-Controlled Studies

The preliminary placebo-controlled trial conducted by Steiger et al.[3] was a phase II study that included 37 patients with motor fluctuations. The subsequent trial was a multicentre phase III double-blind parallel-group study in which 188 patients were randomised to treatment with either cabergoline or placebo, at a ratio of 2:1.[2]

Cabergoline showed superior efficacy to placebo in improving motor fluctuations and reducing the percentage of 'off' time (table II). Motor function was improved during both the 'on' and 'off' periods. In the study by Steiger et al.,[3] 63% of cabergoline recipients experienced an improvement in the CGI scale *vs* 28% of placebo recipients ($p < 0.05$), and the mean reduction in time 'off' was 45 *vs* 18% in cabergoline- and placebo-treated patients, respectively ($p < 0.05$). The reduction in time spent 'off' per day was not associated with an increase in dyskinesia in either treatment group. Differences between treatment groups in favour of cabergoline were also apparent in the larger study by Hutton et al.[2] These investigators measured improvements in activities of daily living and reported response rates of 23 *vs* 4% in cabergoline and placebo recipients, respectively. In addition, a

Table II. Summary of the results of 4 randomised double-blind studies comparing the efficacy of cabergoline (CBG) with placebo (P) and bromocriptine (BRC) in patients with advanced Parkinson's disease and motor fluctuations resulting from long term levodopa therapy

Reference	No. of patients	Treatment	Response rate[a]	Reduction in time 'off' (%)	Reduction in levodopa dosage (%)
Placebo-controlled studies					
Steiger et al.[3]	19	CBG titration (≤22 weeks) 0.5 to 10mg (median 5mg)	63*	45*	45
	18	P	28	18	38
Hutton et al.[2]	123	CBG titration (≤10 weeks) 0.5 to 5mg (median 3.5mg)	23 (ADL)	39	18**
	65	P	4 (ADL)	15	3
Comparisons with bromocriptine					
Destée et al.[1]	191[b]	CBG titration (≤15 weeks) 0.5 to 6mg (median 4 to 5mg) 3 months at stable dose	59	63	8
	193[b]	BRC titration (≤15 weeks) 5 to 40mg (median 25mg)	53	55	3
Schneider et al.[4]	181	CBG titration (≤13 weeks) 0.5 to 6mg (median 4 to 5mg) 3 months at stable dose	49	51	8
	185	BRC titration (≤13 weeks) 5 to 40mg (median 25mg)	52	45	1

a Defined as the % of patients showing a 'very much' or 'much' improved score on the Clinical Global Impression (CGI) scale.

b No previous exposure to dopamine agonists.

Abbreviation and symbols: ADL = activities of daily living; * $p < 0.05$; ** $p < 0.01$.

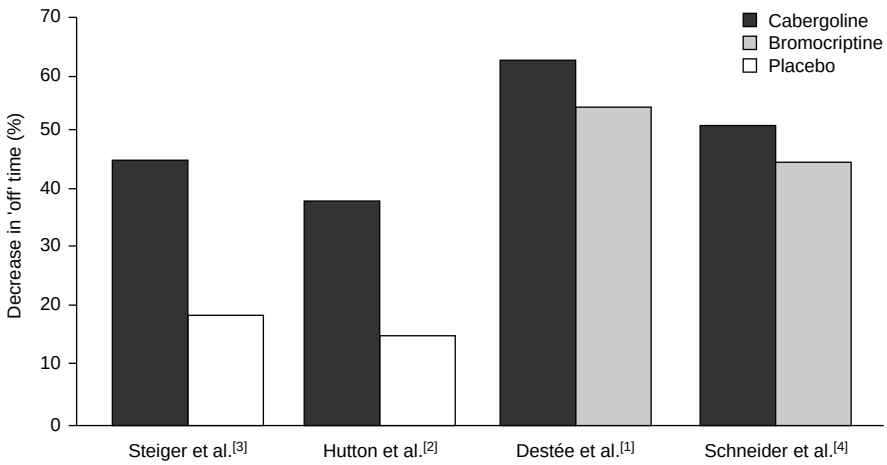

Fig. 1. Reduction in the percentage of time 'off' in patients treated with cabergoline, placebo or bromocriptine in double-blind comparative clinical trials.

significantly greater reduction in levodopa dosage was evident in cabergoline recipients (18 vs 3%).

