

Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists

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The present paper reviews clinical studies on the use of dihydroergocriptine (DHEC), an ergot derivative with dopamine agonist activity, for the treatment of Parkinson's disease. This compound is a hydrogenated ergot derivative structurally quite similar to bromocriptine, from which it differs because of the hydrogenation in C₉–C₁₀ and the lack of bromine in C₂. DHEC has a potent D₂-like receptor agonist and a partial D₁-like receptor agonist activity; because of this biochemical profile, it has been suggested that DHEC may produce fewer side-effects and have clinical efficacy equal to that of a classical dopamine agonist. Several open-label and double-blind studies indicate that DHEC is an efficacious remedy for parkinsonian signs and symptoms. Further studies are necessary to compare DHEC to new dopamine agonists (pergolide, cabergoline, ropinirole, and pramipexole) which have been more recently marketed.

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Motor fluctuations in Parkinson's disease (PD) remain a difficult phenomenon to explain (1, 2). Several recent studies suggest that central pharmacodynamic factors are the main event responsible for the fluctuating response observed after a few years of levodopa therapy (3, 4). Levodopa has a very short plasmatic half-life, which determines subsequent peaks and troughs of its plasmatic and striatal levels, leading on the long-term to modifications of sensitivity in striatal dopamine receptors.

It has, therefore, been hypothesized that more continuous dopaminergic stimulation may be beneficial in patients affected by PD (5). Some success has been achieved with sustained-release formulations of levodopa, but it is conceivable that most of the long-term pharmacodynamic effects seen with oral levodopa might be avoided only with anti-parkinsonian drugs having a different pharmacologic profile, such as the dopamine agonists. Dopamine agonists are a heterogeneous group of drugs, which share the capacity to determine an antiparkinsonian effect through the activation of post-synaptic dopamine receptors. Since the first clinical studies with bromocriptine (BCR) in 1973, dopamine agonists have been

widely used as anti-parkinsonian drugs, either in combination with levodopa or as monotherapy (6). They present two main pharmacokinetic advantages as compared with levodopa: a longer plasmatic half-life and the lack of dietary influence on drug absorption. Their use may determine more sustained dopamine receptor stimulation and may diminish or even prevent the development of motor fluctuations (7). With the exception of apomorphine, that is the only dopamine agonist with a pharmacological profile recalling that of dopamine (8, 9), all the available dopamine agonists, show a therapeutic index lower than that of levodopa. BCR has been the first dopamine agonist available in clinical practice and represents the standard of reference for all the other drugs in this category. Despite some differences in biochemical structure, pharmacodynamic profile and peripheral metabolism, all other ergot derivatives marketed after BCR, i.e. lisuride (LIS), pergolide and cabergoline, are thought to be less potent than levodopa.

Not only the symptomatic efficacy of dopamine agonists on PD is weaker than that of levodopa, but also a higher incidence of side-effects (such as nausea, vomiting, sedation, hallucinations, anxiety, orthostatic hypotension and cardiac arrhythmias)

has been observed. Two main reasons account for the different therapeutic efficacy of levodopa and dopamine agonists. (a) All ergot derivatives are mainly, or uniquely, D2-like receptor agonists, while a full symptomatic effect on motor symptoms of PD would probably also require the activation of other dopamine receptor subtypes (10). (b) Dopamine agonists show a variable degree of agonist activity on other monoaminergic receptors (particularly, adrenergic and serotonergic), whose activation is thought to be responsible for many adverse effects (11). The poor tolerability of classical dopamine agonists represents a major therapeutic problem in PD, as it may hamper the achievement of the most appropriate dosage necessary to obtain adequate control of motor symptoms. Peripheral side-effects of dopamine agonists can be partly counteracted by the administration of domperidone, a peripheral dopamine receptor antagonist (12); however, no valid therapeutic measure is currently available to suppress the central side-effects of dopamine agonists.

In order to overcome these limitations, new compounds with dopamine agonist properties have been developed in the last decade. The search for new dopamine agonists is also fostered by some preliminary evidence that their chronic use may protect from the progression of PD (13, 14). To the contrary, levodopa is thought to accelerate disease progression, as it increases striatal dopamine turnover and is transformed into methylated compounds that may be toxic to nerve cells (15).

