ORIGINAL ARTICLE

Less Pulsatile Levodopa Therapy (6 Doses Daily) Is Associated with a Reduced Incidence of Dyskinesia

Mark M. Lin, Robert Laureno

Department of Neurology, Medstar Washington Hospital Center, Medstar Georgetown University Hospital and Georgetown University School of Medicine, Washington, DC, USA

ABSTRACT

Objective To evaluate whether less pulsatile levodopa therapy (LPT) can reduce the development of levodopa-induced dyskinesia (LID).

Methods This is a retrospective cohort study of patients with Parkinson's disease at the movement disorders clinic of Medstar Washington Hospital Center. The study was not blinded or randomized. Patients were seen between August 2002 and August 2018. During these years, we treated patients with less pulsatile (6 doses daily) levodopa treatment to reduce LID. Occurrence of LID was recorded.

Results Ninety-five patients with Parkinson's disease taking levodopa were divided into two groups: 1) patients who were initially managed on LPT or who switched from traditional therapy (TT) (n = 61) (mean disease duration: 7.7 ± 4.8 years, mean levodopa duration: 5.6 ± 4.5 years and mean observation time: 4.3 ± 3.4 years), and 2) patients on TT throughout the observation period or until they developed dyskinesia (n = 34) (mean disease duration: 8.3 ± 3.8 years, mean levodopa duration: 6.2 ± 4.2 years and mean observation time: 4.1 ± 3.4 years). Three of the 61 LPT patients developed dyskinesia during the observation period. One of the patients developed dyskinesia after being switched to pulsatile doses by another doctor. In the other two, dyskinesia was minimal. In contrast to this 4.9% cumulative incidence, dyskinesia occurred in 50% (17/34) of TT patients, an incidence similar to that in published data (p < 0.001).

Conclusion Less pulsatile levodopa with 6 daily doses was associated with a low incidence of LID. Further study of this method of treatment is warranted.

Key Words Parkinson disease; levodopa; less pulsatile levodopa therapy; continuous dopaminergic stimulation; levodopa-induced dyskinesia.

Levodopa has been the standard treatment for Parkinson's disease for over 40 years; however, it unfortunately causes dyskinesia. For patients with Parkinson's disease on chronic levodopa therapy, the incidence of dyskinesia ranges from 30% to 80%.[1,2] After 4−5 years of exposure, the incidence of dyskinesia was 33% to 45% in clinical trials.[3,4] The risk factors for dyskinesia include higher doses, longer exposure, an advanced stage of Parkinson's disease and pulsatile treatment.[2-6] In one study, the

disease duration was believed to be more important than the levodopa treatment time in the development of dyskinesia.[7] Of these variables, pulsatile dopaminergic stimulation may be a prime cause of dyskinesia.[8-10]

Pulsatile stimulation occurs because levodopa has a short half-life and the medication is typically administered only 2−4 times a day. Pulsatile stimulation also occurs when short acting dopamine agonists are given infrequently.[10-12] In MPTP (1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine) parkinsonism, dosing of levodopa once or twice a day quickly induced dyskinesia, where less dyskinesia was observed with more frequent dosing.[13,14] In advanced Parkinson's disease, less pulsatile treatment with long acting dopamine agonists, continuous IV, or duodenal levodopa infusion has been successful in decreasing overt dyskinesia.[4,15-19]

The proposal that less pulsatile treatment may reduce the occurrence of dyskinesia has not been proven because of a lack of a long acting oral preparation of levodopa.[8,9,15,19-24] Pharmacokinetic data suggest that attaining a steady levodopa level in humans would require levodopa to be given at 2.5−3.0 hour intervals.[20] To date, there has been no prospective trial or case series of patients so treated. In an attempt to reduce levodopa-induced dyskinesia (LID), we prescribed frequent (every 3 hours) doses of levodopa.