Thus, cabergoline demonstrated superior efficacy to placebo in improving motor performance, decreasing 'off' time and sparing levodopa.

1.1.2 Cabergoline vs Bromocriptine

The clinical efficacy of cabergoline has been compared with that of bromocriptine in 2 multicentre phase III double-blind parallel-group studies, which included a total of 750 patients.[1,4] Both studies followed an identical protocol, except that patients previously treated with dopamine agonists were excluded in one study[1] and allowed to enter the other.[4]

The response rate did not differ significantly between treatment groups in either study, and was similar regardless of previous dopamine agonist therapy (59 and 49% with cabergoline, and 53 and 52% in bromocriptine recipients). Although the percentage reduction in time 'off' was greater with cabergoline in both studies, the difference was not statistically significant (63 and 51% *vs* 55 and 45% in cabergoline and bromocriptine recipients, respectively). The levodopa dosage, which was between 670 and 680 mg/day in both studies, remained essentially unchanged during cabergoline or bromocriptine therapy.

1.2 Tolerability

The tolerability profiles of cabergoline, bromocriptine and placebo in patients with Parkinson's disease are summarised in figure 2. These data are derived from all clinical trials conducted with cabergoline, which included a total of 1069 cabergoline-treated patients.

The overall incidence of adverse events in patients treated with cabergoline was similar to that in placebo recipients (74 *vs* 68%), and the same as that in patients treated with bromocriptine (74%). A few adverse events were more frequent in patients treated with either dopamine agonist than in placebo recipients. Most of these events, which included hypotension-related symptoms, gastric disturbance, hallucinations and peripheral oedema, were typical of those associated with an ergolinic dopamine agonist. Withdrawal from therapy because of intolerable adverse events was lower with placebo (7%) than with cabergoline (15%) and bromocriptine (19%). CNS events were the most common cause of treatment withdrawal (9 and 11% in the cabergoline and bromocriptine treatment

groups, respectively). Bromocriptine was associated with a higher withdrawal rate because of gastrointestinal-related events (6 *vs* 2%). Other reasons for treatment withdrawal in cabergoline recipients were cardiovascular events (3%), events related to the body as a whole (1%), respiratory events (1%) and urogenital events (1%); the incidence was similar to that observed with bromocriptine.

With regard to laboratory measurements, clinically relevant decreases in blood pressure (<90mm Hg systolic, <50mm Hg diastolic) were reported at least once in 23, 20 and 27% of patients treated with cabergoline, placebo and bromocriptine, respectively. Analysis of chest x-ray findings indicated that cabergoline was not associated with an increased frequency of respiratory abnormalities. 11 cases of pleuro-pulmonary effusion or fibrosis, an event known to be associated with ergolinic dopamine agonists, were reported with cabergoline. Most of these patients had a history of previous treatment with other dopamine agonists. ECG abnormalities were observed with a similar frequency in the active drug and placebo treatment groups, with no indication of treatment-associated changes in cardiac function.

Haematology and blood chemistry tests found cabergoline to have no clinically relevant toxic effects on variables relating to haemopoietic, hepatic, renal and metabolic function.

2. Conclusions

Cabergoline is a dopamine agonist with a high affinity for the dopamine D_2 receptor. *In vitro* studies have shown that, although cabergoline has an affinity comparable to that of bromocriptine and pergolide, it has a longer lasting dopamine agonist activity than either of these agents.[6,7] This long lasting effect has been confirmed in humans, cabergoline having a significantly longer plasma elimination half-life (63 to 68 hours) than other dopamine agonists.[8] This pharmacokinetic property of cabergoline is likely to prove advantageous compared with other agents such as bromocriptine and pergolide, which are taken 2 or 3 times daily.

