Should levodopa dose be reduced when switched to stalevo?

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The addition of entacapone to levodopa-carbidopa (LC) or the switch from LC to a tablet containing levodopa–carbidopa–entacapone (LCE) improves the wearing-off phenomenon, increases the 'on' time and decreases the 'off' time, but the appearance or exacerbation of dyskinesias is the more frequent side-effect. Thus, a reduction of the total levodopa dosage would be recommended. However, this could result in a lack of efficacy against the wearing-off. We report on the results of a clinical trial conducted to determine the best way in terms of efficacy, tolerability and safety of switching from LC to LCE in patients with Parkinson's disease (PD) and end of dose wearing-off. 39 patients with PD and wearing-off without or with mild dyskinesias were randomly assigned to either a group receiving the same LC dosage or to a group in which the total LC amount was reduced by 15–25%. Four weeks after the change, both groups showed an increase in daily 'on' time and a reduction in the daily time spent in 'off'. Two patients in each group experienced an increase in basal dyskinesias. No differences in clinical assessment between groups were found. Tolerance was excellent. This study suggests that switching from LC to LCE in patients with mild-to-moderate wearing-off can be done safely with or without reducing the total LD amount, but in the clinical setting it would be more practical to keep the dosage of LC unchanged unless severe dyskinesias are present.

Introduction

Long-term treatment with levodopa is associated with fluctuations in motor response and the development of dyskinesias [1]. Many treatments have been developed with the aim to overcome these complications, including dopamine agonists, monoamine-oxidase-B inhibitors and cathecol-O-methyl-transferase (COMT) inhibitors.

It has been shown in acute studies that 400 mg of entacapone selectively and reversibly inhibits COMT in the periphery thereby extending the half-life of levodopa elimination by 85% and increasing the plasma levodopa area under the curve by up to 50% [2]. When administered chronically, entacapone decreases the plasma elimination of orally and intravenously administered levodopa [3]. Daily levodopa dosages can be reduced by 27% yet mean plasma levodopa concentrations are increased by 23% [3]. Entacapone increases the duration of action of single doses of levodopa by a mean of 56% [3]. Therefore, it increases the bioavailability of levodopa and minimizes variability in levodopa plasma concentrations. In patients with PD, entacapone given with levodopa and dopa-decarboxylase inhibitor, combines the rapid onset of standard levodopa with a prolonged duration of action [3]. In clinical practice, the response per dose is about 30–60 min longer with 1–2 h more 'on' time per day [4–7].

A preparation combining levodopa–carbidopa–entacapone (LCE) has been developed. These new tablets (Stalevo®) combine 200 mg entacapone with several doses of levodopa and carbidopa (LC). This approach has similar tolerability and efficacy than two separate tablets of LC and entacapone [8].

As entacapone prolongs the elimination half-life of levodopa, it has been used to increase the duration of levodopa action in patients who experience wearing-off motor fluctuations [4–7]. These patients can also have

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dyskinesias. The main side-effect of adding entacapone to LC is the appearance or exacerbation of dyskinesias, particularly in patients with pre-existing dyskinesias and in those taking high doses of LC [4–7]. Dyskinesias usually appear at the beginning of treatment with entacapone. These facts raise an important practical question in the clinical setting when switching from LC to LCE is planned; if total dose of levodopa is maintained, dyskinesias could appear whereas if levodopa dosage is decreased from the very moment of the change, the wearing-off phenomenon could remain unchanged or even worse. This logical reasoning has not been adequately addressed in a clinical trial, although clinical practice indicates that keeping unchanged the dose of levodopa when switching from LC to LCE is a good option. Thus, we hypothesize that this way of changing could be recommended, provided that there are no statistically significant differences in the adverse events between groups. To demonstrate this hypothesis, we conducted a clinical trial to compare the efficacy and safety of maintaining the same dose of LC or reducing it by 20% when switching to LCE in patients with PD and wearing-off phenomenon.

