Response to Levodopa Treatment in Dopa-Responsive Dystonia

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Background: Dopa-responsive dystonia (DRD) is similar to Parkinson disease in that both disorders have impaired dopamine synthesis and respond to levodopa treatment. Dopa-responsive dystonia differs in that dopamine storage is intact in contrast to Parkinson disease in which it is markedly reduced.

Objective: To examine the short- and long-duration responses to levodopa dosing in subjects with DRD.

Methods: The response to brief infusions of levodopa was examined in 4 subjects with DRD and the effects of withdrawal of levodopa for 3 to 7 days studied in the 3 subjects receiving long-term levodopa therapy. Motor function was measured with tapping speed, Unified Parkinson's Disease Rating Scale motor score, and global dystonia score.

Results: The short-duration response to levodopa dosing seems to develop more slowly and persists longer in subjects with DRD than in subjects with Parkinson disease. Withdrawal of levodopa leads to a gradual decline in tapping speed and reemergence of dystonia over several days, similar to the rate of decay of motor function in Parkinson disease. The short- and long-duration responses were not clearly differentiated in DRD.

Conclusions: This pilot study suggests that retained dopamine storage in DRD may prolong the short-duration response and blur the distinction of the short- and long-duration responses. The decline in motor function in DRD on withdrawal of long-term levodopa therapy resembles that in Parkinson disease, suggesting that a long-duration response, if it exists in DRD, is unrelated to dopamine storage.

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DOPA-RESPONSIVE dystonia (DRD) is generally an autosomal dominant disorder manifest as dystonia and particularly in older patients, as parkinsonism. Most cases of DRD are related to a mutation in GTP cyclohydrolase I, impairing the production of tetrahydrobiopterin, an essential cofactor for tyrosine and tryptophan hydroxylases. Consequently, synthesis of dopamine is compromised in DRD as it is idiopathic Parkinson disease (PD). Consistent with this neurochemical pathology, both DRD and PD respond to the dopamine precursor levodopa.

Dopamine storage is normal in DRD, as judged by positron emission tomographic studies with fluorodopa and biochemical studies of markers for dopamine nerve terminals. In contrast, in PD, dopamine storage and dopamine nerve terminals are reduced. The importance of impaired dopamine storage to the response to exogenous levodopa treatment in PD is unknown. Storage may influence the duration of the short-duration response, an immediate response to levodopa dosing measured in hours. The “storage hypothesis” proposes that development of motor fluctuations in PD is due to reduction in the duration of response to each dose of levodopa caused by the progressive loss of dopamine nerve terminals and dopamine storage capacity.

Storage of dopamine synthesized from exogenous levodopa treatment has also been proposed to be the basis of the long-duration response. The long-duration response is a therapeutic effect that builds up over days with repeated levodopa dosing and likewise decays over days on cessation of levodopa treatment. Diminishing storage capacity could reduce the magnitude of the long-duration response or speed its decline on stopping levodopa treatment.

This study examined the short- and long-duration responses to levodopa treatment in subjects with DRD and, by com-
SUBJECTS AND METHODS

SUBJECTS

Three subjects with DRD and 1 asymptomatic mutation carrier participated in these studies after giving informed consent to a protocol approved by the Oregon Health Sciences University institutional review board and the General Clinical Research Center (GCRC) Advisory Committee, Portland. Subject 1 was the proband in a previous report of DRD\textsuperscript{15} and her family has been included in other studies of DRD.\textsuperscript{4,7} Subject 2 had the DRD phenotype and a similarly affected daughter. Subjects 3 and 4 were third-degree relatives whose family has been included in previous studies of DRD.\textsuperscript{1,16-18} The subjects’ clinical features are described in Table 1. Subject 3 had also participated in another study of the effects of levodopa treatment withdrawal.\textsuperscript{13} Data from 18 subjects with PD who were studied after 1 year of long-term levodopa therapy\textsuperscript{19} are included for comparison.

