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

THESE

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Résumé

La levodopa (LD) est le traitement antiparkinsonien le plus efficace et le plus répandu. Son effet est composé d'une réponse de courte (quelques heures) et de longue durée (jours à semaines). La persistance de cette dernière dans les phases avancées de la maladie de Parkinson est controversée, et sa mesure directe n'a jamais été faite en raison des risques liés à un sevrage complet de LD. La stimulation du noyau sous-thalamique est un nouveau traitement neurochirurgical de la maladie de Parkinson, indiqué dans les formes avancées, qui permet l'arrêt complet du traitement médicamenteux chez certains patients.

Nous avons étudié 30 patients qui ont bénéficié d'un telle stimulation, et les avons évalués avant l'intervention sans médicaments, et à 6 mois postopératoires, sans médicaments et sans stimulation. Chez 19 patients, la médication a pu être complètement arrêtée, alors qu'elle a du être réintroduite chez les 11 patients restants.

Au cours des 6 mois qui ont suivi l'intervention, le parkinsonisme s'est aggravé de façon significative dans le groupe sans LD, et non dans le groupe avec LD. Cette différence d'évolution s'explique par la perte de l'effet à long terme de la LD dans le groupe chez qui ce médicament a pu être arrêté. En comparant cette aggravation à la magnitude de l'effet à court terme, la réponse de longue durée correspond environ à 80 pourcent de la réponse de courte durée, et elle lui est inversement corrélée. Parmi les signes cardinaux de la maladie, la réponse de longue durée affecte surtout la bradycinésie et la rigidité, mais pas le tremblement ni la composante axiale. La comparaison du parkinsonisme avec traitement (stimulation et LD si applicable) ne montre aucune différence d'évolution entre les 2 groupes, suggérant que la stimulation compense tant la réponse de courte que de longue durée.

Notre travail montre que la réponse de longue durée à la LD demeure significative chez les patients parkinsoniens après plus de 15 ans d'évolution, et suggère que la stimulation du noyau sous-thalamique compense les réponses de courte et de longue durée.

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Long Duration Response to Levodopa in Advanced Parkinson's Disease Patients Treated With STN-DBS

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Abstract

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

Objective: To study the long duration response to levodopa in advanced PD patients treated with subthalamic deep-brain stimulation.

Design and settings: We studied 30 consecutive PD patients who underwent subthalamic deep-brain stimulation. One group had no antiparkinsonian treatment since surgery (no-levodopa), while medical treatment had to be reinitiated in the other group (levodopa).

Main outcome measures: motor Unified Parkinson's Disease Rating Scale (UPDRS).

Results: In comparison with preoperative assessment, evaluation six months postoperatively with stimulation turned off for three hours found a worsening of the motor part of UPDRS in the no-levodopa group. This worsening being absent in the levodopa group, it most probably reflected the loss of the long duration response to levodopa in the no-levodopa group. Stimulation turned on, postoperative motor UPDRS in both groups were similar to preoperative on medication scores, suggesting that subthalamic deep-brain stimulation compensated for both the short and long duration responses to levodopa.

Conclusions: Our results suggest that the long duration response to levodopa remains significant even in advanced PD, and that subthalamic deep-brain stimulation compensates for both the short and the long duration resposes to levodopa.

Introduction

Long duration response (LDR) to levodopa is defined as a sustained motor improvement induced by chronic levodopa therapy, that slowly builds up after levodopa initiation and lasts many days after treatment discontinuation.(1) The pharmacodynamic mechanisms underlying LDR are still unclear. In contrast to short duration response (SDR), LDR does not depend on levodopa plasmatic pharmacokinetics. According to current views, total motor response to levodopa results from the combination of endogenous dopamine production, and both SDR and LDR to exogenous levodopa.(2) The proportion of SDR and LDR can vary according to disease progression, LDR being more prominent in early stages, accounting for the stable response seen in the "honeymoon" period of treatment.(3;4) LDR can even mask SDR, the magnitude of which is clearly reduced in treated patients compared to subjects after a 15-day washout.(5) As the disease progresses, apparent SDR magnitude increases, fluctuations appear and LDR supposedly becomes less prominent.

