Effects of a Dopamine Agonist on the Pharmacodynamics of Levodopa in Parkinson Disease

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Background: Treatment of Parkinson disease commonly includes levodopa and dopamine agonists; however, the interaction of these 2 drugs is poorly understood.

Objective: To examine the effects of a dopamine agonist on the motor response to levodopa.

Design: Double-blind, randomized, placebo-controlled, crossover clinical trial.

Setting: Ambulatory academic referral center.

Patients: Thirteen patients with idiopathic Parkinson disease taking levodopa and experiencing motor fluctuations and dyskinesia.

Interventions: Eligible individuals were randomly assigned to receive pramipexole dihydrochloride or placebo for 4 weeks followed by a 2-hour intravenous levodopa infusion on consecutive days at 2 rates and with blinded assessments. They were then crossed over to the alternate oral therapy for 4 weeks followed by levodopa infusion and reassessment.

Main Outcome Measures: Change in finger-tapping speed, measured using the area under the curve (AUC) for finger taps per minute across time; peak finger-tapping speed; duration of response; time to “ON” (defined as a 10% increase in finger-tapping speed above baseline); walking speed; and dyskinesia AUC.

Results: Pramipexole with levodopa infusion increased finger-tapping speed beyond the change in baseline by a mean (SE) of 170 (47.2) per minute × minutes (P = .006) and more than doubled the AUC for finger-tapping speed. Pramipexole increased peak finger-tapping speed by a mean (SE) of 18 (8.5) taps per minute (P = .02) and improved mean (SE) walking speed (15.9 [0.70] vs 18.9 [0.70] seconds, P = .004). Pramipexole prolonged duration of response after levodopa infusion and shortened time to ON. Pramipexole increased mean (SE) baseline dyskinesia scores (26.0 [5.85] vs 12.1 [5.85] points, P = .05) and peak dyskinesia scores with levodopa infusion.

Conclusions: Pramipexole augmented the motor response to levodopa beyond a simple additive effect and increased the severity of levodopa-induced dyskinesia. When considering a combination of these therapies, an appropriate balance should be maintained regarding gain of motor function vs worsening of dyskinesia.

Trial Registration: clinicaltrials.gov Identifier: NCT00666653

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would be superimposed on this altered baseline. Another, not mutually exclusive, mechanism is an interaction between a DA and levodopa. In this case, DAs may potentiate the effects of levodopa, increasing the peak response, duration of response, or both to each dose of levodopa. Finally, because DAs have a low propensity to produce dyskinesia as monotherapy, how do they affect levodopa-induced dyskinesia?

Levodopa infusions have provided a useful tool for studying the effects of drugs on motor response in patients with PD. This experimental paradigm avoids the variability of oral absorption of levodopa and allows for precise examination of time course and dose response. We performed a double-blind, randomized, placebo-controlled, crossover clinical trial to examine the interaction of DAs and levodopa by measuring the motor response to a 2-hour intravenous levodopa infusion in patients with PD taking a DA, pramipexole dihydrochloride, for 1 month and taking placebo for 1 month.

**METHODS**

Patients aged 30 to 80 years with idiopathic PD as determined by an Oregon Health & Science University (OHSU) movement disorder specialist (M.A.B.) based on London Brain Bank criteria enrolled in the study. Patients were excluded if they had atypical features of parkinsonism, had a Mini-Mental State Examination score less than 25, or had unstable cardiovascular disease or active peptic ulcer disease. They gave informed consent to a protocol approved by the OHSU institutional review board and General Clinical Research Center (GCRC) Scientific Advisory Committee.

Patients were undergoing long-term levodopa therapy and had motor fluctuations and dyskinesia as determined during screening. Patients were screened using finger tapping in the practically defined OFF motor state, having been without levodopa overnight, and in the practically defined ON motor state, approximately 1 hour after taking their usual levodopa dose. To qualify, they had to have a minimum of 10% improvement in finger-tapping speed in the ON state. The trial was a double-blind, randomized, placebo-controlled, crossover study with patients taking a stable dose of pramipexole for 4 weeks and an identical-appearing placebo for 4 weeks. Responses to 2-hour levodopa infusions at 0.5 mg/kg/h (threshold) and 1.0 mg/kg/h (therapeutic rate) were calculated as the mean of the 7:30, 8, 8:30, and 9 AM scores when patients went overnight without antiparkinson medications, except for placebo or pramipexole at 7 AM, but before levodopa infusions started at 9 AM.