MATERIALS & METHODS

Study design

This is a retrospective cohort study of patients with Parkinson's disease treated at the movement disorders clinic of Medstar Washington Hospital Center (MWHC). This study was approved by the Medstar Institutional Review Board (IRB no. 2017-068).

Subjects

Digitalized medical charts were searched for patients with Parkinson's disease seen between August 2002 and August 2018. During this period, all patients with Parkinson's disease for whom levodopa was to be prescribed, were given information about the short half-life of levodopa and the risk of dyskinesia. They were given the option of taking levodopa 6 times per day (Q3 hours) as a form of relatively nonpulsatile dosing.[11,20] To

further reduce the fluctuation of levodopa in blood levels, entacapone [a catechol-O-methyltransferase (COMT) inhibitor] was also prescribed to most of the patients (Table 1). Up-titration from 3 times per day to 6 times per day took place for one week to a few months. The search revealed 135 patients with Parkinson's disease. Excluded from analysis were thirty-nine patients who either attended our clinic for less than 6 months or who never took levodopa. Also excluded was one patient whose final diagnosis was multisystem atrophy type C rather than Parkinson's disease. For analysis, we divided the remaining ninety-five patients with Parkinson's disease into two groups. Group 1: Less pulsatile levodopa therapy (LPT) comprised patients who took 6 daily doses for the initial therapy with levodopa ($n = 31$), and dyskinesia-free patients who were switched to LPT at MWHC after treatment with traditional therapy (TT) elsewhere ($n = 30$). Group 2: TT comprised patients who received only TT (the patients in this group took levodopa 3−4 times per day, $n = 34$) before the onset of dyskinesia. The duration of levodopa treatment was defined as the levodopa exposure time before the onset of dyskinesia or the levodopa exposure time prior to the patients' most recent visit. Levodopa equivalent doses at the last visit were calculated using conversion factors.[25]

Statistical analysis

Included as dyskinesia were any involuntary movements (consistent with dyskinesia) reported by family or medical professionals or observed in our clinic. The time of onset of dyskinesia was recorded. The statistical analyses were two-tailed with an alpha level of 0.05. Due to unequal variances, Welch's t-test and chi-squared test were used as the primary statistical tests. The total numbers of both groups in Table 2 were used for statistical consideration. Due to the small sample size, subgroup statistical analyses in Table 2 should be used with caution.

Table 1. Baseline characteristics of patients with Parkinson's disease

Characteristics	Total (n = 95)	LPT (n = 61)	TT (n = 34)	p value
Male/female	46/49	32/29	14/20	0.29
Age, first visit*	69.6 ± 10.1	69.0 ± 7.9	70.7 ± 13.2	0.50
Age, last visit*	73.8 ± 9.9	73.2 ± 7.6	74.8 ± 13.2	0.52
Hoehn & Yahr stage, first visit*	2.64 ± 0.94	2.52 ± 0.87	2.85 ± 1.03	0.11
Weight, last visit (kg)*	72.1 ± 18.7	72.1 ± 19.3	72.2 ± 17.8	0.98
Levodopa equivalent dose, last visit (mg)*	811 ± 330	847 ± 340	747 ± 307	0.15
Levodopa equivalent dose by weight (mg/kg)*	11.8 ± 5.2	12.5 ± 5.6	10.6 ± 4.0	0.06
Mean observation time (years)*	4.3 ± 3.4	4.3 ± 3.4	4.1 ± 3.4	0.75
COMT inhibitor, last visit	66/95	43/61	23/34	0.77
Dopamine agonist, last visit	21/95	13/61	8/34	0.80
MAO-B inhibitor, last visit	3/95	1/61	2/34	0.26
Amantadine, last visit	2/95	0/61	2/34	0.06

Welch's t-test and chi-squared test were used for statistical analysis. *Data are presented as mean ± SD. Levodopa dose is the daily dose in milligrams. LPT: less pulsatile levodopa therapy, TT: traditional levodopa therapy, COMT: catechol-O-methyltransferase, MAO-B: monoamine oxidase B.

