Impact of Pramipexole on the Onset of Levodopa-Related Dyskinesias

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Abstract: **Dyskinesias are a major complication of dopaminergic therapy in the long-term treatment of Parkinson's disease. In the CALM-PD trial, subjects were initially randomized to levodopa or pramipexole and could later add levodopa if needed. After adjusting for disease duration and daily levodopa dosage, the incidence of dyskinesias after initiating levodopa was not significantly different among subjects initially randomized to levodopa and those initially randomized to pramipexole.** © 2007 Movement Disorder Society

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Parkinson's disease (PD) is a common progressively disabling neurodegenerative movement disorder, with a prevalence approaching 1% in people over 65 years old. Long-term management of PD is complicated by the emergence of response fluctuations (wearing-off, *on–off*) and motor complications such as dyskinesias and *off* dystonia.[1] These complications are in part a consequence of prolonged use of dopaminergic therapy, with levodopa playing a predominant role.

Two major contributing factors for the development of motor complications are disease duration, nowadays generally reflected by the duration of treatment, and daily levodopa dosage. After 4 to 6 years of levodopa treatment, the risk of experiencing motor fluctuations or dyskinesias has been reported to range from 8% to 64%,[2] and at 15-year follow-up, 94% of PD patients showed dyskinesias or wearing-off.[3] Higher dosages of levodopa result in more dyskinesias and wearing-off, as shown in the Earlier Versus Later Levodopa Therapy in Parkinson's Disease Trial (ELLDOPA), which evaluated the effects of three different dosages of levodopa on the progression of early PD.[4] The incidence of dyskinesias can be reduced by initiating treatment with dopamine agonists instead of levodopa.[5] However, one recent ropinirole study showed that this was no longer the case, once levodopa was supplemented to the initial dopamine agonist monotherapy.[6]

The Comparison of the Agonist Pramipexole Versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) trial compared pramipexole, a nonergot dopaminergic agonist, with levodopa as initial treatment for PD. The primary analysis found that the incidence of dyskinesias was lower at both 2 and 4 years of follow-up, following initial treatment with pramipexole versus levodopa.[7,8] However, initial treatment with levodopa provided for better symptomatic control, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS),[9] and was associated with lower incidences of freezing, somnolence, and edema. Both options resulted in similar quality of life outcomes at 4 years.[7,8]

We examined the CALM-PD database to see if the risk of developing dyskinesias after the introduction of levodopa differed between subjects initially assigned to pramipexole (in whom the introduction of levodopa was delayed) and subjects initially assigned to levodopa. Our goal was to determine whether the lower incidence of dyskinesias in the pramipexole group reflects a lower risk of dyskinesias due to the initial treatment with pramipexole, suggesting a protective effect, or whether it is a feature of the temporal delay in initiating levodopa.

PATIENTS AND METHODS

The CALM-PD trial was a multicenter randomized double-blind controlled clinical trial enrolling subjects with early PD who were just at the point of requiring initiation of dopaminergic therapy. Reports detailing the subjects and methods of the CALM-PD study are published.[7,10]

After the initial 10 weeks of dosage escalation, subjects had adjusted experimental treatment to one of three dosage levels: 1.5 mg pramipexole or 75/300 mg carbidopa/levodopa; 3.0 mg pramipexole or 112.5/450 mg carbidopa/levodopa; or 4.5 mg pramipexole or 150/600 mg carbidopa/levodopa. Open-label carbidopa/levodopa could be added at any point after the initial 10-week escalation to treat emerging symptoms. After the first 24 months of follow-up, subjects who

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had reached the primary endpoint (development of wearing-off, dyskinesias, or *on–off* fluctuations) could add any antiparkinsonian medication. Consequently, only data up to the 24-month visit are included in this report.

Dyskinesias were defined as abnormal involuntary movements that included chorea, dystonia, myoclonus, or tics that could be either peak dose or end of dose. Dyskinesias did not include early-morning dystonia or other *off* dystonias.

Subjects in the CALM-PD study (n = 301) were evaluated at 3-month intervals. There were 223 subjects exposed to levodopa during the first 24 months of follow-up, including 150 who were randomized to initial treatment with levodopa and 73 who were randomized to initial treatment with pramipexole but later added open-label levodopa; our analysis pertains to the follow-up of these subjects once levodopa was initiated. Of the remaining 78 subjects randomized to pramipexole, 70 were excluded because they never added levodopa within the first 24 months of follow-up and 8 because they developed dyskinesias before receiving supplemental levodopa.

Statistical Analysis

The primary outcome variable in our analysis was the time from initiation of levodopa to the onset of dyskinesias. The two groups under study (initial pramipexole, n = 73; initial levodopa, n = 150) are not comparable because the initial pramipexole group is a select subset of the originally randomized group (n = 151), levodopa was initiated at a later time in this group, and the dosage of levodopa provided as supplemental therapy was generally much lower in this group than the dosage taken by those in the initial levodopa group. In addition, *t* tests and χ^2 tests were used to compare the two groups with regard to the characteristics of subjects at the time of levodopa initiation. We used a Cox proportional-hazards model to compare the groups with regard to the time to onset of dyskinesias, adjusting for daily levodopa dosage and duration of PD at the time of initiation of levodopa. The model also included center as a stratification factor. This model was also used to construct estimated survival functions for the two treatment groups at the mean of each covariate (daily levodopa dosage and duration of PD).