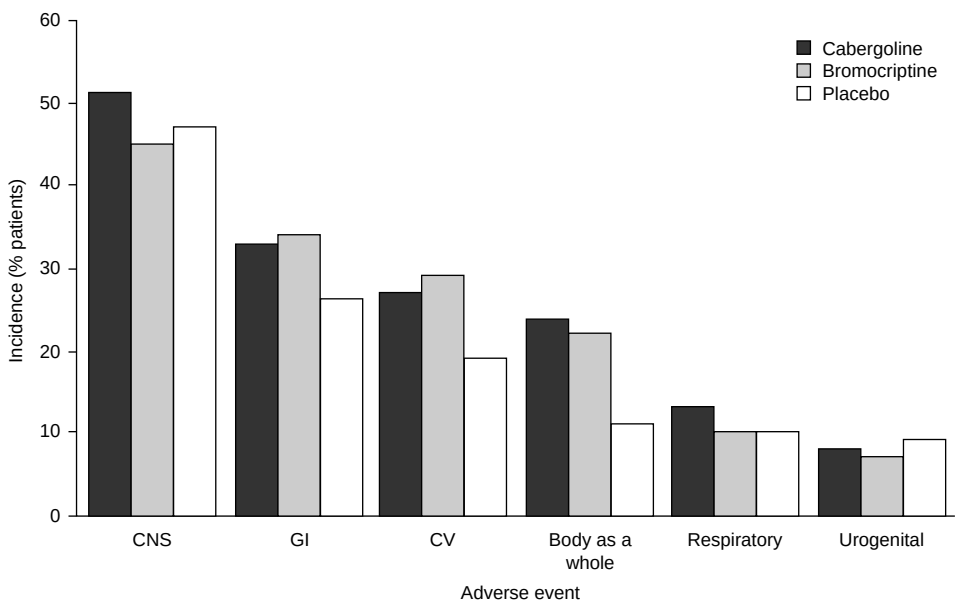

Fig. 2. Tolerability of cabergoline compared with placebo and bromocriptine in patients receiving long term levodopa therapy for advanced Parkinson's disease. *Abbreviations:* CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal.

Importantly, the long elimination half-life of cabergoline may render this drug more effective than other agents in controlling response fluctuations in patients receiving long term levodopa, by allowing continuous dopaminergic stimulation. Recent clinical trials, summarised above, have shown that cabergoline provides continuous dopaminergic stimulation when administered once daily.

Preliminary noncomparative clinical trials have shown that cabergoline used in conjunction with levodopa/carbidopa therapy alleviates signs and symptoms in patients with advanced Parkinson's disease. Reductions have been observed in the Unified Parkinson's Disease Rating Scale scores for activities of daily living and motor function in the 'on' and 'off' periods after treatment with cabergoline. In addition, the percentage of time 'off' is reduced. Importantly, the 'effective' daily dosage of levodopa may be lower during combination therapy with cabergoline, and this may reduce the incidence and severity of adverse motor disturbances associated with long term levodopa therapy (i.e. it may increase the threshold for the development of dyskinesia).

Overall, in double-blind comparative studies the efficacy of cabergoline was similar to that of bromocriptine. Cabergoline tended to cause a greater reduction in the number of 'off' hours, although the difference did not reach statistical significance. Both drugs showed similar tolerability with regard to the incidence and nature of adverse events, most of which involved the CNS or gastrointestinal system.

In conclusion, cabergoline is an effective dopamine agonist for the treatment of patients with advanced Parkinson's disease and motor fluctuations resulting from long term levodopa therapy. Its long elimination half-life, which allows for continuous dopaminergic stimulation, may improve compliance and control of response fluctuations during long term therapy, compared with other dopamine agonists.

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