Table 2. Disease duration and levodopa treatment duration prior to onset of dyskinesia or last visit

Patients with dyskinesia	Total (n = 95)	LPT (n = 61)	TT (n = 34)	p
Disease duration at the onset of dyskinesia or last visit				
Total dyskinesia	20/95	3/61 (4.9%)	17/34 (50%)	< 0.001
Disease duration < 3 years	1/11	0/10	1/1	< 0.001
Disease duration 3–5 years	3/14	0/8	3/6	0.024
Disease duration 5–10 years	7/45	0/29	7/16	< 0.001
Disease duration > 10 years	9/25	3/14	6/11	0.087
Disease duration, (mean ± SD, years)	7.9 ± 4.5	7.7 ± 4.8	8.3 ± 3.8	0.50
Levodopa treatment duration at the onset of dyskinesia or last visit				
Total dyskinesia	20/95	3/61 (4.9%)	17/34 (50%)	< 0.001
Levodopa duration < 3 years	3/28	0/21	3/7	0.001
Levodopa duration 3–5 years	4/22	0/14	4/8	0.003
Levodopa duration 5–10 years	7/29	1/17	6/12	0.006
Levodopa duration > 10 years	6/16	2/9	4/7	0.152
Levodopa duration, (mean ± SD, years)	5.8 ± 4.3	5.6 ± 4.5	6.2 ± 4.2	0.51

Chi-squared test and Welch's *t*-test were used for statistical analysis.

RESULTS

A total of ninety-five patients, who were followed for 6 months to 15 years, were divided into two groups: group LPT (*n* = 61) and group TT (*n* = 34). Baseline characteristics of the patients in these 2 groups are summarized in Table 1. The mean observation time was 4.3 ± 3.4 years for the LPT group and 4.1 ± 3.4 years for the TT group (Table 1). The mean disease duration was 7.7 ± 4.8 years for the LPT group and 8.3 ± 3.8 years for the TT group. The mean number of years taking levodopa was 5.6 ± 4.5 years for the LPT group and 6.2 ± 4.2 years for the TT group (Table 2). In addition to levodopa, 70% of patients in the LPT group and 68% of patients in the TT group also took entacapone. There were more women and a lower levodopa equivalent dose in the TT group than in the LPT group. Amantadine was only used in the TT group. All the other characteristics were similar in the two groups (Table 1). None of the differences in baseline characteristics between these two groups were significant (Table 1 and 2).

The incidence of dyskinesia in the TT group was 50% (Table 2). The incidence of dyskinesia in this group is comparable to what was reported in two major long term clinical trials.[3,4] Dyskinesia developed after levodopa treatment in as quickly as 6 months. The lowest daily dose of levodopa resulting in dyskinesia was 250 mg. The longest latency to the onset of LID was over 15 years (Table 2).

As shown in Table 2, we observed 3 (4.9%) of 61 patients in the LPT group as having developed dyskinesia during levodopa treatment. One of these three patients complied with LPT. After 6 years of levodopa treatment, she was found to have mild dyskinesia in the left foot during a clinic visit. We then learned that 7 months earlier, the nursing home doctor had changed the pa-

tient's prescription of 100 mg levodopa 6 times per day to 200 mg 3 times per day without neurological consultation. Thus, this patient's dyskinesia developed during traditional pulsatile therapy. Five months after we reinstituted less pulsatile treatment, her mild dyskinesia ceased. The second patient was reported by the patient's family to have intermittent facial dyskinesia after more than 10 years of levodopa treatment. His dyskinesia, which was never observed by the doctor on many clinic visits, resolved after a slight decrease in levodopa dose. All three of these patients had a disease duration of 14−15 years and had received a few years of TT before switching to LPT. No dyskinesia developed in 31 patients who received LPT from the onset of treatment.

