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

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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 base line levels of disbility 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.

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[1] or to end-of-dose motor inhibitory effects.[2] 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.[3] Following the acute subcutaneous administration of apomorphine[4] 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.[4] 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 1 Delay and duration of therapeutic effect of levodopa and begining-of-dose motor deterioration

Patient	Levodopa test		Beginning-of-dose deterioration	
	Latency (min)	Duration (min)	Latency (min)	Duration (min)
1·1*	60	180	20	20
1·2*	30	180	10	10
2·1*	50	180	10	20
2·2*	20	220	10	10
3	40	150	20	10
4	30	90	10	10
5	20	100	10	10
6	40	40	10	20
Median	30	165	10	10
Range	40	180	10	10

*Patients reassessed with levodopa.

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

Patient	Tapping score (%)	Webster score
1	50	3
2	50	2
3	18·7	2
4	15·6	1
5	14·5	2
6	12·5	2
Median	17·1	2

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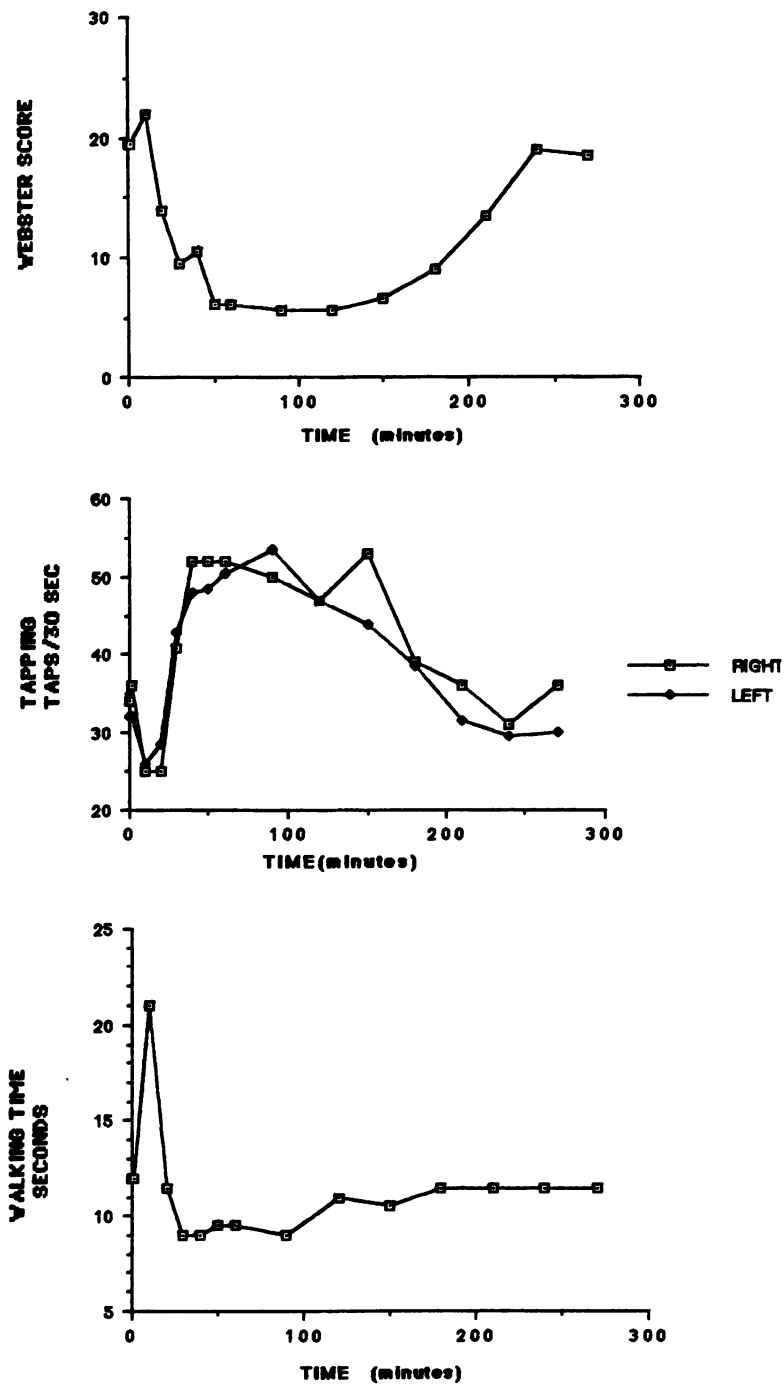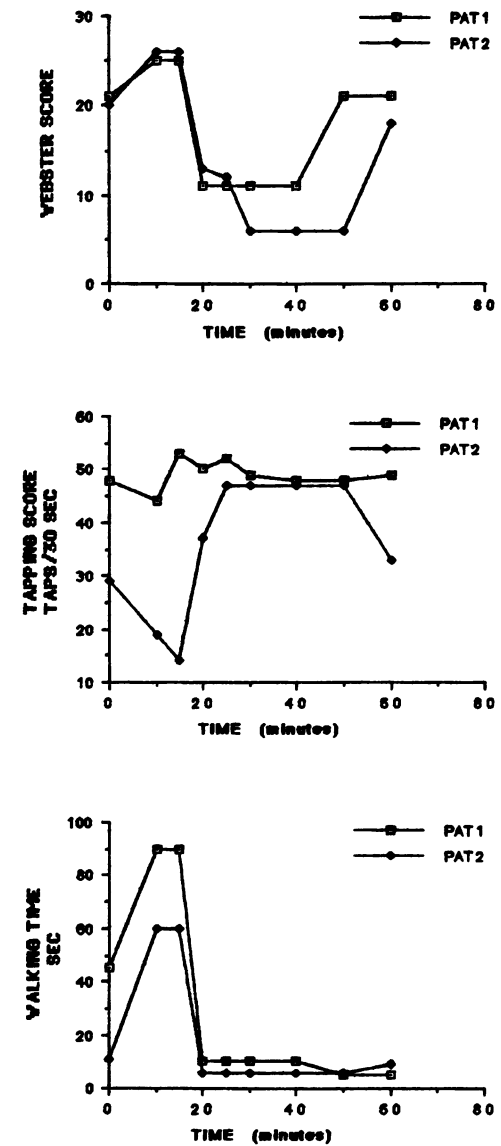
Figure 1   Median scores for the six patients on the Webster score tapping test and walking time after levodopa, showing beginning-of-dose deterioration in all three parameters.