Dyskinesia was graded on a scale from 0 to 4 points (0 indicating none; 1, mild; 2, definite/mild to moderate; 3, moderate, may interfere with some activities; and 4, severe, markedly impairs voluntary activities) in the face, neck, and trunk and each of the 4 limbs, and a total score (range, 0-28) was assigned. Ambulation was assessed by measuring the time it took the patient to stand up from a chair, walk 6 m, turn around, return to the chair, and sit. An mUPDRS was collected at 9 AM, just before the levodopa infusion was started, and at 11 AM, at peak levodopa concentration.

After their first stay in the GCRC, patients were switched from pramipexole to placebo or vice versa, and the doses were simultaneously titrated down from one study medication while being titrated up on the other study medication for 9 days. The patients were then maintained on study medication for 4 weeks and were readmitted for 2 days to the GCRC for levodopa infusion and analysis.

**STATISTICAL ANALYSIS**

A randomized, double-blinded, placebo-controlled crossover design was used to examine the effect of oral DA therapy and levodopa infusion. Because a crossover design has the advantage of eliminating individual patient differences from the overall treatment effect, it provides more statistical power. Demographic and clinical characteristics were summarized using descriptive statistics. To compare the pramipexole effect and the infusion effect, the interaction between pramipexole and infusion, and the carryover effect due to the study design, we used the mixed model. The Bayesian information criterion was used to determine a covariance structure for the model. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), and P < .05 was considered statistically significant.

Change in the total finger-tapping score was calculated as the total finger-tapping score from 9:30 AM to 2 PM minus the baseline finger-tapping score from 7:30 to 9 AM. The AUC was calculated from the scores from 9:30 AM until 2 PM minus the mean baseline scores from 7:30 to 9 AM, setting any negative
scores to zero. The peak score was the single fastest finger-tapping time or dyskinesia score. Onset of clinical response was measured as the time to a 10% increase in the finger-tapping score, and time to ON was defined as the time point after the start of the infusion at which a 10% improvement in the finger-tapping score above the mean baseline score was attained in patients who had an ON response. Duration of ON time was determined as the total time that finger tapping was at least 10% faster than the mean baseline value.

**RESULTS**

Thirteen patients consented to participate and were screened and enrolled in the study. Three patients dropped out of the study: 1 after developing a urinary tract infection and 2 because they could not tolerate discontinuation of the DA during the placebo phase. Ten patients completed the protocol and are included in all of the analyses. During the maintenance phase, 2 patients had to increase their levodopa intake by 50 mg per dose owing to a slight worsening of parkinsonian symptoms. All other patients maintained the same dose of antiparkinson medications throughout the study except for tapering off of their DA. The mean (SD) patient age was 61.9 (8.0) years (age range, 50-74 years). The mean (SD) OFF mUPDRS score at enrollment was 28.4 (8.8) (range, 15-43), and the mean (SD) ON mUPDRS score at enrollment was 6.5 (4.5) (range, 0-15) (Table 1).

**EFFECTS OF PRAMIPEXOLE TREATMENT ON BASELINE BRADYKINESIA**

Pramipexole administered at 7 AM improved mean (SD) baseline (8, 8.30, and 9 AM) finger-tapping scores (133.4 [4] vs 122.0 [5] taps per minute, P = .001), an increase of 10% over placebo. The effect of pramipexole on baseline scores was less evident at the end of the study, 7 hours after pramipexole administration at 7 AM. The baseline mUPDRS score was improved in the pramipexole group by 31%, a 6.2-point reduction from a mean (SE) of 26.25 (1.91) to 20.05 (2.29) (P = .006).

**EFFECTS OF PRAMIPEXOLE TREATMENT ON MOTOR RESPONSE TO LEVODOPA INFUSION**

Pramipexole increased the AUC, measured as finger taps per minute × minutes, beyond the change in baseline pre-levodopa infusion finger-tapping speed. The total number of finger taps in the pramipexole-treated group was 940.4 per minute × minutes and in the placebo group was 770.6 per minute × minutes (a difference of 169.8 finger taps per minute × minutes, SE = 47.15, P = .006 (Figure 1)).