While many studies have looked at LDR to levodopa in the first years of PD, current knowledge is scarce regarding what occurs in advanced PD, as prolonged drug holidays required to directly study LDR waning are currently proscribed. Very early observations found LDR to remain significant after 9 years of disease progression,(6) and more recent indirect estimates support such findings.(7;8) However, it has also been suggested that LDR becomes smaller with disease progression, while SDR increases and leads to disabling fluctuations.(2;9)

While SDR has been carefully studied in advanced PD patients after subthalamic deep-brain stimulation (STN-DBS),(10) evaluation of LDR to levodopa in such patients, to our knowledge, has never been performed yet.

STN-DBS allows to decrease the need for antiparkinsonian medication, which may be completely withdrawn in some patients,(11;12) representing a unique opportunity to study LDR in advanced PD.

Patients and Method

We prospectively studied 66 consecutive patients who underwent bilateral STN-DBS for advanced idiopathic PD (see table).(13) Levodopa equivalent per day (LED) was calculated as previously published.(11) Unified PD rating scale (UPDRS) was performed preoperatively in a "practically off" state.(14) Antiparkinsonian medication was discontinued for 12 hours before evaluation, except for most dopamine agonists (24 hours discontinuation), catechol-O-methyltransferase inhibitors and cabergoline (72 hours discontinuation). Domperidone was prescribed during the 3 days preceding evaluation, and on test day. Response to an acute challenge was assessed by the motor part of UPDRS (UPDRSm) performed 1 hour after 250 mg levodopa / 25 mg carbidopa (Sinemet®) intake. We used the magnitude of this response as an estimate of SDR magnitude.

Thirty-six patients gave informed consent to have STN-DBS turned off for 150 to 180 minutes,(15) 6 months postoperatively (mean 174±49 days). In patients still on antiparkinsonian medication, this was performed in a "med off" condition similar to the "practically off" state.

Six patients were excluded: 4 because they had their medication reintroduced or withdrawn at later stage (see below), or because compliance was not ascertained, and 2 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 group (see table).

In 11 patients, levodopa was reintroduced within 4 weeks after the operation (levodopa group), and thereafter continuously administered until postoperative evaluation. In 19

patients, levodopa was completely stopped either at the time of surgery or within 4 weeks postoperatively (no-levodopa group). Baseline characteristics of the 2 subgroups showed a significantly higher "med off" UPDRSm in the levodopa group, a trend toward a higher "med on" UPDRSm, but both subgroups were similar for LED, levodopa intake, age and PD duration (see table and figure 1).

In addition to levodopa, preoperative treatment in the no-levodopa group contained agonists in 17 patients, 9 being on pergolide, 6 on cabergoline, 1 on ropinirole, and 1 on pramipexole. In the levodopa group, 10 patients were also on agonists, 6 on pergolide, 1 on pramipexole, 1 on ropinirole, 1 on bromocriptine, 1 on apomorphine, and 1 on cabergoline.

We studied the changes in UPDRSm between preoperative "practically off" and postoperative "treatment off" states. We hypothesized that differences in UPDRSm changes between the no-levodopa group and the levodopa group would reflect the loss of the clinical effect of LDR to levodopa. We expressed LDR magnitude in 2 ways. First as a percentage of SDR, by averaging individual percentages (LDR expressed as a percentage of SDR). Second as a percentage of total levodopa response, defined as the difference between postoperative "stim off" and preoperative "med on" scores.

Results were compared using paired and unpaired Student's *t*-test when appropriate (eg. for UPDRSm comparison). For non-parametric statistics (eg. subscores analysis), the Wilcoxon signed ranks and Mann-Whitney tests were used. The Bonferroni correction was applied when looking at UPDRSm subscores, for which corrected p values are given.

Results

In the no-levodopa group, "stim off" UPDRSm performed 6 months postoperatively showed a 16.52±14.64 points worsening compared to preoperative "med off" values, the difference being highly statistically significant (58.26±11.44 versus 41.74±11.77, $p<0.001$) (see figure 1). The same comparison in the levodopa group showed slight worsening which did not reach

statistical significance (55.73±13.27 versus 50.73±10.51, p=0.18). The worsening of "treatment off" UPDRSm ("stim off" and "med off" when applicable) was significantly higher in the no-levodopa group compared to the levodopa group (16.53±14.64 versus 5.00±11.64 points, p<0.03). There was no significant worsening of "treatment on" UPDRSm ("stim on" and "med on" when applicable) either in the no-levodopa (22.05±10.75 versus 21.16±9.46, p=0.75) or in the levodopa group (30.41±13.60 versus 28.73±11.37, p=0.73). SDR magnitude was similar in both groups (see table).

