



Controlled-Release Levodopa for the Treatment of Rapid Motor Fluctuations in Parkinson's Disease Subjects with Subthalamic Nucleus Deep Brain Stimulation

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Abstract

Objectives We aimed to investigate the efficiency of controlled-release levodopa/benserazide (Madopar HBS) use during daytime in our pilot study on advanced-stage Parkinson's disease (PD) subjects with deep brain stimulation of the subthalamic nucleus (STN-DBS) therapy.

Methods We have evaluated all PD subjects with STN-DBS who had admitted to our outpatient polyclinic between February 2022 and March 2022. Among these patients, those who were taking levodopa therapy at least five times throughout the day and the efficiency of levodopa lasted less than 3 hours were detected. The standard levodopa therapy was switched to Madopar HBS in all patients who accepted the therapy chance and the clinical evaluation of the patients on Madopar HBS therapy was performed in the second month of the therapy.

Results Ultimately, the follow-up of all four patients in whom the levodopa therapy was changed to Madopar HBS yielded a significant reduction in the “off” periods and improvement in the PSQ-39 scores.

Conclusion We suggest the use of Madopar HBS in PD patients with STN-DBS surgery suffering from motor fluctuations, particularly in the subgroup with milder dyskinesias. Future study results of a large number of PD subjects with STN-DBS therapy are warranted to confirm our observations. The results of these studies may provide critical applications in clinical practice.

Keywords

- ▶ controlled-release levodopa
- ▶ rapid motor fluctuations
- ▶ short-duration response
- ▶ Parkinson's disease
- ▶ STN-DBS

Introduction

Levodopa is a potent therapy in relieving the symptoms of Parkinson's disease (PD); however, in the advanced stage of the disease, duration of response to levodopa doses reduces and “wearing-off” periods emerge.^{1,2} These motor fluctua-

tions are partly due to the progression of the loss of dopamine-containing neurons in the substantia nigra pars compacta and the short half-life of levodopa preparations.² Adding catechol-O methyltransferase inhibitors, such as entacapone, increases levodopa half-life by 25 to 50%

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without increasing peak concentration.^{1,3} However, controlled-release levodopa/benserazide (Madopar HBS) provides a further sustained efficiency, which is classically used for a long time for the treatment of severe nocturnal and early-morning off-states developing in the advanced stage of PD.^{4,5} Madopar HBS (sustained-release Madopar) reaches maximum concentration levels later than standard levodopa, 1.3 to 1.8 hours compared with 0.8 to 1.2 hour.⁶ Besides, Madopar HBS produces a larger area under the curve with more sustained plasma levels than standard Madopar 125 mg TB and a 50% reduction of peak concentrations.⁷ Remarkably, early open trials indicated that Madopar HBS could alleviate motor fluctuations in moderately advanced and advanced PD.^{8,9} However, its clinical use throughout the day is uncommon due to the reported severe dyskinesia and unpredictable pharmacokinetics as well as side effects.^{8,9}

In this study, we aimed to present our observations regarding the use of Madopar HBS in a PD patient group with deep brain stimulation of the subthalamic nucleus (STN-DBS) who had been suffering from “short-duration responses (SDR)” to the standard levodopa preparations. We aimed to interrogate the use of Madopar HBS throughout the day for motor fluctuations in PD patients with STN-DBS. Arrestingly, we discuss some hypotheses regarding the mechanisms responsible for the benefit of Madopar HBS, particularly in those patients with STN-DBS therapy.