Dihydroergocriptine (DHEC) is a hydrogenated ergot derivative: it is structurally similar to BCR from which it differs because of the hydrogenation in C₉–C₁₀ and the lack of bromine in C₂. It has a potent D2-like receptor agonist and a partial D1-like receptor agonist activity (16); because of this biochemical profile, it has been suggested that DHEC may produce fewer side-effects and have clinical efficacy equal to that of a classical dopamine agonist. This review will focus on the efficacy of DHEC in PD, based on available clinical trials

performed in untreated patients and in the patients taking levodopa.

Pharmacology

The peripheral pharmacokinetics of DHEC has been recently elucidated in humans. Distribution half-life is 15 ± 1.6 h (mean $\pm$ SD), allowing the maintenance of a steady-state with a b.i.d. intake schedule. Following a single oral dose, DHEC is rapidly absorbed, and peak plasma concentration occurs between 30 and 120 min after its administration. The potency after oral administration is rather low on a milligram basis, as a result of poor bioavailability of DHEC (less than 5% of the administered dose reaches systemic circulation). This is mainly related to a strong *first-pass* hepatic metabolism, which generates active metabolites (17, 18). DHEC binding with serum albumin is around 50%, and there is no interference with levodopa metabolism (19).

The antiparkinsonian effect of DHEC is related to its strong D2-like receptor agonist activity, as shown by several *in vitro* and *in vivo* studies (20): DHEC activity on D1-like receptors is, instead, still controversial (it is possibly a partial agonist). It is remarkable that DHEC lacks any significant interaction with serotonergic or adrenergic receptors.

Symptomatic therapy of Parkinson's disease

Open studies

The efficacy and the tolerability of DHEC have been the object of a number of open studies (Table 1): two were short-term studies (21, 22), while a long-term study has been later published (23). In a pilot open label design, nine PD patients were evaluated under chronic treatment with BCR as monotherapy (22). Discontinuation of BCR was followed by a worsening of Webster rating score from 7.2 to 13.2. Subsequent treatment with DHEC (dosage up to 120 mg/day) was followed

Table 1 Synopsis of open label trials on the efficacy of DHEC in PD patients

	Ref. 22	Ref. 21	Ref. 23
Patients (number)	9	21 (7 <i>de novo</i>)	22 (9 <i>de novo</i>)
Hoehn and Yahr stage	I–IV	I–III	I–III
Study design	BCR substitution (2–4:1)	New therapy* or BCR substitution**	New therapy or BCR substitution
Treatment duration (months)	2	4	36
DHEC average daily dose (range)	(30–120 mg)	*37.7 (22–45) mg **43.1 (24–66) mg	64.0 mg
Drop-outs (number)	2	0	2

by a reduction of Webster score from an average 13.2–8.5. Another group of nine patients under chronic treatment with levodopa and BCR received DHEC as a substitute to BCR. The Webster score did not vary significantly (from 13 to 14.2), showing that DHEC is as efficacious as BCR.

A dose-finding study in seven PD patients with *de novo* disease has been performed (21). The starting dose of 3 mg b.i.d. or t.i.d. was increased by 3 mg every fortnight to reach a final mean dose of 37 mg/day. The duration of the study was 16 weeks; Webster score and Columbia University Rating Scale showed a significant reduction in the severity of parkinsonian signs ($P < 0.01$ with either scale). The same study also reported on seven patients already under treatment with levodopa and BCR. After withdrawal of BCR and replacement with placebo for 15 days, DHEC was administered at increasing doses while levodopa dose was maintained unchanged. The comparison of Webster score at the beginning of the study and after replacement with DHEC did not show differences, confirming that DHEC is as efficacious as BCR.

In a longer follow-up of the same series (23) it was reported that the drug was still effective after very long-term treatment in 20 patients given

DHEC for 36 months. Columbia and Webster scores improved until the second year of treatment and remained stable up to the third year, without need to introduce or increase levodopa dose during 3 years. Side-effects included gastric pain (six patients), dizziness (three patients), orthostatic hypotension (two patients) and headache (two patients) in the early period of treatment: no long-term induced side-effects occurred.