Methodology

Patients with PD according to the criteria of the United Kingdom Parkinson's Disease Brain Bank [9] on a stable regime of LC and experiencing the wearing-off phenomenon were included in this multicentric, prospective, single-blind, randomized and clinically controlled study. As patients with advanced PD, complex motor fluctuations and severe dyskinesias could not be good candidates to receive LCE, only patients with wearing-off without or with mild dyskinesias were included. Patients were randomly assigned to either a group receiving the same LC dosage (group A) or to a group in which the total LC amount was reduced by a 15–25% (group B). Patients were randomized to receive LC or LCE according to a computer-generated randomization schedule. Switching was carried out according to a guide designed to fit the total dose of LC with available formulations of LCE. After the inclusion of patients in the corresponding group, LCE dosage could not be modified unless a deterioration in the clinical situation or the appearance of dose-related side-effects indicate the need of making changes. The duration of the study was 4 weeks. Efficacy was determined by the change in the clinical situation between the basal and the final visits. Clinical situation was assessed by administering the UPDRS [10] and home on–off diaries which were completed by the patient 3 days prior to the basal visit and 3 days before the end of the study. PDQ-39 questionnaire [11] to assess quality of life and clinical global impression (CGI) questionnaire fulfilled by the patient and the neurologist were also administered. Tolerability and safety were determined by monitoring the adverse events in every visit by a check list. The blind investigator was unaware of the treatment group and administered the rating scales, the on–off diaries and the adverse events check list. Informed consent from patients and protocol approval by corresponding Ethics and Clinical Research Committees were obtained. Statistical analysis of data was performed by applying the Student's *t*-test to compare basal and final data. Sample size (60 patients) was based on the assumption that the proportion of withdrawal due to adverse events would be 6% (CI 93%). The level of significance was $P < 0.05$ for all data.

Results

Fifty-four patients were included in the study but five of them were not assigned to any treatment group because of unreliable home diaries ($n = 3$) and abnormalities in laboratory tests ($n = 2$). Only 39 of the 49 patients assigned to a treatment group could be evaluated. The reason for not including the above-mentioned 10 patients in the analysis is attributable to protocol violations. Violations were minimal but relevant for the purposes of the study (i.e. greater than recommended dose reductions). Of the final 39 evaluated patients, 17 were in group A and 22 in group B.

Clinical characteristics of the 39 evaluable patients are shown in Table 1. There were no statistically significant differences in the distribution by sex, race, smoking habit and education level. Both groups were matched according to first symptom of PD and Hoehn & Yahr stage which was II or III in 75% of cases. However, it could be interesting to mention that the proportion of patients in stage IV of Hoehn and Yahr was higher in group A than in group B (23.5% vs. 9%), although this difference did not reach the level of statistical significance. Furthermore, total score of UPDRS was comparable between both groups (55.3 in group A vs. 58 in group B). No statistically significant differences in the presence and intensity of dyskinesias between both treatment groups were observed, although more patients in group B referred early-morning dystonia (18.2% vs. 5.9% of cases).

Table 1 Demographics of evaluable patients

	Group A ($n = 17$)	Group B ($n = 22$)	*P*
Age	68.3 (±8.10)	66.8 (±6.98)	0.54 (NS)
PD duration	8.53 (±5.96)	9.38 (±5.19)	0.64 (NS)
Levodopa duration	7.46 (±5.46)	8.67 (±5.79)	0.53 (NS)

Table 2 Adverse events

	Group A	Group B	*P*-value
Adverse events related to the study drug	6 (35.3%)	5 (22.7%)	0.387 (NS)
Dyskinesias	4 (23.5%)	3 (13.6%)	0.423 (NS)

Six patients in group A and five in group B experienced adverse events related to the drug (P = NS) (Table 2). Nausea (n = 3), dizziness (n = 2), somnolence (n = 3) and abdominal pain (n = 3) were always mild and transient. All patients reported urine discolouration. Four patients in group A and three patients in group B reported an increase in dyskinesias relative to the basal situation. This increase was objectively demonstrated by the corresponding subscale of the UPDRS in only two patients in each group (Tables 2 and 3). Levodopa dose was modified in these four cases and in another one included in group B who showed a worsening in the wearing-off. Only one patient in group A discontinued treatment owing to exacerbation of dyskinesias. Three patients included in group B withdrew the study because of insatisfactory clinical outcome (n = 2) and vomiting with lip oedema (n = 1). Overall, 15 of the 17 assigned to group A and 20 of 22 included in group B, decided to continue with the new treatment.