Amplitude of UPDRSm worsening in the no-levodopa group (LDR) was negatively correlated to preoperative response to acute levodopa challenge (SDR) (r=-0.7; p<0.001) (see figure 2). LDR was negatively correlated to DBS effect (UPDRSm difference between postoperative "stim on" and preoperative "med off" evaluations) (r=-0.82, p<0.0001). There was no correlation between LDR and preoperative dyskinesia subscores (r=-0.12, p=0.62), disease duration (r=0.09; p=0.7) or preoperative levodopa intake (r=-0.24; p=0.33). Taking into account the non significant worsening found in the levodopa group, the estimate of LDR magnitude was equivalent to 79.75% (standard error: 28%) of SDR. Expressed as a percentage of total levodopa effect, it reached 37.65%.

Looking at specific subscales in the no-levodopa group, LDR affected mainly bradykinesia (32.32±4.97 versus 21.32±6.59, p<0.0001; difference of 11.00±6.91) and rigidity (11.53±3.95 versus 8.16±2.11, p=0.013; difference of 3.37±4.57), but not tremor (7.63±5.08 versus 6.47±5.14, p>0.5; difference of 1.16±5.56) and axial signs (6.79±3.87 versus 5.79±2.97, p>0.5; difference of 1.00±3.87).

When looking at baseline "med off" UPDRSm subscales, the difference between levodopa and no-levodopa groups was significant for axial signs (9.91±2.98 versus 5.79±2.97, p=0.0049), but not for bradykinesia (26.45±5.52 versus 21.32±6.59, p>0.5), tremor (4.82±3.57 versus 6.47±5.14, p>0.5) and rigidity (9.55±2.38 versus 8.16±2.11, p>0.5).

Comment

In patients in whom levodopa was discontinued at the time of operation, we found a significant worsening in "treatment off" UPDRSm six months after surgery, compared to preoperative values. Since such a difference was not observed in the levodopa group, we propose this worsening to reflect the loss of LDR to levodopa. Possible confounders include disease progression and direct deleterious effect of intervention. The latter is not expected to lead to an inter-group difference, but disease progression might, if a neuroprotective effect of levodopa restricted to patients still on this treatment is at work.(16) However, the five points worsening of UPDRSm over six months in the levodopa group is not smaller than expected in advanced PD,(17;18) and the eleven points inter-group difference clearly exceeds the difference reported between levodopa and placebo treated patients after two weeks washout in the ELLDOPA study.(16) All these points favor the loss of the symptomatic effect (LDR) by our prolonged washout period, rather than a suddenly accelerating disease.

Since there was a significant difference in preoperative "med off" UPDRSm between levodopa and no-levodopa groups, a selection bias might have been at work with the two groups differing in their pharmacological response or biological characteristics. However, preoperative response to acute levodopa challenge was similar in the two groups, and the difference in preoperative UPDRSm was mostly due to the axial subscale, which is known to be partially LD-resistant and to be marginally affected by the LDR to levodopa. In addition subjects not requiring levodopa ended up with worse scores at six months, whereas they had better ones 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 total LD response. This is only an estimate of LDR amplitude, since SDR was assessed one hour after levodopa intake, which may not always correspond to its maximal

effect, and may lead to an underestimation of SDR. Also, "treatment off" UPDRSm was assessed 3 hours after switching off stimulation.(15) STN-DBS effect may last up to 24 hours,(15;19) and has been reported to reduce the magnitude of SDR to levodopa in advanced PD, reflecting some long-term plastic changes in the basal ganglia.(10). Even if we have shown that 3 hours STN-DBS withdrawal allows an adequate washout of its effects, particularly on tremor, bradykinesia and rigidity,(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 reported in earlier phases of the disease: between a third of total levodopa response (disability progression following drug withdrawal),(6) and more than hundred percent of SDR by using tapping speed recordings.(20;21)

Our results suggest that LDR persists and is still of significant magnitude after a mean disease duration of more than fifteen years in STN-DBS treated PD patients who do not require medication after surgery. This extends previous observations with no reduction in LDR magnitude over a four-year period,(8) and with similar LDR magnitude after eight years of PD progression.(5). 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 selected and our observation limited to 6 months, with no data on the kinetics over time. Confirmation would need repeated and prolonged "treatment off" evaluations that are not acceptable in advanced PD.