Materials and Methods

In this prospective interventional study, we have specifically evaluated the treatment regimens and the “on” and “off” periods of all advanced-stage PD subjects with STN-DBS who were admitted to our outpatient polyclinic between February 2022 and March 2022. Among these patients, patients who were taking levodopa therapy at least five times throughout the day and the efficiency of levodopa lasted less than three hours were detected. After informing about the pharmacokinetics of the Madopar HBS (levodopa/benserazide [100/25 mg]), the switch of the levodopa therapy to the Madopar HBS 100/25 mg capsule was suggested. In those patients who accepted the therapy chance, the standard levodopa therapy was switched to the Madopar HBS 100/25 mg by adjusting the levodopa equivalent dose (LED) to approximately the same as the previous therapy. The dose interval of the Madopar HBS 100/25 mg was prescribed two or three times a day that was decided individually according to the optimal clinical outcome made during the weekly polyclinic visits. The clinical evaluation of the patients on Madopar HBS therapy was performed in the second month of the therapy. One of these patients did not attend the polyclinic visits and, therefore, data could be attained regarding this patient. Ultimately, data regarding the remaining patients were analyzed. Of note, therapies for PD other than levodopa were not changed during this trial (pramipexole in one patient, rasagiline in two patients, and amantadine in two patients). The demographic and clinical parameters including the disease duration, disease onset side, disease subtype, the duration of STN-DBS therapy, basal LED were

noted. The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scores, freezing of gait (FOG) Questionnaire scores, and Parkinson's disease Questionnaire (PDQ-39) scores were calculated in all these subjects. At follow-up visits on Madopar HBS therapy, the time spent in the “off” state (MDS-UPDRS 4.3) and PSQ-39 were also evaluated in addition to the basal state assessments. The alterations in these scores were evaluated to reveal the impact of Madopar HBS in the patients' clinics.

Results

Among the 40 PD subjects with STN-DBS therapy who were admitted to our outpatient clinics between February 2022 and March 2022, five patients were detected to receive levodopa therapy at least five times throughout the day and the efficiency of levodopa lasted less than three hours. The follow-up data of one patient was unavailable. The follow-up of the remaining four patients in whom the levodopa therapy was changed to Madopar HBS yielded a significant reduction in the “off” periods and improvement in the PSQ-39 scores. The data of these patients are presented in ▶ **Table 1**.

Case Reports

Case 1

A 41-year-old male patient with PD who had undergone STN-DBS for advanced-stage disease (1 year ago) including motor fluctuations or dyskinesias was admitted to the routine neurology polyclinic visit. The PD has started 15 years ago with symptoms of slowness on the right side. At admission to our polyclinic, the patient was receiving medications of pramipexole 1.5 mg, rasagiline 1 × 1 mg, and levodopa/carbidopa/entacapone [75/18.75/200] 6 × 0.5 TB. The patient suffered from severe akinesia during medication off periods and FOG episodes were prominent and severely disabling. The administration of levodopa/carbidopa/entacapone provided the “on” periods for the furthest 2 hours. Remarkably, the patient did not develop dyskinesia during these periods, but could not tolerate higher levodopa dosages due to the severe headache and nausea that were associated with levodopa dosages. The MDS-UPDRS motor score during the medication “on” period was 25 points, whereas it was 52 during the medication “off” period. Madopar HBS 100/25 mg capsule 2 × 2 TB was initiated that provided substantial improvement in the daily living activities, and a reduction in the total “off” period. Such that, the time spent in the “off” state reduced from 50 to 75% of waking day to 25% or less of waking day. The 39-item Parkinson's Disease Questionnaire score improved from 70 to 50 points (▶ **Table 1**).

Case 2

A 57-year-old male patient with PD had applied due to severe “off” periods and “on” period dyskinesias despite taking levodopa/benserazide dose 6 × 2 TB daily. The patient had received the diagnosis of PD 13 years ago due to right-sided slowness. The patient was born to first-degree consanguineous parents and there was no affected individual in the

