Journal of Neurology, Neurosurgery, and Psychiatry 1996;**61**:634–637

Motor response to acute dopaminergic challenge with apomorphine and levodopa in Parkinson's disease: implications for the pathogenesis of the on-off phenomenon

Carlo Colosimo, Marcelo Merello, Andrew J Hughes, Katarzyna Sieradzan, Andrew J Lees

Abstract

***Objectives*—To evaluate the contribution of postsynaptic changes to motor fluctuations, three groups of parkinsonian patients with differing responses to treatment were acutely challenged with two dopaminergic drugs—apomorphine and levodopa—having different mechanisms of action.**

***Methods*—Forty two patients with Parkinson's disease (14 untreated, eight with a stable response to levodopa, and 20 with levodopa induced motor fluctuations) were challenged on two consecutive days with apomorphine and levodopa. The latency, duration, and magnitude of motor response was measured.**

***Results*—A progressive shortening of mean latency after levodopa challenge was found passing from the untreated to the stable and fluctuating groups; the difference between untreated and fluctuating patients was statistically significant ($P < 0{\cdot}01$). Response duration after levodopa challenge was similar in untreated and stable patients, whereas it showed a significant shortening in patients with motor fluctuations ($P < 0{\cdot}05$ *v* both untreated and stable patients). When subcutaneous apomorphine was given, untreated patients had a longer response duration than those who had developed motor fluctuations ($P < 0{\cdot}05$). Although baseline disability was significantly greater in the fluctuating patients than in the untreated and stable patients, the severity of residual parkinsonian signs after both apomorphine and levodopa challenge was similar for all three groups; as a result, the degree of improvement in parkinsonian signs after dopaminergic stimulation was substantially greater in more advanced than in early cases. Linear regression analysis also indicated that latency and duration after apomorphine challenge did not significantly correlate with those after levodopa challenge, whereas magnitude of response to apomorphine showed a strong positive correlation with that after levodopa challenge ($r = 0{\cdot}9$, $P < 0{\cdot}001$).**

***Conclusion*—The progressive shortening of motor response after both apomorphine and levodopa suggests that pharmacodynamic factors play an important part in determining the duration of motor response and argue against altered central pharmacokinetics of levodopa being principally responsible for the *on-off* effect. The widening response amplitude and increasing *off* phase disability occurring during disease progression are also critical factors in determining the appearance of motor fluctuations.**

(*J Neurol Neurosurg Psychiatry* 1996;**61**:634–637)

Keywords: apomorphine; levodopa; on-off effect; Parkinson's disease

Department of Neurology, Middlesex and University College Hospitals, London, UK
C Colosimo
M Merello
A J Hughes
K Sieradzan
A J Lees

Correspondence to:
Dr Andrew J Lees, Department of Neurology, The Middlesex Hospital, Mortimer Street, London W1P 8AA, UK.

Received 14 August 1995
and in revised form
29 January 1996
Accepted 23 February 1996

The pathophysiology of levodopa related motor fluctuations remains poorly understood[1] with peripheral pharmacokinetic factors unable to provide a complete explanation for the oscillating response elicited in more than 70% of parkinsonian patients after more than five years of treatment.[2] Chase and colleagues initially proposed that the basic mechanism underlying fluctuations in Parkinson's disease was a presynaptic defect in buffering the variations in plasma levodopa concentrations.[3 4] The same group subsequently noted that the occurrence of postsynaptic receptor abnormalities in advanced Parkinson's disease may also influence the pattern of therapeutic response to levodopa.[5] The relative importance of presynaptic events and postsynaptic receptor changes in the mechanisms underlying the on-off phenomenon is not known.[6–8]

To evaluate the contribution of postsynaptic changes to clinical fluctuations, 42 parkinsonian patients with differing responses to treatment were acutely challenged with two dopaminergic drugs, apomorphine and levodopa. Apomorphine is a dopamine receptor agonist that does not require metabolic conversion to a pharmacologically active metabolite and which has an activity that depends on the integrity of striatal dopamine receptors. On the other hand, levodopa, the natural precursor of dopamine, is a "prodrug" and relies also on the presence of dopa decarboxylase in surviving dopaminergic terminals. The different pharmacological action of these two agents provides clinical opportunities for exploring the mechanisms which underlie levodopa induced motor fluctuations.