LDR to levodopa predominated on bradykinesia and rigidity and seemed not to affect the two other major signs of PD. This different magnitude of effects over parkinsonian signs is the same for LDR than for SDR to levodopa, suggesting a common pathway for both components of levodopa action, different from those affecting axial signs and tremor.(22)

We found no significant change in "treatment on" UPDRSm between preoperative and postoperative states, indicating that DBS fully compensates for both SDR and LDR to levodopa. This 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.(8) Given that "treatment 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 LDR and DBS effect in the no-levodopa group, which is due to the way DBS effect is defined in this measurement – comparing preoperative "med off" and postoperative "med off"/"stim on" scores.

In patients still requiring levodopa, LDR persisted although mean postoperative levodopa intake was 418 mg per day, 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 levodopa dose was found to have little impact on LDR magnitude or duration, once a minimum of around 250 mg per day was reached.(20;21;23) On the other hand, recent data in early disease showed LDR to be dose dependent up to 600 mg per day.(16) Our findings suggest that, if such a dose effect remains significant as disease progresses,(9) it is either minimal, or has a ceiling around 400 mg per day.

Although the exact mechanisms underlying 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".(2;20) Also, LDR is not restricted to levodopa, but can occur with dopamine agonists,(24) and in dopa-responsive dystonia, in which there is no presynaptic storage defect.(25) These data along with our findings strongly support a

postsynaptic mechanism, in the form of long term plastic changes at a receptor level, or of cellular metabolic or gene expression changes.

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

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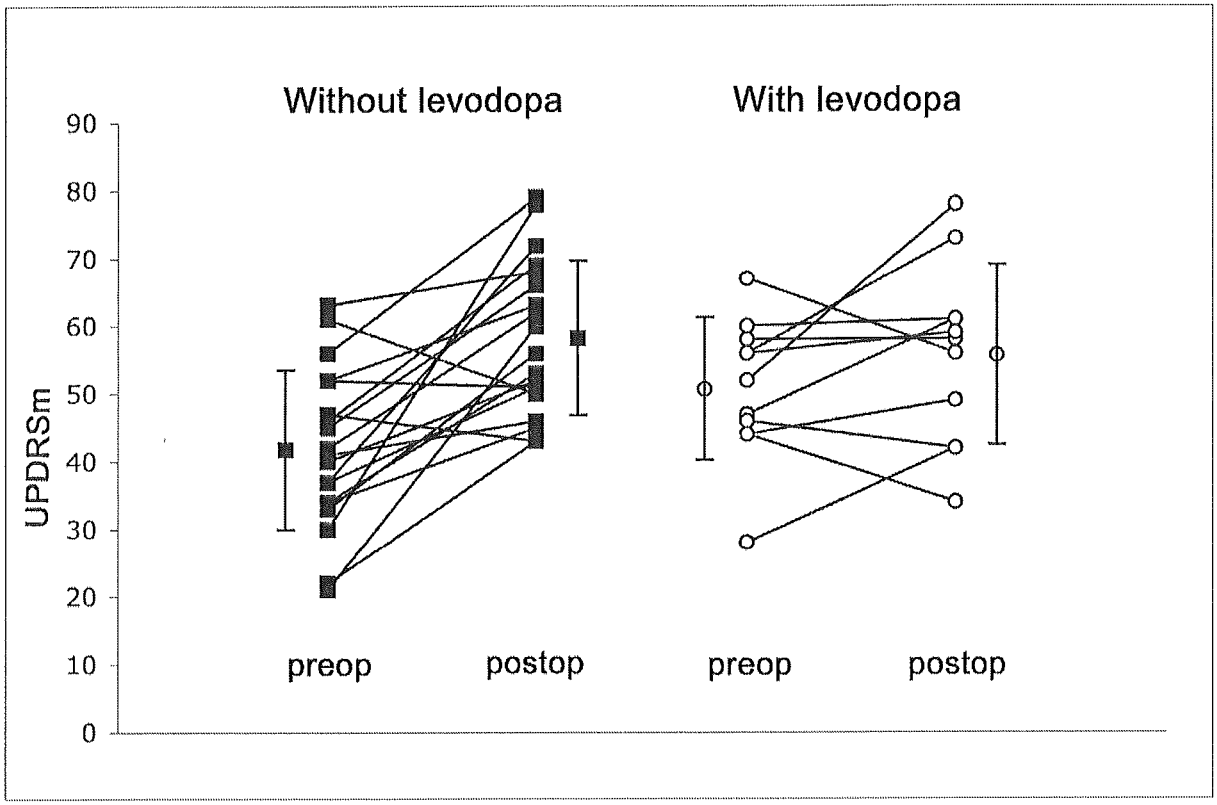
Table. Baseline characteristics