Table 1 The demographic and clinical characteristics of the patients

Case number	1	2	3	4
Age	41	57	72	50
Gender (F/M)	M	M	M	M
Disease duration	15	13 years	20 years	13 years
Disease subtype (AR/T)	AR	AR	AR	AR
Disease onset side	Right	Right	Right	Left
STN-DBS duration	5	1 years	8 years	7 years
DBS settings	Lead location (R/L)	Monopolar (ventral)	Monopolar (most ventral)	Monopolar (dorsal)
	Voltage (R/L)	3 V/3.5V	1.6 V/2 V	3.2 V/3.9 V
	Frequency	130 HZ	160 Hz	110 Hz
	Pulse width /R/L)	60 us/60 us	60 us/60 us	60 us/60 us
FOG questionnaire score	7	19		18
LED	550	500	950	1,125
MDS-UPDRS motor (STIM-on. Med-on)	25	18	40	17
MDS-UPDRS motor (STIM-off. Med-on)	50	77	75	62
Improvement in the MDS-UPDRS motor with STIM	50%	77%	47%	73%
The initial number of levodopa dosages daily	6 × 0.5 TB 75 mg ^a	6 × 0.5 Madopar TB	6 × 1.5 Madopar TB	6 × 1 TB 150 mg ^a
The dosage of daily Madopar HBS (levodopa/benserazide) ^b	400/100 mg	400/100 mg	1,000/250 mg	900/225 mg
Improvement in the “on” periods (%)	25–50%	50–75%	25–50%	25–50%
PDQ-39-before Madopar HBS	70	25	85	74
PDQ-39-after Madopar HBS	50	10	53	49
The percentage of improvement of PDQ-30 score	29%	60%	38%	34%

Abbreviations: AR, akinetic/rigid; FOG, freezing of gait; LED, levodopa equivalent dose; STN-DBS, deep brain stimulation of the subthalamic nucleus.

^aLevodopa/carbidopa/entacapone.

^bAfter switch to Madopar HBS.

pedigree. The patient had been suffering from rapid motor fluctuations over the past 7 years and he spent most of the daytime during “off” periods, albeit he received levodopa six to seven times a day. The MDS-UPDRS motor score was 75 during on period and 32 during off periods. The effect of levodopa/benserazide started 1 hour after the dosage and lasted for 1 hour, and half of the daytime lasted with severe dyskinesia and disabling bilaterally resting tremor. Due to this advanced stage of PD, STN-DBS was inserted 1 year ago that provided substantial improvement in the clinic. Besides, the levodopa dosage was reduced to a quarter. On the other hand, the rapid motor fluctuation persisted that he had to spend more than half of the day during “off” period, albeit taking levodopa/benserazide 0.5 TB six times a day. At this point, we switched the therapy to Madopar HBS 100/25 mg 2 × 2 capsule that provided a substantial reduction in the “off” periods (50–75%) and dramatic improvement in the daily living activities (► **Table 1**).

Case 3

A 72-year-old male patient with PD who had undergone STN-DBS surgery 8 years ago applied to the polyclinic visit for routine evaluations. The patient had received the diagnosis of PD 20 years ago that had manifested with left-sided slowness. The extrapyramidal exams revealed severe akinesia and FOG episodes that were apparent during off-periods. The adjustments of the stimulation parameters including the decrement of the stimulation (STIM) frequency and increment of the voltage provided mild improvement in his parkinsonian signs of akinesia, bradykinesia, and rigidity. The MDS-UPDRS motor score was 60 during the STIM-on medication-off period and it was 40 during the STIM-on medication-on period. The duration effect of the levodopa was short, and he had to receive the Madopar 1.5 TB five times a day that only provided an “on” period of 7 to 8 hours a day. The therapy was switched to Madopar HBS 100/25 mg three times a day (3 × 3) that ensured a dramatic improvement in the patient's clinic. The patient

spent three quarters of the daytime during the “on” period at Madopar HBS therapy (► **Table 1**).

Case 4

A 50-year-old PD subject who had undergone STN-DBS surgery 7 years ago due to advanced-stage PD including motor complications and fluctuations applied to our polyclinic for routine control. The PD had emerged 13 years ago with symptoms of slowness on his left hand, and he had been suffering from severe FOG episodes and also moderate dyskinesia during the medication “on” period. After the DBS surgery with optimal adjustment of the STIM parameters, a 73% decrease in the MDS-UPDRS-3 score (from 62 points to 17 points) was achieved and the LED could be reduced by half. However, the benefit of levodopa/carbidopa/entacapone sustained 1 to 2 hours. The patient suffered from “off” periods for more than half of the daytime. The therapy was switched to Madopar HBS 100/25 mg (9 capsules) that provided a 25 to 50% reduction in the total off periods throughout the day.