RESULTS

There were no significant differences between the two groups at the time of initiation of levodopa therapy with regard to age, gender, Hoehn and Yahr stage,[11] quality-of-life scores (the Parkinson's Disease Quality of Life Scale, or PDQUALIF,[12] and the EuroQol Visual Analog Scale, or EuroQol VAS[13]), and Mini Mental State Examination (MMSE) scores[14] (Table 1). There was a difference in the mean number of years since diagnosis, the mean daily levodopa dosage (as determined 10 weeks after initiation), and the mean UPDRS total score. We did not adjust for the UPDRS total score in this analysis as it did not have a significant association with the time until onset of dyskinesias; a secondary analysis that included this covariate in the model did not alter our conclusions.

TABLE 1. *Subject characteristics at the time of initiation of levodopa*

Variable	Pramipexole (n = 73)	Levodopa (n = 150)
Age	60.7 ± 10.2	60.9 ± 10.5
Male (%)	58.9	66.0
Caucasian (%)	93.2	95.3
Years since diagnosis	2.5 ± 1.5	1.8 ± 1.7[a]
Total UPDRS score	26.7 ± 12.7	31.1 ± 12.8[b]
Hoehn and Yahr stage	1.8 ± 0.5	1.9 ± 0.5
Mini-Mental State Examination	29.2 ± 1.3	29.3 ± 1.1
Parkinson's Disease Quality of Life Scale	27.1 ± 14.0	26.7 ± 11.4
EuroQol Visual Analog Scale	79.5 ± 11.9	77.6 ± 12.0

[a] $P < 0.01$;
[b] $P < 0.05$.

The 73 subjects randomized to pramipexole were followed for an average of 11.3 months (median, 9.6 months) prior to initiation of levodopa and for an average of 11.2 months (median, 11.6 months; range, 1–679 days) on levodopa. Seven (9.6%) of these 73 subjects experienced dyskinesias following initiation of levodopa.

The 150 subjects randomized to levodopa were followed for a median of 23.7 months (range, 23–735 days). Twenty-eight (19%) of these subjects experienced dyskinesias within 12 months and 45 (30%) experienced dyskinesias within 24 months after initiation of levodopa.

During the follow-up period on levodopa, the pramipexole dosage was 2.75 ± 1.03 mg/day. The levodopa dosage after 10 weeks of exposure was 233.6 ± 80.8 mg/day in the pramipexole group versus 427 ± 112.3 mg/day levodopa in the levodopa monotherapy group. One single withdrawal due to dyskinesias occurred during this time, and that was in the levodopa group.

After adjustment for daily levodopa dosage at 10 weeks and for the number of years since PD diagnosis (both being significantly associated with the time to onset of dyskinesias), the risk of onset of dyskinesias did not significantly differ between subjects who added levodopa after the initial randomization to pramipexole and those originally randomized to receive levodopa (hazard ratio = 1.3; 95% CI = 0.4–4.3; $P = 0.6$; Fig. 1).

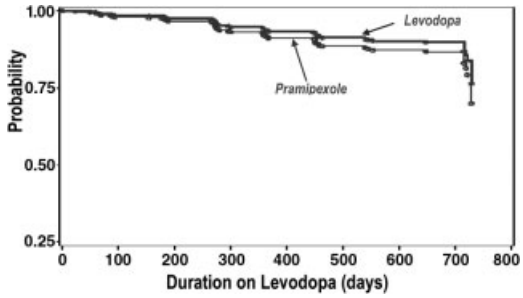

FIG. 1. Probability of not having dyskinesias onset throughout time on levodopa (adjusted for center, levodopa dose, and duration of Parkinson's disease diagnosis).

DISCUSSION

Our analysis found that the incidence of dyskinesias after initiation of levodopa among subjects with Parkinson's disease initially treated with pramipexole was not significantly different (neither better nor worse) from that of those who only received levodopa, after adjusting for years since diagnosis and the daily levodopa dosage at 10 weeks. Although initial treatment with pramipexole (vs. levodopa) significantly delays the onset of dyskinesias, this appears to be primarily through a levodopa-delaying effect rather than a protective effect.

We used levodopa dosage at 10 weeks as a covariate in the analysis mainly because we wanted to adjust for subject characteristics measured at (or approximately at) the time of levodopa initiation, and the levodopa dosage in the subjects initially treated with levodopa alone was required to be stabilized at 10 weeks. Also, the increase in dosage after 10 weeks was relatively small. The mean daily dosages at month 24 were 509 mg in the initial levodopa group and 264 mg in the initial pramipexole group[1]; at 10 weeks, these values were 427 and 234 mg, respectively.

Our findings must be interpreted with appropriate caution given that this was a retrospective subgroup analysis. Despite the fact that we accounted for known factors that are associated with the development of dyskinesias (duration of PD diagnosis and daily dosage of levodopa), it is possible that our results may be affected by residual confounding. Also, there were only 52 events (7 in the initial pramipexole group), which limits the power to detect hazard ratios that may be clinically important. While the hazard ratio (1.3) is fairly close to 1, its associated 95% confidence interval (0.4–4.3) is wide and contains values that may be considered to represent clinically important group differences.

While our findings support the practice of favoring initial treatment with dopamine agonists in PD patients in order to delay onset of dyskinesias, they do not support the concept of treating with agonists in order to achieve protection from dyskinesias.

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