Controlled studies

Controlled trials evaluated the efficacy of DHEC in monotherapy or in combination with levodopa. DHEC was compared with placebo (24) or with other antiparkinsonian agents such as BCR (25–29), and LIS (30). The potency ratio on a milligram with basis between DHEC and BCR was 4/1. No study has yet compared DHEC with pergolide and cabergoline, the most recent ergot derivatives available in Europe or the other, non-ergot derived, dopamine agonists (ropinirole, pramipexole). The results concerning the use of DHEC in levodopa-treated patients are summarized in Table 2, whereas Table 3 reports the data from studies assessing DHEC monotherapy in early PD.

Table 2 Synopsis of double-blind trials on the efficacy of DHEC in levodopa-treated patients

	Ref. 25	Ref. 30	Ref. 27	Ref. 24
Patients (number)	20	68	20	20
Hoehn and Yahr stage	I–III	I–V	II–IV	II–III
Study design*	Parallel vs BCR (4:1)	Parallel vs LIS (50:1)	Parallel vs BCR (4:1)	Parallel vs placebo
Treatment duration (months)	1.5	3	6	6
DHEC average daily dose (range)	30–120 mg	60.0 mg	30–80 mg	40–80 mg
Outcome	DHEC = BCR	DHEC = LIS	DHEC = BCR	DHEC > placebo
Side-effects (number)	DHEC < BCR	DHEC < LIS	DHEC = BCR	DHEC > placebo
Drop-outs (number)	BCR: 1 DHEC: 0	LIS: 23 DHEC: 3	BCR: 1 DHEC: 0	DHEC: 0 placebo: 0

* The DHEC/dopamine agonist ratio is shown in parentheses.

Table 3 Synopsis of double-blind trials on the efficacy of DHEC in untreated patients

	Ref. 26	Ref. 28	Ref. 29	Ref. 31
Patients (number)	28	20	14	123
Hoehn and Yahr stage	I–III	I–II	I–III	I–II
Design*	Parallel vs BCR (4:1)	Parallel vs BCR (4:1)	Cross-over vs BCR (4:1)	Parallel vs placebo
Treatment duration (months)	6	2	3	3
DHEC average daily dose (range)	30–100 mg	120.0 mg	60.0 mg	40–120 mg
Outcome	DHEC = BCR	DHEC = BCR	DHEC > BCR (during the first sequence only)	DHEC > placebo
Side-effects	DHEC < BCR	DHEC < BCR	DHEC = BCR	DHEC = placebo
Drop-outs (number)	BCR = 3 DHEC = 1	DHEC = 0 BCR = 1	DHEC = 0 BCR = 1	DHEC = 4 Placebo = 3

* The DHEC/dopamine agonist ratio is shown in parentheses.

In one placebo-controlled study, 20 PD patients were included (24); they had been treated with levodopa and unsatisfactorily managed with monotherapy. Ten of these patients were randomly given DHEC and 10 placebo for 6 months: clinical assessment of parkinsonian signs was made by means of Columbia score and North-western University Disability Scale. Patients treated with DHEC had average Columbia scores showing a reduction in the severity of symptoms, particularly rigidity and tremor. They had side-effects, mainly concerning the gastrointestinal system, which were mild and did never lead to either a dose reduction or drug withdrawal. This study, in summary, showed that DHEC, in combination with levodopa, has a significantly higher antiparkinsonian efficacy than placebo.

Comparison of DHEC and BCR was provided by five controlled studies (four with a parallel design and one cross-over), in which a total of 102 patients were studied. Four studies reported that DHEC has a therapeutic efficacy comparable with that of BCR (25–28). Contrasting results were observed in the cross-over study (29), which reported on 14 *de novo* parkinsonian patients treated with DHEC or BCR for 3 months and then switched to cross-over. The authors reported that the motor examination score of the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) during the DHEC–BCR sequence prior to cross-over improved significantly compared with the baseline, whereas no significant change occurred in the BCR–DHEC sequence prior to cross-over. Notwithstanding, after cross-over, the efficacy of DHEC and BCR were comparable. The authors explained this intriguing difference related to the administration sequence, with a possible interference caused by a short wash-out time. However, this study suffers from the main limitation of having used rather low doses of dopamine agonists (up to 60 mg DHEC and 15 mg BCR), that could have hampered a full comparison of their efficacy in untreated PD patients.