Discussion

In this study, we present the beneficial effects of Madopar HBS in all four advanced-stage PD patients with STN-DBS therapy who had suffered from “SDRs” to levodopa despite taking low dosages of therapy. The data regarding the use of Madopar HBS therapy in PD patients is derived from ancient studies, and the results are not consistent to support the widespread use of Madopar HBS throughout the day in those patients with SDR and motor fluctuations.^{9–13} Up to our knowledge, this is the first study presenting the utility of controlled release levodopa therapy in PD subjects with STN-DBS. Although we enrolled a strictly small number of patients, we think that our results are important that need to be carefully discussed in the clinical settings and STN-DBS pathophysiology.

In an ancient randomized double-blind parallel-group study, the therapeutic responses were compared during 5 years in 65 PD subjects taking Madopar HBS and 69 subjects taking standard Madopar TB.⁸ In conclusion, they found that Madopar HBS thus proved to be as effective as standard Madopar TB in the long-term treatment of de novo parkinsonian patients, but the drug showed no advantage in postponing or reducing the long-term levodopa treatment problems.⁸ In the other study by Pezzoli et al including long-term follow-up of 18 patients,¹⁴ positive results on levodopa-induced psychiatric and dyskinesic disorders were demonstrated on Madopar HBS therapy. However, the authors noted a general trend of deterioration including akinesias due to a delayed response worsened after 1 year of treatment.¹⁴ MacMahon et al also presented the positive results of Madopar HBS on 37 PD subjects with dose-related fluctuations in motor performance in response to conventional levodopa preparations.¹³ Olanow et al investigated the efficiency of Sinemet CR in 45 levodopa naïve PD patients in a 12-week, open-label, multicenter study. In conclusion of the study, a statistically significant improvement compared with

baseline was observed for total Parkinson’s score, as well as motor sub-items.¹¹ They proposed Sinemet CR as a primary therapy for PD subjects that is well-tolerated and effective.¹¹ An interesting topic of discussion is the possible benefit of sustained-release levodopa therapy that may be beneficial to avoid the occurrence of dyskinesias and motor fluctuations.¹⁵ However, in general, we know that serious pharmacokinetic alterations resulting in delayed onset of clinical efficiency and unpredictable motor fluctuations including severe dyskinesias constitute the deleterious handicaps of the use of Madopar HBS throughout the daytime.¹⁴ Taken together, currently, the use of Madopar HBS is generally restricted for the nocturnal akinesia and early-morning symptoms in advanced-stage PD subjects.^{4,16}

Concerning the early stages of the disease, a single study compared the efficiency of Madopar HBS and standard Madopar TB therapy.⁸ They found Madopar HBS as effective as standard Madopar TB in the long-term treatment of de novo parkinsonian patients, but the drug showed no advantage in postponing or reducing the long-term levodopa treatment problems.⁸ Of note, the authors mainly investigated the prognostic effect of Madopar HBS therapy in the disease course. Considering that the motor fluctuations and levodopa-related side effects do not emerge in the early PD subjects, the symptomatic relief was not mainly focused on these early-stage patients requiring low LED. However, in the advancing phase of the disease, the duration of levodopa response shortens and motor fluctuations, and dyskinesias occur that all lead to crucial clinical problems. At this stage of the disease, patients suffer from sustained “off” periods and dyskinesia episodes albeit taking multiple levodopa dosages a day. The motor fluctuations and motor symptoms of PD do substantially respond to STN-surgery; however, the SDR to levodopa may persist in some of the patients undergoing STN-DBS.^{17,18}

Obeso et al¹⁹ defined the main features of the “SDR” as follows: (a) relatively abrupt onset; (b) large magnitude of motor response (i.e., difference between “off” and “on” motor scores); (c) relatively brief duration of motor improvement that may range from minutes (15–30 minutes) to hours (2–3 hours); and (d) aggravation of the motor score below the original “off” baseline state at the end of some (or all) treatment-related “on-off” cycles. As dopamine depletion increases with disease progression and the deleterious effects of intermittent levodopa stimulation become more prominent, the SDR becomes more overt.¹⁹ With the advancing phase of the disease, a predictable wearing-off pattern will turn into a complicated “on-off” pattern, in which the relationship between single levodopa doses and motor benefit is not readily apparent that may suggest the need for sustained levodopa preparations.