The disease duration and the levodopa treatment duration of all 95 patients in the TT group and the LPT group are summarized in Table 2. The risk of dyskinesia for all patients who started on or switched to Q3 hour dosing (6 times per day) was very low. The incidence of dyskinesia was 4.9% for all 61 patients in the LPT group. In contrast, the incidence of dyskinesia for the 34 patients in the TT group was 50% (Table 2). Thus, the relative risk of acquiring dyskinesia for the LPT group was 0.1 compared to the TT group. Comparing the LPT group to the TT group for dyskinesia occurrence, there was also a highly significant difference determined by a chi-squared test (Table 2), with *p* < 0.001. The decreased dyskinesia observed in the LPT group did not occur at the expense of decreased overall motor status during the day. Most of these patients who were switched from TT to LPT with an unchanged total daily dose reported improved motor and functional status with LPT.

Table 3 compares the two LPT subgroups, which included patients who began treatment with 6 doses daily (Initial-6T) and patients who had been switched from TT to LPT (Switched-

Table 3. Less pulsatile levodopa therapy subgroup characteristics

Characteristics	Initial-6T (n = 31)	Switched-6T (n = 30)
Male/Female	19/12	13/17
Age, first visit	68.5 ± 8.0	69.4 ± 8.0
Hoehn & Yahr stage, first visit	2.21 ± 0.82	2.83 ± 0.80
Levodopa equivalent dose, last visit (mg)	750 ± 293	949 ± 360
Mean observation time (years)	3.4 ± 2.3	5.3 ± 4.0
Disease duration (years)	5.1 ± 2.8	10.5 ± 4.9
Levodopa duration (years)	3.2 ± 2.3	8.1 ± 4.8

Data are presented as mean ± SD. Levodopa dose is the daily dose in milligrams. Initial-6T: levodopa 6 times per day as initial therapy, Switched-6T: switched from traditional levodopa therapy to levodopa 6 times per day.

6T). There was a longer disease duration, a longer levodopa treatment duration and a higher levodopa equivalent dose in the Switch-6T subgroup than in the Initial-6T subgroup or the TT group. Both LPT subgroups showed significantly less incidence of dyskinesia compared to the TT group ($p < 0.001$).

DISCUSSION

In the 1980s, continuous dopaminergic stimulation was proposed as a way to reduce the incidence of dyskinesia during levodopa therapy.[8-10] For patients in the advanced stages of Parkinson's disease, this less pulsatile method was eventually shown to reduce these motor complications.[16-18] In early stage Parkinson's disease, however, this approach has not previously been used to try to minimize motor complications. Our preference for frequent levodopa dosing as a form of LPT was based on the short half-life of levodopa,[11] the successful use of frequent dosing in patients with advanced Parkinson's disease, and the association of dyskinesia with pulsatile levodopa administration in animal models.

Over many years of using 6 daily doses of levodopa, we had noticed negligible dyskinesia in our patients with Parkinson's disease. This clinical observation encouraged us to formally analyze our experience. We included only patients observed for more than 6 months. As seen in Table 2, the risk of developing dyskinesia in the TT group was 10 times higher than that for patients using less pulsatile administration of levodopa ($p < 0.001$). Our study is imperfect in that it is not prospective and the data are drawn from clinical practice. No matter how one looks at the data, however, one cannot ignore the fact that dyskinesia was almost negligible in patients treated with the less pulsatile method, with a mean disease duration of 7.7 years and a mean duration of levodopa therapy of 5.6 years. Of the three dyskinesia cases reported, one was due to the nursing home stopping the LPT; the second reported that "dyskinesia" was searched

for but never observed in the clinic; and the third was very mild.

Our 6 times a day regimen has not been previously reported, probably because of the inconvenience of such frequent dosing. The less than 90 minute levodopa $T_{1/2}$ (120 minutes when entacapone is added[11]) suggests that avoiding a low trough level would require dosing at 2 hour intervals, i.e., a total of 7−8 times per day. However, Stocchi and Olanow[20] have stated that 2.5−3.0 hour dose intervals may be adequate to avoid low trough levels.

