Beginning-of-dose motor deterioration following the acute administration of levodopa and apomorphine in Parkinson's disease

M Merello, A J Lees

Abstract
Six Parkinsonian patients on long term levodopa therapy complained of short-lived deterioration of Parkinsonian symptoms immediately after levodopa intake. After withdrawal of the drug overnight, and following an oral challenge with levodopa/carbidopa (250/25) in all six cases, and with subcutaneous apomorphine (3 mg) in two, deterioration below baseline levels of disability were observed which would not be explained by loss of sleep benefit. This occurred 10–20 minutes after levodopa challenge and lasted for 10–20 minutes. The latency and duration of this phenomenon were shorter with apomorphine but the characteristics were similar. This phenomenon may be due to an inhibitory effect of levodopa acting via presynaptic dopamine receptors.

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Many patients with Parkinson's disease report a worsening of disabilities immediately after each dose of levodopa. This has been attributed to the wearing-off of the previous dose or to end-of-dose motor inhibitory effects. The tendency for many patients to take their doses with meals may also compound this problem, with dietary protein competition leading to absent or delayed therapeutic effect from the next dose. Following the acute subcutaneous administration of apomorphine to treat refractory off-period disabilities, in some patients we have observed a transient worsening of Parkinsonian symptoms before improvement. This study was designed to investigate this phenomenon using acute apomorphine and levodopa challenges in patients with Parkinson's disease receiving long term levodopa therapy.

Patients and methods
Six patients with Parkinson's disease and levodopa-related motor fluctuations who described a clear deterioration after intake of their anti-Parkinsonian therapy were studied. The patients had a mean age of 53.5 years (range 44–60), a mean duration of disease of 13 years (range 7–26) and all were experiencing motor fluctuations and dyskinesias. Four of the patients had biphasic dyskinesias and the remaining two had interdose dyskinesias. Three of the patients were receiving apomorphine subcutaneously in addition to levodopa therapy. The mean daily levodopa dose was 600 mg (range 300–800).

The patients were given 250 mg of levodopa in combination with 25 mg of carbidopa (Sinemet 275) as a single dose in the fasting state after an overnight drug holiday. The motor response was assessed every 10 minutes for the first hour and then every 30 minutes for the next four hours using a modified Webster score, and timed tapping and walking tests. Two patients had two levodopa challenges on different days to confirm reproducibility. In two patients, an acute apomorphine test was also carried out in the fasting state and motor scores were assessed every five minutes until the end of the motor response.

Results
All six patients experienced a transient worsening of their Parkinsonian symptoms following levodopa and apomorphine challenges. The phenomenon was reproducible in the patients who had two levodopa tests. The median delay before the onset of therapeutic improvement following levodopa administration was 30 minutes (range 60–20) and the median duration of the therapeutic effect was 165 minutes (range 40–220). The median delay before motor

<table>
<thead>
<tr>
<th>Patient</th>
<th>Levodopa test</th>
<th>Beginning-of-dose deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency (min)</td>
<td>Duration (min)</td>
</tr>
<tr>
<td>1:1*</td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>1:2*</td>
<td>30</td>
<td>180</td>
</tr>
<tr>
<td>2:1*</td>
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<td>20</td>
<td>220</td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>165</td>
</tr>
<tr>
<td>Range</td>
<td>40</td>
<td>180</td>
</tr>
</tbody>
</table>

*Patients assessed with levodopa.

Table 2 Magnitude of deterioration in the levodopa test during beginning-of-dose deterioration

<table>
<thead>
<tr>
<th>Patient</th>
<th>Topping score (%)</th>
<th>Webster score</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>2</td>
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<td>3</td>
<td>18-7</td>
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<td>4</td>
<td>15-6</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>14-5</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>12-5</td>
<td>2</td>
</tr>
<tr>
<td>Median</td>
<td>17-1</td>
<td>2</td>
</tr>
</tbody>
</table>
Beginning-of-dose motor deterioration following the acute administration of levodopa and apomorphine in Parkinson's disease

Beginning-of-dose deterioration following the acute administration of levodopa and apomorphine in Parkinson's disease. The median scores for the six patients on the Webster score tapping test and walking time after levodopa, showing beginning-of-dose deterioration in all three parameters. The beginning-of-dose deterioration noted in the levodopa test was 10 minutes (range 10–20) and the duration of worsening of symptoms was also 10 minutes (range 10–20). No correlation existed between this early deterioration and the start-up time or duration of benefit from levodopa (table 1).

Motor improvement occurred after a median time of 15 minutes following the subcutaneous injection of 3 mg of apomorphine and the duration of effect lasted for 35 minutes. Initial deterioration in motor response occurred after 3.5 minutes and lasted for 7.5 minutes; again, there was no correlation between these figures and start-up time or duration of motor response to apomorphine.

In the tapping test, a median deterioration of 17.1% (range 12.5–50%) for the levodopa and 18.6% for the apomorphine test occurred during the period of deterioration (table 2); in addition, two patients became unable to walk. Figures 1 and 2 show the median of tapping times. Webster scores and walking speeds.

During the test three patients also exhibited end-of-dose motor inhibitory effects, two had interdose dyskinesias and four biphasic dyskinesias. There was no correlation between the timing of the initial motor deterioration and the onset of biphasic dyskinesias. Figure 3 shows the relationship between the increase in tremor which was the main component of the beginning-of-dose motor deterioration in one patient and the onset of biphasic dyskinesias.

Discussion
We believe that beginning-of-dose motor deterioration lasting for 10–20 minutes may be a

Figure 1 Median scores for the six patients on the Webster score tapping test and walking time after levodopa, showing beginning-of-dose deterioration in all three parameters.

Figure 2 Scores for two patients on the Webster score tapping test and walking time after apomorphine challenge, showing beginning-of-dose deterioration in all three parameters.
common and under-reported phenomenon, probably because it is not easy to demonstrate objectively. In some of the patients, deterioration was striking and apparent to both the patient and observer. Deterioration in the motor assessments was also considered to be significant. Two baseline motor examinations were carried out before each challenge test and there was no suggestion of deterioration between the first and second observation, making it improbable that the observed phenomenon was due to sleep benefit wearing off. We also studied a further six patients who did not complain of beginning-of-dose deterioration and were unable to demonstrate the phenomenon. No obvious clinical differences were seen between the two groups.

End-of-dose motor deterioration has been studied carefully but beginning-of-dose motor deterioration, although postulated as likely to occur, has not been specifically studied before. Biphasic motor responses to dopaminergic agonists are well recognised in preclinical studies. It is possible that the motor inhibition may be due to selective autoreceptor activation on the terminals of the surviving nigrostriatal neurons at subthreshold levodopa doses. This may explain the use of small doses of dopamine receptor agonist drugs to improve chorea and psychosis. Dopamine receptor agonists such as apomorphine and bromocriptine cause biphasic yawning in rats, indicating differential presynaptic and postsynaptic temporal activation. The fact that apomorphine caused inhibitory responses similar to levodopa suggests that the formation of levodopa metabolites is not likely to be responsible for “pre-improvement worsening”.

The increasing use of continuous dopaminergic stimulation in the management of refractory on-off oscillations may represent the best strategy for attempting to overcome biphasic motor deteriorations related to pharmacokinetic properties of levodopa.


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