Pramipexole converted a motor response seen with a threshold levodopa infusion rate (0.5 mg/kg/h) into a motor response seen with a therapeutic infusion rate (1.0 mg/kg/h). Pramipexole more than quadrupled the AUC at the threshold levodopa infusion rate and more than

### Table 1. Baseline Characteristics of 13 Patients With Idiopathic PD

<table>
<thead>
<tr>
<th>Patient No./Age at Enrollment, y</th>
<th>No. of Years Since PD Diagnosis</th>
<th>Taking LD</th>
<th>With Fluctuations</th>
<th>Daily LD Dose, mg a</th>
<th>Taking a DA?</th>
<th>OFF mUPDRS Score</th>
<th>ON mUPDRS Score</th>
</tr>
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<tr>
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<td>16</td>
<td>10</td>
<td>5</td>
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<td>43</td>
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<td>2/65</td>
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<td>8</td>
<td>10</td>
<td>1150</td>
<td>Yes</td>
<td>36</td>
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<td>4/55</td>
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<td>5</td>
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<td>5</td>
<td>5</td>
<td>550</td>
<td>Yes</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: DA, dopamine agonist; LD, levodopa; mUPDRS, motor score of the Unified Parkinson’s Disease Rating Scale; PD, Parkinson disease.

aCalculated as immediate-release LD (×1.25 with a Component Object Model Transaction Integrator) + 75% of continuous-release LD.
bDropped out before the first infusion.
cDropped out before the second infusion.
Table 2. Effects of Pramipexole on Motor Response to LD Infusion

<table>
<thead>
<tr>
<th>Placebo + threshold infusion</th>
<th>Pramipexole dihydrochloride + threshold infusion</th>
<th>Pramipexole + therapeutic infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders, No.</td>
<td>Finger Taps/min, Mean</td>
<td>Time to ON in Responders, Mean, h</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>119.5</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>8</td>
<td>124.5</td>
</tr>
<tr>
<td>Pramipexole + therapeutic infusion</td>
<td>8</td>
<td>134.0</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; LD, levodopa.

Figure 2. Dyskinesia vs time in 13 patients with idiopathic Parkinson disease. LD indicates levodopa.

doubled the AUC at the therapeutic infusion rate (Table 2).

Responders to levodopa infusion were defined as having a 10% increase above their baseline mean finger-tapping score (between 8 and 9 AM) in at least one time point. At the threshold levodopa infusion rate, there were 7 responders taking placebo and 8 taking pramipexole. At the therapeutic levodopa infusion rate, there were 6 responders taking placebo and 8 taking pramipexole (Table 2).

At the therapeutic levodopa infusion rate, pramipexole increased peak finger-tapping speed over baseline by approximately 8%, approximating the 11% increase induced by pramipexole alone. However, pramipexole increased the peak finger-tapping response by 19% over baseline at the threshold infusion rate, almost double the increase induced by pramipexole alone. Overall, the increase in peak finger-tapping speed above the mean baseline value was greater with pramipexole treatment by a mean (SE) of 18 (8.47) finger taps per minute ($P=0.02$).

Duration of response after the end of levodopa infusion was prolonged by pramipexole. Once an ON effect (10% increase in finger-tapping speed above baseline) was achieved, mean finger-tapping speed was maintained above 10% of baseline for 3.5 hours with pramipexole and therapeutic levodopa infusion ($n=8$), for 1.5 hours with pramipexole and threshold LD infusion ($n=8$), and for 1 hour with the combination of placebo and therapeutic levodopa infusion ($n=6$); mean finger-tapping speed did not produce an ON response with placebo and threshold levodopa infusion. Time to ON was 1 hour sooner with pramipexole treatment vs placebo at the threshold levodopa infusion rate but was not significantly different at the therapeutic infusion rate (Table 2). Ambulation improved, as measured by the timed walking test, with pramipexole vs placebo during levodopa infusion (mean [SE] duration, 15.9 [0.70] vs 18.9 [0.70] seconds; $P=0.004$).

The mean (SE) baseline total dyskinesia score was greater with pramipexole treatment vs placebo (26.0 [5.85] vs 12.1 [5.85] points, $P=0.05$). The therapeutic infusion rate also caused more dyskinesia than did the threshold infusion rate, regardless of oral treatment (mean [SE]: 28.0 [6.75] vs 10.0 [6.75] points, $P=0.04$). Pramipexole increased peak dyskinesia scores by 2.1 points at threshold infusion and by 3.4 points at the therapeutic infusion rate (Table 2 and Figure 2).

The mean mUPDRS score improved with levodopa infusion regardless of the infusion rate ($P<0.001$). The change in the mUPDRS score with levodopa infusion was not significantly greater with pramipexole treatment than with placebo at either infusion rate. Visual analog scales of anxiety, fatigue, and mood did not show significant differences between pramipexole treatment and placebo. There were no carryover effects for finger tapping. The order of the levodopa infusions (0.5 or 1.0 mg/kg/h) ($P=0.72$) and the order of the oral drug phases (pramipexole or placebo) ($P=0.96$) did not affect finger tapping.