Table 3 Dyskinesias: number of patients with dyskinesias and mean severity of dyskinesias before and after treatment. Severity is rated according to the subscale IV of the UPDRS

	Group A		Group B	
	Basal	Final	Basal	Final
Patients	7	9	8	10
Severity (mean)	1.4	1.5	1.2	1.4

Table 4 Levodopa dosages (SD) and number of daily doses (SD)

	Group A	Group B
Basal levodopa dose (mg/day)	566 (±257)	670 (±330)
Basal daily number of doses	5 (±1)	5 (±1)
Final levodopa dose (mg/day)	594 (±249)	520 (±254)
Final daily number of doses	5 (±1)	5 (±1)

Levodopa doses are shown in Table 4. As per protocol, final levodopa dose was considerably reduced in group B whilst remained virtually unchanged in group A. Number of daily intakes was not modified. During the short follow-up period, both groups of patients experienced an increase in the number of daily hours in the 'on' situation and a decrease in the time spent in the 'off' situation (Table 5). Although the difference between groups did not reach statistically significant levels, a clear trend in favour of group A was observed. Compared with basal situation, patients in group A experienced a significant increase in daily 'on' time of 76 min (P = 0.045) and a decrease in 'off' time of 123 min (P = 0.018). In contrast, patients included in group B showed a modest increment of 38 min in 'on' time and a mild reduction of 32 min in 'off' time. Quite unexpectedly, patients assigned to group A showed an increase of 33 min in the daily 'on' time with dyskinesias, whereas this time was prolonged in 98 min in group B patients. As it happened with 'on' and 'off' time, these differences failed to reach statistical significance level. There is a discordance between the gain in daily 'on' time and the reduction in daily 'off' time. This is quite commonly observed in clinical trials using patient diaries and it can be due to a gain in sleeping time or to problems with diary fulfilment. In fact, a slight increase in sleep time was observed, yet it does not correct totally the discordance. Total and partial scores of the UPDRS in 'on' and 'off' showed a mild, not significant improvement in both groups during the study (Table 6).

Quality of life, as assessed by the PDQ-39 questionnaire, remained unchanged during the study. CGI questionnaires showed no statistically significant differences. More than 60% of patients felt better after the change (64.5% in group A and 67% in group B). Neurologists considered that 45% of patients in group A and 70% in group B improved after the switching.

Discussion

This study did not show any significant difference in tolerability, safety and efficacy amongst reducing or

Table 5 Results of home diaries completed by patients (SD). Time is given in minutes

	Group A			Group B		
	Basal	Final	Difference	Basal	Final	Difference
On without dyskinesias	563.9 (±136.6)	640 (±210.7)	+76*	542.9 (±212.7)	580.25 (±279.1)	+38
On with dyskinesias	276.6 (±28.8)	310 (±103.9)	+33	264.3 (±64.5)	361.67 (±152.37)	+98
Off	347.7 (±170.7)	224.6 (±130.5)	−123**	367.7 (±184)	315.26 (±212.8)	−52

P = NS for all values except for *P = 0.045 and **P = 0.018.