PROTOCOL

Three subjects were admitted to the Oregon Health Sciences University GCRC for 6 days; the fourth subject was admitted for 38 hours on 2 occasions separated by 1 week. Subjects received a 2-hour infusion of levodopa (1 mg/kg per hour) with concomitant oral carbidopa on the first GCRC day and a second infusion 4 to 8 days later. No levodopa was administered between the 2 infusions (ie, a “levodopa holiday”). Bradykinesia was monitored by the speed of tapping 2 manual counters 20 cm apart\textsuperscript{20} at half to hourly intervals throughout the waking day (7 AM-10 PM). The motor Unified Parkinson’s Disease Rating Scale\textsuperscript{21} and dystonia were monitored by the investigators 3 times per day. This protocol is identical to the protocol we have used to investigate the short- and long-duration responses in PD.\textsuperscript{19}

The baseline tapping rate was the mean of 2 or 3 determinations obtained in the hour before each infusion. The latency of the short-duration response to levodopa treatment was the time from the beginning of the infusion until the tapping rate increased 10% over the baseline tapping rate. The duration of response was the time that the tapping rate exceeded baseline by 10%. The peak response was the mean of the 3 consecutive highest tapping scores. The time to peak response was the time from the beginning of the infusion to the first of the 3 consecutive highest tapping rates. A short-duration response was considered absent if the tapping rate did not increase by 10%. The long-duration response was considered the decrement in tapping speed from the baseline scores (8-9 AM) prior to the first infusion of levodopa to the 8 to 9 AM scores on the morning of the second infusion which marked the end of the levodopa holiday.

RESULTS

CLINICAL MANIFESTATIONS

Subjects 1 and 4 had mild parkinsonism as evidenced by the Unified Parkinson’s Disease Rating Scale motor scores and baseline tapping rates on the first GCRC day that were 2.5 (subject 1) and 1.8 (subject 4) SDs below the average tapping rate of age-matched normal control subjects.\textsuperscript{22} The Unified Parkinson’s Disease Rating Scale motor score increased, tapping rate declined, and dystonia appeared in subject 1 when levodopa was withdrawn (Table 2). Subject 4 had never previously received levodopa treatment and, therefore, the Unified Parkinson’s Disease Rating Scale motor score and tapping speed did not deteriorate during the GCRC admission. She did not have dystonia (Table 2).

Subjects 2 and 3 primarily manifest dystonia that only became evident with the withdrawal of levodopa treatment. The baseline tapping speeds in subjects 2 and 3 were initially faster than average normal controls.\textsuperscript{21} Tapping speed deteriorated primarily in 1 hand in each subject on the withdrawal of levodopa treatment, but improved in both hands when levodopa treatment was restarted (Table 2). There was not clearly more-affected side in either subject so the asymmetric deterioration in tapping could not be related to asymmetric disease as commonly seen in idiopathic PD.

The averages of the 8 to 9 AM tapping rates in right and left hands for each subject at the beginning of the levodopa holiday (mean, 151 taps per minute), at the end of the levodopa holiday (138 taps per minute) and the day after the second infusion of levodopa (161 taps per minute) (Table 2) were compared by analysis of variance with repeated measures. The 3 days differed ($P=.02$) with a statistically significant difference between the tapping rates at the end of the levodopa holiday and the day after the holiday when the administration of levodopa treatment had been restarted ($P<.05$, Student-Newman-Keuls test).

SHORT-DURATION RESPONSE

Following the first infusion, a short-duration response, defined as a 10% or greater increase in tapping speed to a 2 mg/kg dose of levodopa administered at a constant infusion rate over 2 hours, was only evident in subject 2. The response magnitude (27 taps per minute) and response duration (2.0 hours) in the right hand were very similar to the mean responses in patients with idiopathic PD (Table 3).