ADVERSE EVENTS

Aside from increasing OFF time in 2 patients from their baseline during the placebo phase, there were no adverse events associated with this study.

COMMENT

Pramipexole, a mixed D2/D3-receptor DA, had robust effects on levodopa action in this study. It modestly improved OFF or “trough” scores before the levodopa infusion, suggesting an independent action of pramipexole that has been seen in other clinical trials.11 The effects of pramipexole at the end of the infusion, when levodopa effects had dissipated, was less clear, but trough effects at this time may have been affected by a
dissipation of pramipexole effects (with a half-life of 8-12 hours) or by an end-of-dose worsening phenomenon. Scoring of patients through several dose cycles is necessary to determine whether the interdose troughs were altered. However, the effect on the pre-levodopa infusion scores suggests an addition of independent effects of the DA and levodopa. Furthermore, the peak finger-tapping rate during levodopa infusions was increased by pramipexole to the same extent as the improvement in the preinfusion baseline scores, also suggesting an addition of actions of the DA and levodopa.

Pramipexole markedly augmented the effects of a dose of levodopa and in the present paradigm more than doubled the antiparkinsonian effects as measured by the AUC for finger-tapping speed. This was accomplished by 3 effects: the time to onset of the levodopa effect was shortened with the addition of pramipexole, the duration of motor improvement with levodopa infusion was prolonged with pramipexole, and, at the threshold levodopa infusion, the peak finger-tapping rate was increased beyond the increase in baseline speed. These effects were not confined to finger-tapping scores; ambulation, measured by the speed-of-walking task, improved with pramipexole during levodopa treatment. These changes in the AUC are more than just additive effects and suggest that pramipexole also augments the effects of levodopa.

Concomitant with the motor improvement, pramipexole increased levodopa-induced dyskinesia severity and the AUC. Because DAs alone rarely cause dyskinesia, physicians sometimes think that it will not increase dyskinesia when added to levodopa. The present results show that pramipexole increased dyskinesia, increasing peak severity and prolonging dyskinesia. Because DAs have a low propensity to produce dyskinesia as monotherapy, this observation also indicates an interaction between DAs and levodopa beyond simple additive effects. These findings are in contrast to those of Bonnet et al., who found that pergolide and bromocriptine augment anti-PD effects and suppress dyskinesia. The present data suggest that the levodopa dose may need to be decreased when DAs are added in patients with levodopa-induced dyskinesia.

How do these results fit with the basic pharmacologic actions of DAs? It is known that some agonists depend on residual striatal dopamine for their antiparkinsonian actions. For example, bromocriptine is inactive in rodent models of PD in which dopamine is depleted by inhibition of vesicular monoamine storage by reserpine. This observation supports the interaction of DAs and dopamine produced from exogenous levodopa. However, pramipexole has pharmacologic actions in this animal model, indicating that some DAs could have an antiparkinsonian action independent of dopamine synthesized from endogenous or exogenous levodopa.

What are the clinical implications of these studies? First, DAs markedly augment the antiparkinsonian and dyskinetic actions of levodopa. Thus, addition of a DA to levodopa would be expected to augment the antiparkinsonian benefits of levodopa but will likely increase dyskinesia. These results indicate that dyskinesia will be improved with the addition of a DA only if there is a reduction in the levodopa dose. The fact that a threshold infusion rate of levodopa was converted to a suprathermal rate with the addition of a DA indicates that the reduction in levodopa would need to be more than just a token reduction. The DAs may also be helpful for patients with delayed ON because they reduced the time to turning ON in this study. The effect of DA on interdose trough dysfunction awaits a study examining repeated dosing during the day.

In conclusion, the addition of a DA to levodopa in the treatment of PD augments motor response probably via interaction with levodopa rather than just addition of the effects of the two drugs. At the same time, levodopa-induced dyskinesia is also augmented. When considering a combination of these dopaminergic therapies, an appropriate balance should be maintained regarding gain of motor function vs worsening of dyskinesia.

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Author Contributions: Dr Brodsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brodsky and Nutt. Acquisition of data: Brodsky. Analysis and interpretation of data: Brodsky, Park, and Nutt. Drafting of the manuscript: Brodsky. Critical revision of the manuscript for important intellectual content: Brodsky, Park, and Nutt. Statistical analysis: Park. Obtained funding: Brodsky. Administrative, technical, and material support: Brodsky. Study supervision: Nutt.

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REFERENCES