Encouraged by this suggestion, we provided patients with the option of taking levodopa 6 times per day at 3 hour intervals. The interval between the first daily dose and the last dose is 15 hours, which is acceptable to many patients. When provided detailed information about the short $T_{1/2}$ of levodopa, the risk of dyskinesia and current research data, two thirds of our clinic patients decided to accept the 6 times daily regimen. Close to 70% of our patients with Parkinson's disease in both the LPT and TT groups also took entacapone to increase the $T_{1/2}$ of levodopa. Interestingly, the incidence of dyskinesia in patients taking levodopa at 3.0 hour intervals in our clinic is much lower than that in patients taking levodopa at 3.5 hour intervals in the STRIDE-PD.[3] Since each levodopa equivalent dose was 141 mg in the LPT group and 187−249 mg (3 to 4 times per day) in the TT group, it is conceivable that the lower dyskinesia incidence in the LPT group was due in part to the difference in peak level. The low incidence of dyskinesia in the LPT group was not due to a lower levodopa equivalent dose (Table 1) or reduced overall motor function.

In summary, the data shown here strongly suggest that the clinician may be able to lessen the occurrence of dyskinesia in early and advanced Parkinson's disease patients by using frequent doses of levodopa. The data also indicate that a switch from traditional to less pulsatile levodopa treatment is safer than continuing traditional levodopa therapy. In other words, there is a benefit to less pulsatile treatment whether patients are levodopa-naïve or have already been receiving TT. To the best of our knowledge, there has never been a controlled prospective trial or case series addressing this question. A prospective clinical trial is needed to further clarify this subject.

Motor fluctuation data have not been shown here due to the lack of comparable Unified Parkinson's disease rating scales (UPDRS) in this retrospective study. However, we have observed that the LPT group patients, who received LPT from the onset, and those who were switched to LPT at an early stage of Parkinson's disease, do not experience significant motor fluctuations or an on/off phenomena. Lessened motor fluctuation may be related to decreased variation in the level of levodopa. Motor fluctuation was commonly observed in patients under TT. Remarkably, due to the lack of dyskinesia and the absence

of significant motor fluctuation, deep brain stimulation treatment was not needed in any of the patients who were treated solely with the less pulsatile method.

As discussed above, there is compelling evidence that pulsatile dopaminergic stimulation may be one of the primary causes of LID.[8-10,12-14] Pulsatile dopaminergic stimulation may disrupt the physiological functions of dopaminergic neurons or related cells. We must consider the possibility that prolonged pulsatile dopaminergic stimulation causes neuronal degeneration as well as physiologic change. This concept could provide an explanation for the ELLDOPA study showing worsened imaging after 40 weeks of levodopa treatment.[6] Similar imaging findings have also been noted in other clinical trials.[26,27] There are other possible explanations for these imaging results, such as incomplete washout.[6,28] A clinical trial comparing the motor and functional status as well as imaging for patients on 3 times daily dosing to those patients on 6 times daily dosing would be beneficial.

These speculations notwithstanding, the data presented here suggest that the clinician may be able to prevent early and advanced Parkinson's disease patients from developing dyskinesia by prescribing frequent doses of levodopa. Before starting treatment, the neurologist can explain the benefits of frequent dosing compared to the more convenient pulsatile dosing. Once educated, many patients are willing to comply with this LPT.

In conclusion, LID appears to be minimized when levodopa is given 6 times daily. This benefit occurs in both levodopa-naïve patients and in dyskinesia-free patients switched from TT to LPT therapy. The present report raises important questions regarding dyskinesia prevention, motor fluctuation and neuroprotection. We hope that future clinical trials will provide further insight.

Conflicts of Interest

The authors have no financial conflicts of interest.

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