The remaining four studies comparing DHEC with BCR with parallel design used higher DHEC dosages (25–28). In one study (25), 50% of the daily levodopa dose was replaced with either DHEC or BCR in stable PD patients. The dopamine agonists were slowly titrated up to a final daily dose of DHEC (ranges: 30–120 mg) and to a final daily dose of BCR (ranges: 7.5–30 mg). The patients were evaluated every fortnight until 45 days after, by means of Hoehn and Yahr staging, Webster score and the Gibson spiral maze. Results showed a comparable efficacy between the two drugs but two patients of the

BCR group required a further increase of levodopa dose as a result of poor efficacy of BCR. A higher tolerability was recorded in the DHEC group. In the BCR group one patient dropped-out because of severe diarrhoea. In another parallel study on patients taking levodopa (27), 20 parkinsonian subjects with variable disease stages (II–IV Hoehn and Yahr) were included. DHEC doses of 30–80 mg daily were compared with BCR (7.5–20 mg/day) for 6 months; clinical disability was measured by means of the Columbia score. At the end of treatment, the patients treated with DHEC and those treated with BCR had a similar pattern of improvement, without any significant difference. Side-effects were quantitatively similar in the two groups; in the BCR-treated group there was one drop-out because of severe orthostatic hypotension. Unfortunately, the groups treated with DHEC and BCR were not comparable with respect to disability (the BCR group had a baseline Columbia University Rating Scale score about 30% greater than the DHEC treated group), which limited a proper comparison of the symptomatic efficacy of the two compounds.

In three small studies (two parallel and one cross-over) concerning untreated PD patients (26, 28, 29) DHEC was given in monotherapy. In the first study, the daily dose was between 30 and 100 mg/day for 6 months (26); while in the second study, which also comprised a 2-month open phase, the daily dose was the highest averaging 120 mg/day, for 2 months (28). Assessment of disability was carried out by means of Hoehn and Yahr staging and UPDRS-III. In all studies, the clinical efficacy of DHEC was not significantly different from that of BCR, but the side-effects of DHEC were usually less severe than those of BCR. In one of these studies (26), three patients treated with BCR dropped-out (because of gastralgia, nausea or lipothymia), while in another (28) it was reported that one patient on BCR dropped out, because of hallucinations and severe agitation. A larger study recently confirmed the efficiency and safety of DHEC given as monotherapy in the symptomatic treatment of PD (31). A multicentre, randomized, double-blind, placebo-controlled, parallel group study was carried out in 123 patients suffering from *de novo* PD. The total score of the UPDRS was identified as the efficacy target variable. Sixty-two patients were randomized to DHEC and 61 to placebo. According to the experimental design, an 18-month double-blind phase vs placebo was followed. Two interim analyses were planned both at the third and twelfth month of treatment, in order to avoid continuation on placebo, if clear differences between groups

were found. Analysis of variance was performed both on the per protocol (PP) and intent-to-treat (ITT) sample. The results on the first interim analysis showed significant differences between treatment groups of the UPDRS total score both in the ITT (115 patients, DHEC: no. 56; placebo: no. 59; $P = 0.019$) and PP (96 patients, DHEC: no. 46; placebo: no. 50; $P = 0.001$) sample, when the trial was stopped. At the time of stopping the trial, 73 patients (DHEC: no. 37; placebo: no. 36) had reached the 6-month observation visit; the analysis carried out on this subset of patients confirmed the efficacy of DHEC in early PD and the correctness of the decision to stop. The incidence of adverse drug reactions did not differ between DHEC and placebo recipients, gastrointestinal complaints being the most frequent. The results of this study confirmed that DHEC is safe and effective in improving symptoms of *de novo* parkinsonian patients.

Overall, in controlled studies, a better tolerability of DHEC, as compared with BCR, was reported. This was also confirmed indirectly by the observation that none of the patients taking DHEC had side-effects severe enough to require drug withdrawal, whereas a total of seven patients taking BCR discontinued the treatment.