The second infusion of 2 mg/kg was administered when subjects 1 through 3 had been without levodopa treatment for 3 to 8 days. Levodopa-naive subject 4 was administered 2 mg/kg of levodopa as a 6-hour instead of a 2-hour infusion because she experienced nausea and vomiting with the first infusion. Subjects 1, 2, and 4 had a measurable response to the second infusion of levodopa. Subject 3 did not acutely respond to the second infusion but tapping was faster the next day after an additional oral dose of 10 mg/100 mg carbidopa/levodopa, respectively, was administered 9 hours after the infusion of levodopa (Figure). The time course of the immediate (presumed to be a short-duration) response seemed to be different in subjects with DRD compared with subjects with PD. The peak
Table 1. Characteristics of 4 Study Subjects*  

<table>
<thead>
<tr>
<th>Subject No./Sex/Age, y</th>
<th>Manifestations</th>
<th>Diurnal Variation†</th>
<th>Dosage of Carbidopa/Levodopa, mg</th>
<th>Genetic/Biochemical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/45</td>
<td>Dystonia and parkinsonism</td>
<td>+</td>
<td>25/100, 3 times daily</td>
<td>Abnormal phenylalanine tolerance test results, normal fluorodopa PET scan (reduced brain biopterin)‡</td>
</tr>
<tr>
<td>2/M/35</td>
<td>Dystonia</td>
<td>+</td>
<td>10/100, 2 times daily</td>
<td>GCH I mutation, normal fluorodopa PET scan</td>
</tr>
<tr>
<td>3/F/47</td>
<td>Dystonia</td>
<td>+</td>
<td>10/100, every day</td>
<td>GCH I mutation, abnormal phenylalanine tolerance test result, and normal fluorodopa PET scan</td>
</tr>
<tr>
<td>4/F/56</td>
<td>Parkinsonism</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*All subjects had a positive family history for dystonia and/or parkinsonism. PET indicates positron emission tomography; ellipsis, not applicable; and GCH I, GTP cyclohydrolase I.†Plus indicates sleep benefit was present before starting long-term therapy with levodopa and disappeared during levodopa therapy.‡Autopsy finding in subject’s mother.

Table 2. Effects of Levodopa Holiday*  

<table>
<thead>
<tr>
<th>Subject No./Handedness</th>
<th>Levodopa Holiday, d</th>
<th>UPDRS†</th>
<th>Tapping‡</th>
<th>Dystonia§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Begin</td>
<td>End</td>
<td>Begin</td>
<td>End</td>
</tr>
<tr>
<td>1/R</td>
<td>3</td>
<td>11</td>
<td>21</td>
<td>R hand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L hand</td>
</tr>
<tr>
<td>2/R</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>R hand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L hand</td>
</tr>
<tr>
<td>3/R</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>R hand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L hand</td>
</tr>
<tr>
<td>4/R</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>R hand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L hand</td>
</tr>
</tbody>
</table>

Subjects with PD, mean ± SD, No. (n = 18)  

|                                       | 3     | 20 ± 10 | 25 ± 9 | 128 | 110 | ... | ... | ... | ... | ... | ... |

*Begin indicates 8 to 9 AM scores before the first infusion of levodopa and before the levodopa holiday; End, 8 to 9 AM scores before the second infusion of levodopa at end of the levodopa holiday; and Post, 8 to 9 AM scores the day after the second infusion of levodopa. Ellipses indicate not applicable.†UPDRS indicates Unified Parkinson’s Disease Rating Scale motor scores.‡Taps per minute for 8 to 9 AM scores.§0 indicates none; +, mild; and ++, moderate.

Table 3. Response to Infusions of Levodopa  

<table>
<thead>
<tr>
<th>Subject No./Hand*</th>
<th>Infusion†</th>
<th>Baseline,‡ Taps/min</th>
<th>Peak,§ Taps/min</th>
<th>Magnitude,¶ Taps/min</th>
<th>Duration,¶ h</th>
<th>T-Max,# h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/R</td>
<td>1</td>
<td>114</td>
<td>121</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>80</td>
<td>102</td>
<td>22</td>
<td>&gt;10.0</td>
<td>4.0</td>
</tr>
<tr>
<td>2/R</td>
<td>1</td>
<td>195</td>
<td>222</td>
<td>27</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>173</td>
<td>199</td>
<td>26</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>3/L</td>
<td>1</td>
<td>180</td>
<td>195</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>166</td>
<td>176</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4/R</td>
<td>1</td>
<td>118</td>
<td>124</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>120</td>
<td>137</td>
<td>17</td>
<td>&gt;18.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Subjects with PD (n = 18)  

|                                       | 1     | 128 | 149 | 21 | 2.7 | 2.6     |
|                                       | 2     | 110 | 141 | 31 | 3.5 | 2.4     |