Table 6 UPDRS (mean values)

	Group A				Group B			
	Basal		Final		Basal		Final	
	On	Off	On	Off	On	Off	On	Off
UPDRS I	2	3	3.3	2.2	1.7	2.7	1.6	2.4
UPDRS II	7.3	15.4	7.4	14.1	6.8	16	5.4	14.1
UPDRS III	17.2	33.6	15.7	29.1	16.2	36	15.2	33.5
UPDRS IV	2.4	3.2	2.6	2.9	3	3.4	2.5	3
UPDRS total	29	55.3	27.9	49.4	27.8	58.1	24.8	53.2

P = NS for all values

keeping unmodified the LC dosage when switching to LCE. Therefore, both possibilities can be recommended. Thus, switching from LC to LCE in patients with PD and mild-to-moderate wearing-off with mild dyskinesias can be done without decreasing the total dosage of LC. In previous studies, worsening of dyskinesias was observed [4–7]. It is thought that this is a side-effect of increased bioavailability of levodopa and can be managed by a 10–30% decrease in the dose of levodopa; reducing the dose of levodopa, dyskinesias return to baseline or improve. In contrast, dyskinesias were not a major problem in present study likely owing to a selection bias as included patients have no or mild dyskinesias and it is well known that this problem appears more frequently in patients with more complex PD and treated with higher doses of LC. Indeed, the only patient who abandoned the trial midway in the study because of dyskinesias, was taking relatively high doses of levodopa (800 mg/day). Finally, the duration of our study was too short as to see dyskinesias yet the majority of them arise few days after starting entacapone [4–7].

The limitations of this study are as follows. Only data from 39 of the originally planned sample (60 patients) could be analysed. Thus, the statistical power of this sample size could not be enough as to reach significance levels. Indeed, a power of 50% is estimated. Moreover, 10 patients (20%) were omitted from the statistical calculations because in non-inferiority and equivalence trials, non-ITT analyses are desirable as a protection from ITT's increase of type I error risk (falsely concluding non-inferiority) [12,13]. There is greater confidence in results when the conclusions are consistent. Additionally, albeit patients were evaluated in the 'on' and 'off' conditions, a specific scale for dyskinesias was not used. Finally, the duration of the study was too short as to make any firm conclusion about the possibility of finding any significant difference in long-term efficacy and safety. Nevertheless, we will comment on the interesting findings of this study.

Both switching strategies lead to an improvement in the clinical status of patients. A reduction of more than 1 h in the number of daily hours spent in 'off' was shown, confirming previous data of double-blind studies [4–7]. Interestingly, dyskinesias did not represent a major management problem in this population of patients, a finding probably related to the inclusion criteria employed. Nonetheless, the proportion of daily 'on' time with dyskinesias was increased in both groups. Unexpectedly this was more frequent in those cases in whom the total LC dose was reduced by 20%. This might be an artifact owing to the small sample size. Indeed, despite these observations, no statistically significant differences amongst both treatment groups were found.

Quality of life was not improved by the change and no significant differences between groups were shown. These results could appear quite paradoxical as the gaining of daily hours in 'on' and the concomitant reduction in 'off' time was evident, particularly in group A patients. However, this paradox could be more apparent than real. Indeed, studies with entacapone in fluctuating and stable PD patients have shown an improvement in quality of life measures not accompanied by changes in motor function [14,15]. It is, thus, likely that quality of life is to some extent independent of the motor situation [16]. In keeping with this, CGI of patients showed a proportion close to 60% of patients in both groups feeling better after the switching. In contrast, neurologists considered that only 45% of patients in group A improved after the change. This contrasts with the mean reduction of 2 h spent every day in the 'off' condition experienced by this group of patients. These findings emphasize the need of using different assessment methods in clinical trials, including motor rating scales and quality of life questionnaires.

Regarding tolerance of LCE, it should be underlined that only one patient withdrew the study due to intolerance to LCE. Two more patients stopped the trial owing to a lack of improvement of the wearing-off phenomenon. Despite these withdrawals, it can be concluded that both switching procedures to LCE were well tolerated.

In summary, despite the methodological limitations, this study suggests that switching from LC to LCE in patients with mild-to-moderate wearing-off (with and without mild dyskinesias) can be done safely with or without reducing the total LD amount. Thus, in the clinical setting it would be more practical to keep the dosage of LC unchanged unless severe dyskinesias are also present.

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