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.
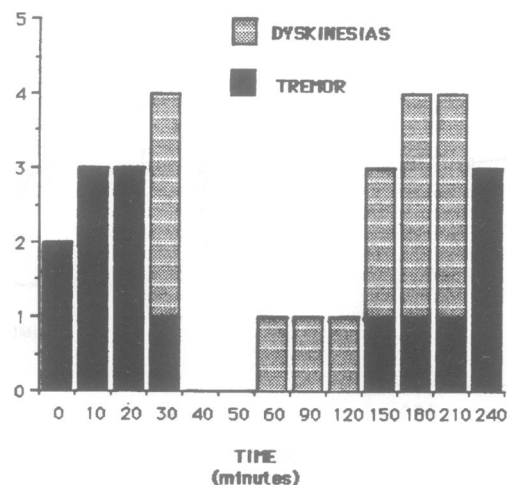
In the tapping test, a median deterioration of 17·1% (range 12·5–50%) for the levodopa and 18·6% for the apomorphine test occurred during the period of deterioration (table 2); in addition, two patients became unable to walk. Figures 1 and 2 show the median of tapping times. Webster scores and walking 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 3 Relationship between the appearance of tremor (the main component of beginning-of-dose deterioration) and biphasic dyskinesias in one patient after acute levodopa administration.

chorea and psychosis.[10][11][12][13] Dopamine receptor agonists such as apomorpine and bromocriptine causes biphasic yawning in rats, indicating differential presynaptic and postsynaptic temporal activation.[14] The fact that apomorphine caused inhibitory resposes similar to levodopa suggests that the formation of levodopa catabolites is not likely to be responsible for "pre-improvement worsening".[5]

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.

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[2] but beginning-of-dose motor deterioration, although postulated as likely to occur, has not been specifically studied before.[2][5]

Biphasic motor responses to dopaminergic agonists are well recognised in preclinical studies.[6] 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.[7][8][9] This may explain the use of small doses of dopamine receptor agonist drugs to improve

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