*Hand for which tapping speed is indicated.†Infusion 1 was immediately prior to the beginning of the levodopa holiday; infusion 2 marked end of the levodopa holiday.‡Mean of 8 to 9 AM tapping scores before the first infusion of levodopa.§Mean of 3 consecutive highest tapping speeds.¶Difference between peak and base tapping speeds.¶¶Number of hours that tapping speed exceeded base tapping speed by 10%.#T-Max indicates time from beginning of the infusion of levodopa to the peak tapping speed.
effect was slightly delayed in subject 1 but persisted for 10.5 hours when she received an oral dose of levodopa (Figure). Subject 2 had 4.5 hours of greater than 10% improvement in tapping with the administration of levodopa that waned slightly in the evening. The next morning with no further levodopa doses, tapping speed exceeded the previous morning preinfusion baseline by more than 10% (Figure). Subject 3 had a brief improvement in dystonia, but no improvement in tapping with the infusion of levodopa. It was not until the next day and following an additional administration of 10 mg/100 mg carbidopa/levodopa, respectively, dose in the evening that the improvement in tapping speed was evident (Figure). Subject 4 had no response to a 2-hour infusion on day 1, but 5 days later, the same amount of levodopa administered over 6 hours produced a definite response that was even larger the next day despite no additional administration of levodopa (Figure).

For comparison, the mean response to an infusion of levodopa after a 3-day levodopa holiday in 18 subjects with Parkinson disease (PD) receiving long-term levodopa treatment for 1 year is shown in the Figure. The response in subjects with PD differed in that there was a rapid onset of the short-duration response and a rapid return to the preinfusion baseline.

**LONG-DURATION RESPONSE**

The long-duration response is a deterioration in motor function that appears over days on withdrawal of le-
Dopamine treatment in subjects with PD. The 3 subjects receiving long-term levodopa therapy had a decline in tapping speed and reemergence of dystonia over 3 to 8 days without levodopa. The temporal pattern resembled the rate of deterioration of the long-duration response in PD (Table 2 and Figure). Dystonia was primarily in the legs and did not account for the deterioration in tapping speed. The fourth subject, who had not been receiving long-term levodopa therapy, had no deterioration in tapping speed during the GCRC admission suggesting that the slowing of tapping speed in the other subjects was due to levodopa withdrawal.

DIURNAL MOTOR VARIATION

Subjects 1 through 3 reported diurnal variation or sleep benefit was present prior to starting long-term therapy with levodopa and disappeared during levodopa treatment. Diurnal variation reappeared in subjects 1 and 3, manifested by slowing in tapping and severity of dystonia at the end of the day during levodopa withdrawal.

COMMENT

SHORTCOMINGS

It is first worth mentioning the shortcomings of this study. Only 4 subjects with varied clinical manifestations were studied. Clinical scoring of dystonia was not done with a frequency to allow precise determination of time course of this sign. Despite these problems, the patterns of response to levodopa treatment in these 4 subjects were similar and allow tentative conclusions about the levodopa responses in DRD. Finally, we assume that dopamine storage is responsible for differences in levodopa responses between DRD and PD; other factors could also be important.

SHORT-DURATION RESPONSE

Only in subject 2 did the first infusion of levodopa produce a clinically apparent response. The lack of a response to a brief infusion in the other 3 subjects is consistent with the clinical impression that patients with DRD do not have motor fluctuations despite prolonged treatment with levodopa.

The short-duration response to the second infusion in the subjects with PD differed from that of the subjects with PD in several ways. First, the onset of the clinical response to the infusions of levodopa was delayed in subjects 1, 3, and 4. In PD, the response to the infusions of levodopa is generally prompt, and even in de novo subjects, appears within several hours of beginning the infusion. However, the latency to response to levodopa is shorter in fluctuating than in de novo and subjects with stable PD; an observation that has been attributed to loss of dopamine storage capacity. This explanation would be consistent with our findings in subjects with DRD. Development of supersensitivity in subjects with PD is an alternative explanation for shortened latency in more severely affected patients.

