Long-Duration Response to Levodopa in Patients With Advanced Parkinson Disease Treated With Subthalamic Deep Brain Stimulation

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Background: Long-duration response (LDR) to levodopa is supposed to decrease with Parkinson disease (PD) progression, but direct observation of this response in advanced PD has never been performed.

Objective: To study the LDR to levodopa in patients with advanced PD treated with subthalamic deep brain stimulation (DBS).

Design and Setting: We studied 30 consecutive patients with PD who underwent subthalamic DBS. One group had no antiparkinsonian treatment since surgery (no-levodopa group), whereas medical treatment had to be reinitiated in the other group (levodopa group).

Main Outcome Measure: Motor subscale score of the Unified Parkinson's Disease Rating Scale.

Results: Compared with preoperative assessment, evaluation 6 months postoperatively with DBS turned off for 3 hours found a worsening of the motor subscale score of the Unified Parkinson’s Disease Rating Scale in the no-levodopa group. This worsening being absent in the levodopa group, it probably reflected the loss of the LDR to levodopa in the no-levodopa group. When DBS was turned on, postoperative motor subscale scores of the Unified Parkinson’s Disease Rating Scale in both groups were similar to preoperative scores while receiving medication, suggesting that subthalamic DBS compensated for the short-duration response and LDR to levodopa.

Conclusions: Our results suggest that the LDR to levodopa remains significant even in advanced PD, and that subthalamic DBS compensates for the short-duration response and LDR to levodopa.

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LONG-DURATION RESPONSE (LDR) to levodopa is defined as a sustained motor improvement induced by long-term levodopa therapy that slowly builds up after treatment initiation and lasts many days after treatment discontinuation. The pharmacodynamic mechanisms underlying the LDR are still unclear. In contrast to the short-duration response (SDR), the LDR does not depend on levodopa plasmatic pharmacokinetics. According to current views, the total motor response to levodopa results from the combination of endogenous dopamine production and the SDR and LDR to exogenous levodopa. The proportions of the SDR and LDR can vary according to disease progression, with the LDR being more prominent in early stages, accounting for the stable response seen in the “honeymoon” period of treatment. The LDR can even mask the SDR, the magnitude of which is clearly reduced in treated patients compared with subjects after a 15-day washout. As the disease progresses, apparent SDR magnitude increases, fluctuations appear, and the LDR supposedly becomes less prominent.

Although many studies have looked at the LDR to levodopa in the first years of Parkinson disease (PD), current knowledge is scarce regarding what occurs in advanced PD, as prolonged drug holidays to study the waning of the LDR directly are currently proscribed. Very early observations found the LDR to remain significant after 9 years of disease progression, and more recent indirect estimates support such findings. However, it has also been suggested that the LDR becomes smaller with disease progression, whereas the SDR increases and leads to disabling fluctuations.

Although the SDR has been carefully studied in patients with advanced PD after subthalamic deep brain stimulation (STN-DBS), evaluation of the LDR to levodopa...
We prospectively studied 66 consecutive patients who underwent bilateral STN-DBS for advanced idiopathic PD (Table). We studied the changes in UPDRS motor subscale (UPDRSm) scores when antiparkinsonian medication treatment and stimulation were stopped in the no-levodopa and levodopa groups. Bars are mean ± SD.

Abbreviations: LDED, levodopa equivalent per day attributable only to levodopa treatment; LED, levodopa equivalent per day; off, without medication; on, with medication; UPDRSm, motor subscale of Unified Parkinson’s Disease Rating Scale.

*Data are expressed as mean (SD) unless otherwise indicated.
†Comparison between the levodopa group and the no-levodopa group.

Thirty-six patients gave informed consent to have STN-DBS turned off for 150 to 180 minutes, 6 months postoperatively (mean ± SD, 174 ± 49 postoperative days). In patients still receiving antiparkinsonian medication, levodopa treatment was stopped (hereafter referred to as the medication-off condition) similar to the practically off state.

We excluded 4 patients because they had their medication treatment reintroduced or withdrawn at a later stage or because compliance was not ascertained, and 2 patients because they only took dopamine agonists in the postoperative phase.

Baseline characteristics of the remaining 30 patients were similar to those of the initial 66 patients (Table).

In 11 patients, levodopa treatment was reintroduced within 4 weeks after the operation (levodopa group), and thereafter continuously administered until postoperative evaluation. In 19 patients, levodopa treatment was completely stopped at the time of surgery or within 4 weeks postoperatively (no-levodopa group). Baseline characteristics of the 2 subgroups showed a significantly higher medication-off UPDRSm score in the levodopa group and a trend toward a higher UPDRSm score when receiving medication (hereafter referred to as the medication-on state), but both groups were similar for levodopa equivalent per day, levodopa intake, age, and PD duration (Table and Figure 1).