A crucial hypothesis is that large and multiple doses of levodopa lead to pharmacokinetic problems leading to complex serum levodopa level fluctuations that are associated with dyskinesia.¹⁹ Several factors impact on the progress of levodopa from the time of ingestion until it reaches the brain and is converted to dopamine.²⁰ These factors include the swallowing phase of the medication, absorption in the

stomach and intestine, peripheral conversion of levodopa to dopamine, tissues, transport across the blood–brain barrier, and the conversion of levodopa to dopamine in the striatum.²⁰ Among them, gastroparesis becomes more apparent at the advanced stage of PD, influencing substantially the pharmacokinetic parameters of levodopa.²¹ Besides, with the progression of the disease as well as the increase in the dose of levodopa, the alterations in the pharmacokinetics of levodopa also increase and unpredictable plasma levodopa peaks may occur leading to motor fluctuations including severe dyskinesia. These alterations may be more complicated during the use of Madopar HBS at high dosages in the advanced stage of the disease that may constitute the major limitation of its use throughout the day in the advanced stage PD subjects. The mechanisms of dyskinesia reduction in STN-DBS are rather associated with a reduction in dopaminergic medications following surgery that is an indirect inhibition.¹⁸ Such that, the DBS therapy has the potential of the sustained reduction in LED by 44% after 8 to 15 years of surgery.²² Taken together, we think that the reduction in the LED dose after STN-DBS surgery may be a crucial factor in the persuasive clinical responses to Madopar HBS in our patients with STN-DBS.

However, some authors also remarked that the reduction in dyskinesia following STN-DBS also occurs regardless of whether the levodopa dosage was reduced suggesting direct mechanisms associated with STN-DBS.¹⁷ Obeso et al suggested that the DBS interventions may lead to an immediate attenuation of the motor fluctuations and SDR that occurs without any adjustment in anti-parkinsonian medication that could itself induce pharmacologic changes and confuse the interpretation.¹⁹ Besides, they stated that stopping DBS provokes a return of the SDR to levodopa.¹⁹ They associated this primarily with the increased response magnitude and the modest but significant shortening in the duration of the motor improvement.¹⁹ The authors explained the effect of DBS on the SDR with a mechanism of a direct effect on basal ganglia output activity, rather than a modification in the presynaptic storage capacity or changes in dopamine striatal availability.¹⁹ The stimulation of the above STN area that is a complex localization between the dorsal STN border and the ventral thalamus is particularly emphasized to suppress dyskinesias via mechanisms of stimulation of pallidothalamic, pallidosubthalamic, or subthalamopallidal fibers that are densely distributed in this region.¹⁷ The direct effects of the STN-DBS in avoiding the occurrence of dyskinesias may also be a critical factor in our favorable responses to Madopar HBS in comparison to the ancient trials in patients on medical therapies. Remarkably, the main problem in our patient group was the SDR, whereas the dyskinesias were not the prominent symptomatology following STN-DBS.

In conclusion, our results support the use of Madopar HBS in PD patients undergoing STN-DBS suffering from SDR, particularly in the subgroup with milder dyskinesias. According to our hypothesis, the PD transforms into a distinct type of disease after surgery in which the levodopa requirement decreases substantially and the neural mechanisms in

the basal ganglia network also differ. However, despite STN-DBS therapy, SDR and motor fluctuations may continue to emerge even at low dosages of levodopa. In comparison to those patients without STN-DBS, the reduced LED in patients with STN-DBS may be a crucial point in our favorable results. The pharmacokinetic alterations in the use of Madopar HBS may reduce with low levodopa dosages, avoiding the variance in the plasma levodopa levels that contributes to the unpredictable motor fluctuations. Future study results of larger PD subjects with STN-DBS therapy are warranted to confirm our observations. The results of these studies may provide critical applications in clinical practice. Confirmation of our results may also contribute to our understanding of the pathophysiology of motor fluctuations and the action of DBS.

Ethical Approval

The consent form has been obtained from the patient and his spouse.

Authors' Contributions

HO conceptualized and designed the study. SC supervised the study. HO, SK, and SC helped in providing material. HO and SC helped in data collection and/or processing and analysis and/or interpretation. HO helped in literature search and manuscript writing. SC helped in critical review.

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Conflict of Interest

None declared.

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