The comparative efficacy of DHEC and LIS was evaluated by a multicentre trial involving 68 patients who received DHEC or LIS in combination with levodopa (30). The treatment lasted for 3 months (2 months in 45 patients, according to a protocol amendment). The agonist prescription was increased until 60 mg/day of DHEC or 1.2 mg/day of LIS were reached, while levodopa was kept unchanged. The primary objective of the study was to evaluate complications of therapy, such as motor fluctuations or dyskinesia, by means of UPDRS-IV. The secondary objective was to assess the efficacy of DHEC as compared with LIS on parkinsonian signs, by means of the Columbia University Rating Scale, North-Western University Disability Scale and Hoehn and Yahr staging. The two groups of patients had a similar improvement of motor symptoms, but fluctuations were influenced more positively by DHEC than by LIS, possibly due to the larger half-life of the former drug. In terms of safety, patients treated with DHEC had considerably less side-effects (23 LIS patients dropped out as compared with only three patients treated with DHEC).

Comparison with other new dopamine agonists

All initially available oral dopamine agonists had an ergoline structure. This is the case for BCR,

LIS, pergolide and cabergoline. In order to overcome the limitations (partial efficacy and significant side-effects) common to all these compounds, two new non-ergoline dopamine agonists have been developed in the last decade for the treatment of PD.

Ropinirole has a pharmacologic profile similar to that of BCR, as it binds to D₂-like receptors. Ropinirole has been marketed in 1996 after the disclosure of the favorable results from several phase III trials. This program included two placebo-controlled trials of ropinirole in monotherapy and two comparative trials against levodopa and BCR in early PD patients (one for each reference drug). In addition, there have been three placebo and one BCR-controlled trials of ropinirole as an add-on therapy to levodopa (32, 33). Results showed that ropinirole is effective in both early and advanced PD; as expected, its efficacy is lower than that of levodopa. Some possible advantages over BCR have been supported by the results of a study (33), which needs to be confirmed in early and advanced PD patients.

Pramipexole is a synthetic non-ergot benzothiazol derivative with a selective D₃ dopamine receptor agonist activity. The results of several studies showed that pramipexole is safe and effective in the treatment of early PD in monotherapy and advanced PD as an adjunct to levodopa (34–36). Comparative trials of pramipexole vs DHEC, BCR or other dopamine agonists are not available yet. Unfortunately, the side-effect profile of ropinirole and pramipexole in PD has been shown to be remarkably similar to that of the old ergot-derivatives (visual hallucinations, insomnia, orthostatic hypotension, malaise, and gastrointestinal troubles). Moreover, cases of sudden sleep attacks (occasionally causing to fall asleep at the wheel) have been recently described in persons taking pramipexole and ropinirole (37).

Conclusions

Dopamine agonists are now a well-established therapy in patients affected by PD. In the advanced stages of the disease dopamine agonists can partially correct motor fluctuations observed with long-term levodopa treatment (38). Available evidence also suggests a role for these drugs in *de novo* Parkinsonian patients, with the aim to delay levodopa usage and the occurrence of late motor fluctuations (39, 40). The use of dopamine agonists is, however, marred by a large incidence of side-effects that is responsible for their therapeutic profile being worse than that of levodopa.

Therefore, new efficacious and well tolerated dopamine agonists are warranted: DHEC is such a new drug, that has an efficacy similar to other already known dopamine agonists and less frequent cardiovascular and psychiatric side-effects. In particular, the occurrence of a rare but severe side-effect such as pleural or retroperitoneal fibrosis, which has been described with all other ergoline derivatives, has not been reported in trials with DHEC. The safety of DHEC may be related to the lack of significant interaction with serotonergic or adrenergic receptors and would support the use for DHEC also in the treatment of other chronic neurologic conditions such as the common "restless legs syndrome" (41).

Unfortunately, comparative trials of DHEC vs pergolide, cabergoline, ropinirole or pramipexole are not available at the moment and they are not planned in the near future. Because of the probable lack of financing by drug companies in planning trials of this type, these should be supported from governmental or no-profit organizations in order to solve important therapeutic issues for PD. It would also be interesting to explore the possibility that an early combination of DHEC and levodopa could delay the onset of motor fluctuations; this would expand the preliminary evidence provided by the data reviewed here.

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