Patients and methods

Forty two patients participated in the study, all of whom met the UK Parkinson's disease Society Brain Bank clinical diagnostic criteria

Table 1 Clinical features of the three groups

	Untreated (n = 14)	*Stable (n = 8)*	*Fluctuating (n = 20)*
M/F	11/3	5/3	14/6
Age (y)	52·6 (11·2)	66·5 (10·0)	60·5 (10·2)
Duration (y)	2·1 (0·9)	8·5 (5·5)	12·8 (6·2)
Hoehn and Yahr (on-off conditions)	2·0 (0·6)	2·5 (0·9)	3·2 (0·6)
Levodopa (mg)	0	557·0 (372·4)	715·1 (445·3)

for idiopathic Parkinson's disease.[9] They were divided into three groups: 14 who had never received levodopa or other antiparkinsonian drugs, eight who were showing a stable response to levodopa, and 20 who had developed clear levodopa related motor fluctuations. Table 1 summarises their clinical features. All except one of the stable patients were taking four doses or less of levodopa a day, one was also taking bromocriptine and one was taking selegiline. One patient, a 59 year old man, was being given monotherapy with 70 mg of bromocriptine a day and reported a stable and satisfying response to this drug. Among the 20 fluctuating patients, all on long term levodopa treatment, nine were also receiving subcutaneous apomorphine (by an infusion pump in five cases and intermittent injections in the remaining four), two bromocriptine, one pergolide, one benzehexol, and three selegiline.

The therapeutic response to a single subcutaneous dose of apomorphine (3 mg) and oral dose of levodopa (250 mg plus carbidopa (25 mg)) was measured on two consecutive days. All patients were pretreated with domperidone, a peripheral dopamine receptor antagonist (20 mg thrice daily) during the previous 48 hours and were evaluated in the fasting state after an overnight drug free period, starting each study at 9·00 am. Clinical scoring was carried out at baseline and at 10 minute intervals after apomorphine and 15 minute intervals after levodopa, or at any time during the experiment when the examiner considered that a significant modification in motor state had occurred. The following items were used to assess motor function: (*a*) the time required to rise from an armless chair, walk 6 metres, turn, return to chair, and sit down; (*b*) the number of times the patient could alternately tap two keys placed 30 cm apart in 30 seconds with the more affected hand (mean of two attempts): (*c*) a modified Webster rating score.[10] A variation in tapping exceeding 15%, in walking speed exceeding 20%, or a change in the Webster score greater than 3 points were the criteria adopted to define a significant change in motor function.[11] Latency of motor response was defined as the interval between the time of giving the drug and the time when a significant clinical modification was first noted. Duration of motor response was measured as the interval between the beginning of the response and its clinical end point (the time when patients returned to their prechallenge score). Amplitude of motor response was defined as the difference between Webster score at the time of the peak effect (Webster *on*) and the baseline score (Webster *off*).

The latency, duration, and amplitude of motor response to apomorphine and levodopa were compared in the three groups of patients. Data were evaluated statistically for each drug by analysis of variance (ANOVA) with post hoc analysis (unpaired Student's *t* test) when ANOVA indicated significant differences among means. Linear regression analysis was used to examine correlations between latency, duration, and amplitude of the pharmacological response to the two drugs across the three patient groups. Values are expressed as means (SD).

Table 2 Latency and duration (min) of the motor response after acute challenge with apomorphine and levodopa

	Apomorphine		*Levodopa*	
	Latency	*Duration**	*Latency***	*Duration†*
Untreated	12·3 (3·8)	79·1 (34·0)	46·6 (17·0)	230·4 (46·2)
Stable	9·9 (2·9)	67·9 (26·2)	40·5 (15·5)	229·4 (42·2)
Fluctuating	11·9 (4·7)	57·3 (22·0)	33·5 (11·8)	194·5 (45·6)

Values are means (SD).
*P < 0·05; **P < 0·01: ANOVA, untreated *v* fluctuating.
†P < 0·05: ANOVA, untreated *v* fluctuating and stable *v* fluctuating.

Table 3 Webster motor score (mean (SD)) before and after acute challenge with apomorphine and levodopa

	Apomorphine		*Levodopa*	
	*Off***†*	*On*	*Off****	*On*
Untreated	11·0 (3·5)	6·7 (3·5)	10·6 (3·5)	6·7 (3·5)
Stable	13·8 (8·4)	9·0 (5·9)	16·7 (9·3)	10·1 (7·0)
Fluctuating	21·2 (5·8)	7·5 (3·6)	21·4 (6·3)	7·6 (3·6)

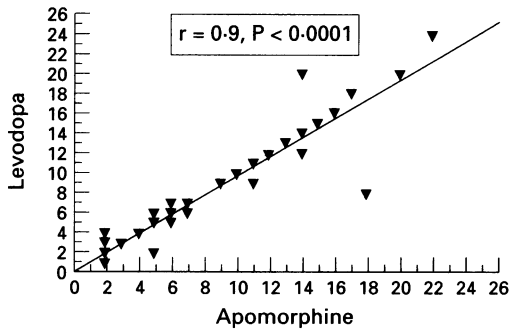
*P < 0·001 ANOVA for difference between untreated and fluctuating and p < 0·05 for difference between stable and fluctuating.
***P < 0·001, ANOVA: untreated *v* fluctuating.
†P < 0·05, ANOVA: stable *v* fluctuating.