Second, the responses of subjects 3 and 4 suggest that in DRD the exposure to levodopa must be longer for its clinical effects to develop. In subject 3, two doses of levodopa and a night’s sleep abolished dystonia and re-established her normal tapping rate. In subject 4, the initial 2-mg/kg dose administered as a 2-hour infusion had no effect but 4 days later, the same dose administered over 6 hours produced an increase in tapping rate. The increase in tapping was even greater the next morning, although she received no further levodopa doses.

Third, the duration of the response to levodopa was prolonged in subjects with DRD after the levodopa holiday. Twenty-four hours after the infusion and with no further administration of oral levodopa, tapping speeds of subjects 2 and 4 had not returned to the baseline rates prior to the infusion. The response in subject 1 lasted at least 10 hours after the second infusion. This is in contrast to PD in which the subjects tapping speed generally returned to the preinfusion baseline within 4 hours after the infusion.

Our results suggest that intact dopamine storage substantially alters the short-duration response to exogenous levodopa treatment. This is consistent with the clinical observations that subjects with DRD require small daily doses of levodopa treatment and rarely develop motor fluctuations and dyskinesia, adverse effects that eventually plague most subjects with PD who respond to levodopa treatment.

LONG-DURATION RESPONSE

The long-duration response to levodopa treatment, a therapeutic action that decays over days after withdrawal of long-term administered levodopa, was apparent in the 3 subjects with DRD who were receiving long-term levodopa therapy. In all, withdrawal of levodopa for 3 to 8 days caused the reemergence of dystonia and slowing in tapping. The rate at which the clinical signs reappeared was similar to the rate at which parkinsonism worsens on withdrawal of levodopa in subjects with PD. Our results confirmed the results of Dewey et al who also found that dystonia reappeared 29 to 38 hours after withdrawal of levodopa treatment in 3 subjects with DRD.

The mechanism underlying the long-duration response is unknown. One hypothesis is that presynaptic dopamine storage is responsible. If this were the case, one might expect that subjects with DRD with intact storage would have a longer long-duration response than would subjects with PD. However, our data and the study results of Dewey et al suggest that this is not the case. Also, the long-duration response was of similar magnitude to that of subjects with PD—certainly not larger as might be postulated if dopamine storage in remaining dopamine nerve terminals was responsible for the long-duration response. These observations implicate a postsynaptic origin for the long-duration response.

Other evidence favors a postsynaptic mechanism for the long-duration response. Ropinirole, a D2 and D3 dopamine receptor agonist, can produce a long-duration response in de novo subjects with PD. Aripiprazole, a D1 and D2 dopamine receptor agonist, can sustain the long-duration response in some subjects with advanced PD in whom levodopa treatment is withdrawn for 3 or 4 days.
SHORT-DURATION VS LONG-DURATION RESPONSES IN DRD

As must be apparent from the discussion above, the concept of a short- and long-duration response in DRD is on less solid footing than in idiopathic PD. In PD, the time courses of the short- and long-duration responses are markedly different and a short infusion of levodopa does not restore the long-duration response. The apparent persistence of the short-duration response into the next day in at least 2 of our subjects with DRD suggests that the motor deterioration with levodopa withdrawal could be just loss of the short-duration response. That is, there is no long-duration response in DRD; decline in motor function with levodopa withdrawal is the wearing off of a prolonged short-duration response in DRD.

Alternatively, one could postulate that there is no short-duration response, just a long-duration response. The slow buildup in the response to levodopa treatment over 24 hours in our subjects with DRD could be superficially consistent with this interpretation. However, development of a long-duration response over 24 hours is much more rapid than what is observed in PD.24,28,30

DIURNAL MOTOR PATTERN

Diurnal motor patterns manifest by declining motor function during the day and improvement by sleep were not apparent in subjects 1, 2, and 3 during long-term levodopa therapy but reappeared in subjects 1 and 3 during the levodopa holiday. This pattern is similar to, but generally more marked than, the diurnal motor pattern seen in PD and identified as sleep benefit.31-33 It suggests that the diurnal motor pattern is a clinical marker of impaired dopaminergic neurotransmission.

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REFERENCES


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