In addition to levodopa, preoperative treatment in the no-levodopa group contained agonists in 17 patients, including pergolide mesylate in 9, cabergoline in 6, ropinirole hydrochloride in 1, and pramipexole in 1. In the levodopa group, 10 patients were receiving agonists, including pergolide in 6, pramipexole in 1, ropinirole in 1, bromocriptine mesylate in 1, apomorphine hydrochloride in 1, and cabergoline in 1. (One patient was taking 2 different agonists at the same time.)

We studied the changes in UPDRSm score between preoperative practically off and postoperative medication-off and stimulation-off states. We hypothesized that differences in UPDRSm score changes between the no-levodopa and levodopa groups would reflect the loss of the clinical effect of the LDR to levodopa. We expressed LDR magnitude in the following 2 ways: (1) as a percentage of the SDR, by averaging individual percentages (LDR expressed as a percentage of SDR); and (2) as a percentage of the total levodopa response, defined as the difference between postoperative stimulation-off and preoperative medication-on scores.

Results were compared using paired and unpaired t tests when appropriate (eg, for UPDRSm score comparison). For nonparametric statistics (eg, subscores analysis), we used the Wilcoxon signed rank and Mann-Whitney tests. The Bonferroni correction was applied when looking at UPDRSm subscores,
RESULTS

In the no-levodopa group, stimulation-off UPDRSm scores measured 6 months postoperatively showed a worsening of 16.52±14.64 points compared with preoperative medication-off values, the difference being highly statistically significant (58.26±11.44 vs 41.74±11.77 \(P<.001\)) (Figure 1). The same comparison in the levodopa group showed slight worsening that did not reach statistical significance (55.73±13.27 vs 50.73±10.51 \(P=.18\)). The worsening of medication-off UPDRSm scores (stimulation-off and medication-off when applicable) was significantly higher in the no-levodopa group compared with the levodopa group (16.53±14.64 vs 5.00±11.64 points \(P<.03\)). There was no significant worsening of medication-on UPDRSm scores (stimulation-on and medication-on when applicable) in the no-levodopa group (22.05±10.75 vs 21.16±9.46 \(P=.75\)) or in the levodopa group (30.41±13.60 vs 28.73±11.37 \(P=.73\)).

The SDR magnitude was similar in both groups (Table).

Amplitude of worsening of UPDRSm scores in the no-levodopa group (LDR) was negatively correlated with preoperative response to acute levodopa challenge (SDR) (\(r=–0.7\ \(P<.001\)) (Figure 2). The LDR was negatively correlated with the DBS effect (UPDRSm difference between postoperative stimulation-on and preoperative medication-off evaluations) (\(r=–0.82\ \(P<.001\)). There was no correlation between LDR and preoperative dyskinesia subscores (\(r=–0.12\ \(P=.62\)), disease duration (\(r=0.09\ \(P=.70\)), or preoperative levodopa intake (\(r=–0.24\ \(P=.33\)). Taking into account the nonsignificant worsening found in the levodopa group, the estimate of LDR magnitude was equivalent to 79.75% (SE. 28.00%) of the SDR. Expressed as a percentage of the total levodopa effect, it reached 37.65%.

Looking at specific subscales in the no-levodopa group, LDR affected mainly bradykinesia (32.32±4.97 vs 21.32±6.59 \(P<.001\); difference, 11.00±6.91) and rigidity (11.53±3.95 vs 8.16±2.11 \(P<.01\); difference, 3.37±3.57), but not tremor (7.63±5.08 vs 6.47±5.14 \(P>.5\); difference, 1.16±3.56) and axial signs (6.79±3.87 vs 5.79±2.97 \(P>.5\); difference, 1.00±3.87).

When looking at baseline medication-off UPDRSm subscores, the difference between the levodopa and no-levodopa groups was significant for axial signs (9.91±2.98 vs 5.79±2.97 \(P=.05\)), but not for bradykinesia (26.45±5.52 vs 21.32±6.59 \(P>.5\)), tremor (4.82±3.57 vs 6.47±5.14 \(P>.5\)), or rigidity (9.55±2.38 vs 8.16±2.11 \(P>.5\)).

In patients in whom levodopa treatment was discontinued at the time of operation, we found a significant worsening in medication-off and stimulation-off UPDRSm scores 6 months after surgery, compared with preoperative values. Because such a difference was not observed in the levodopa group, we propose this worsening to reflect the loss of the LDR to levodopa. Possible confounders include disease progression and direct deleterious effect of intervention. The latter is not expected to lead to an intergroup difference, but disease progression might, if a neuroprotective effect of levodopa restricted to patients still receiving this treatment is at work. However, the 5-point worsening of UPDRSm scores for 6 months in the levodopa group is not smaller than expected in advanced PD, and the 11-point intergroup difference clearly exceeds the difference reported between levodopa- and placebo-treated patients after a 2-week washout in the Earlier vs Later Levodopa in Parkinson’s Disease study. All of these points favor the loss of the symptomatic effect (LDR) by our prolonged washout period, rather than a suddenly accelerating disease.