	Whole cohort	Studied	LD	no-LD	*p*
N (males/females)	66 (40/26)	30 (20/10)	11 (6/5)	19 (14/5)	n.s.
Disease duration (SD), y	15.79 (4.81)	17.03 (3.95)	17.87 (3.27)	16.55 (4.31)	n.s.
Age at operation (SD), y	65.14 (7.75)	65.32 (7.16)	67.11 (5.49)	64.28 (7.92)	n.s.
UPDRSm on (SD)	28.48 (10.56)	23.93 (10.67)	28.73 (11.37)	21.16 (9.46)	n.s.
UPDRSm off (SD)	46.45 (14.12)	45.03 (11.98)	50.73 (10.51)	41.74 (11.77)	**0.041**.
Acute LD challenge (SD)	21.97 (10.26)	21.10 (7.85)	22.00 (9.59)	20.58 (6.94)	n.s.
LED (SD), mg	1138 (507)	1261 (556)	1187 (656)	1304 (503)	n.s.
LDED (SD), mg	842 (428)	936 (469)	837 (503)	993 (452)	n.s.

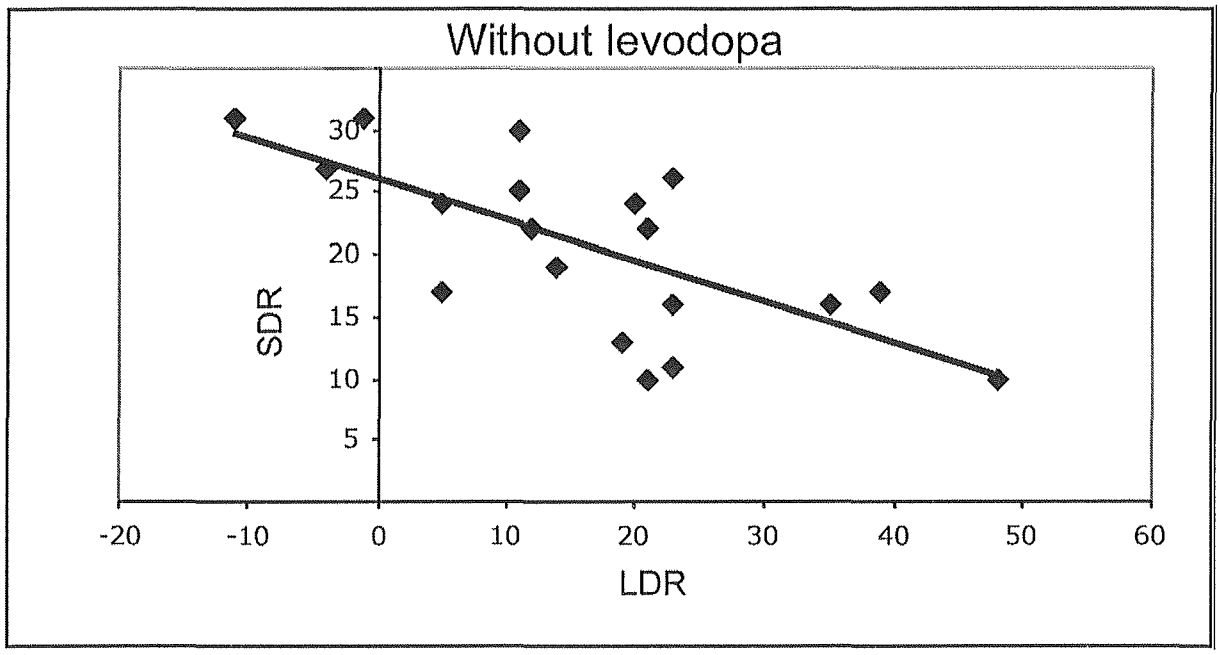
Baseline characteristics of the different groups of patients. LD = levodopa. LDED = LD equivalent per day attributable only to LD. LED = LD equivalent per day.

Figure 1:



Comparison of "treatment off" UPDRSm changes in individual patients between preoperative and postoperative states, in no-LD (black squares ■) and LD groups (open circles ○), with average ± SD.

Figure 2:



LDR = long duration response, SDR = short duration response.