Because there was a significant difference in preoperative medication-off UPDRSm scores between the levodopa and no-levodopa groups, a selection bias might have been at work with the 2 groups differing in their pharmacological response or biological characteristics. However, preoperative response to acute levodopa challenge was similar in both groups, and the difference in preoperative UPDRSm scores was mostly due to the axial subscale, which is known to be partially levodopa resistant and marginally affected by the LDR to levodopa. In addition, subjects not requiring levodopa had worse scores at 6 months, whereas they had better scores at baseline, suggesting that they lost LDR rather than responded differently to STN-DBS or to medication.

We found mean LDR amplitude to represent as much as 80% of preoperative SDR, or nearly 40% of the total levodopa response. This is only an estimate of LDR amplitude, because SDR was assessed 1 hour after levodopa intake, which may not always correspond to its maximal effect, and may lead to an underestimation of SDR. Also, postoperative UPDRSm scores were assessed 3 hours after switching off stimulation. The STN-DBS effect may last up to 24 hours and has been reported to reduce the magnitude of the SDR to levodopa in ad-
advanced PD, reflecting some long-term plastic changes in the basal ganglia.\textsuperscript{10} Even if we have shown that 3-hour STN-DBS withdrawal allows an adequate washout of its effects, particularly on tremor, bradykinesia, and rigidity,\textsuperscript{15} we cannot rule out that we missed part of its prolonged effect, leading to an underestimation of LDR to levodopa. However, our estimate of LDR amplitude corresponds to those estimates reported in earlier phases of the disease, from one third of the total levodopa response (disability progression after drug withdrawal),\textsuperscript{8} to more than 100% of the SDR by using tapping speed recordings.\textsuperscript{19,21}

Our results suggest that the LDR persists and is still of significant magnitude after a mean disease duration of more than 15 years in STN-DBS-treated patients with PD who do not require medication after surgery. This extends previous observations with no reduction in LDR magnitude during a 4-year period\textsuperscript{9} and with similar LDR magnitude after 8 years of PD progression.\textsuperscript{1} These similarities with previous LDR studies suggest that our observation might reflect persistence of LDR in advanced PD, although we acknowledge that our sample was small, our population was selected, and our observation was limited to 6 months, with no data on the kinetics over time. Confirmation would need repeated and prolonged medication-off evaluations that are not acceptable in advanced PD.

The LDR to levodopa predominated on bradykinesia and rigidity and seemed not to affect the 2 other major signs of PD. This different magnitude of effects on parkinsonian signs is the same for the LDR and SDR to levodopa, suggesting a common pathway for both components of levodopa action, different from those affecting axial signs and tremor.\textsuperscript{22}

We found no significant change in medication-on and stimulation-on UPDRSm scores between the preoperative and postoperative states, indicating that DBS fully compensates for the SDR and LDR to levodopa. This finding suggests that a therapeutic intervention at the level of the indirect pathway through high-frequency stimulation of the STN might be enough to compensate for SDR and LDR to levodopa.

Our results showed a negative correlation between LDR magnitude and preoperative SDR, which was previously reported.\textsuperscript{8} Given that medication-on scores did not change, this implies that patients with a larger LDR tend to have a smaller SDR. We also found a negative correlation between the LDR and DBS effect in the no-levodopa group, which is owing to the way the DBS effect is defined in this measurement, ie, comparing preoperative medication-off and postoperative medication-off/stimulation-on scores.

In patients still requiring levodopa, the LDR persisted, although mean postoperative levodopa intake was 418 mg/d, less than 50% of the preoperative values, suggesting that even low doses are sufficient to maintain LDR in advanced disease. This is in keeping with previous work in which the levodopa dose was found to have little effect on LDR magnitude or duration, once a minimum dosage of about 250 mg/d was reached.\textsuperscript{10,21,23} On the other hand, recent data in the early stages of the disease showed the LDR to be dose dependent up to 600 mg/d.\textsuperscript{19} Our findings suggest that, if such a dose effect remains significant as disease progresses,\textsuperscript{8} it is minimal or reaches a plateau at about 400 mg/d.

Although the exact mechanisms underlying the LDR to levodopa at a pharmacodynamic level are yet to be unveiled, its persistence in advanced and fluctuating PD does not support an entirely presynaptic “storage hypothesis.”\textsuperscript{2,20} Also, the LDR is not restricted to levodopa, but can occur with dopamine agonists\textsuperscript{24} and in dopa-responsive dystonia, in which there is no presynaptic storage defect.\textsuperscript{25} These data, along with our findings, strongly support a postsynaptic mechanism in the form of long-term changes at a receptor level or of cellular metabolic or gene expression changes.

Our study shows that the LDR to levodopa remains significant in patients with advanced PD who undergo STN-DBS and suggests that this may be the case in advanced PD. In our patients, stimulation fully compensated for the SDR and LDR.

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