Results

Between group analysis

A progressive shortening of mean latency after levodopa challenge was noted, passing from the untreated to the stable and fluctuating groups: the difference between untreated and fluctuating patients was statistically significant (P = 0·01). On the other hand, no difference was found in response latency between the three groups during acute challenge with apomorphine. Duration of response after acute challenge with levodopa was similar in untreated and stable patients, whereas it showed a significant shortening in patients with motor fluctuations (P < 0·05 *v* both untreated and stable patients). Duration of motor response after apomorphine challenge was also significantly longer in untreated patients than in fluctuating patients (P < 0·05). No significant differences were recorded between untreated *v* stable, and stable *v* fluctuating patients (table 2).

The amplitude of motor response showed significant variations within the patient groups. Indeed, the severity of residual parkinsonian signs after both levodopa and apomorphine challenge (Webster *on*) did not differ. As there was a progressive increase in baseline parkinsonian score (Webster *off*) passing from untreated and stable to fluctuating patients (P < 0·001 and P < 0·05 respectively), the degree of improvement in parkinsonian signs after dopaminergic stimulation was substan-



Linear regression showing correlation between magnitude of motor response to levodopa and response to apomorphine.

tially greater in fluctuating than in stable and untreated cases (table 3). Mean improvement in Webster score averaged 39·1% in untreated, 30·8% in stable, and 74·3% in fluctuating patients after apomorphine challenge, and 36·8% in untreated, 39·5% in stable, and 74·5% in fluctuating patients after levodopa challenge.

CORRELATIONS BETWEEN RESPONSES TO APOMORPHINE AND LEVODOPA

Linear regression analysis indicated that motor response latency and duration after apomorphine challenge did not significantly correlate with those after levodopa challenge ($r = 0·2$, $P = 0·2$, and $r = 0·1$, $P = 0·6$ respectively), whereas magnitude of response to apomorphine was strongly correlated with that occurring after levodopa challenge ($r = 0·9$, $P < 0·0001$, figure). This means that in the single patient the modifications after apomorphine challenge are predictive of the magnitude, but not of the latency and duration of the clinical effect after levodopa challenge.

Discussion

It has been suggested that motor fluctuations in Parkinson's disease may result from progressive loss of striatal dopamine terminals with increasingly impaired dopamine storage capacity.[3 4] This hypothesis predicts a shorter response to single levodopa doses in the group of patients with fluctuations compared with patients either showing a stable response to levodopa or who had never been treated with this drug, but would predict no shortening in duration of motor response to a direct dopamine receptor agonist, such as apomorphine, with a pharmacological action that is not dependent on the integrity of the nigrostriatal pathway.[12]

Our study is the first comparing the motor response latency, duration, and amplitude after acute challenges with both apomorphine and levodopa in the same groups of patients. A significant difference was recorded in the duration of response for untreated and stable versus fluctuating cases after the levodopa test; but, previously untreated patients also had a longer duration of response to apomorphine than patients with response fluctuations related to levodopa.

Thus the development of a fluctuating response is not only accompanied by a major change in the duration of response to levodopa, but also by a change in response to apomorphine. This suggests that pharmacokinetic factors are not the main event in the pathophysiology of motor fluctuations and that factors other than an impaired capacity to store and release dopamine are involved. Support for this derives also from the finding that the response to individual doses of levodopa is not shorter on the more affected side in asymmetrically affected patients with Parkinson's disease[13] and from the difference in motor decay after apomorphine infusions in groups of parkinsonian patients comparable with the present study.[5] The presence of a progressive shortening in duration of response not only after levodopa but also after apomorphine challenge suggests that modifications of striatal dopaminergic receptor function are mainly involved.

Our results relating to motor response duration are broadly in agreement with most previous studies,[3-6 8 14-16] but most of these used either levodopa or apomorphine, and it is difficult to make comparisons directly. Differences may be partly explained by selection criteria (definition of stable and fluctuating cases) and different methods in testing response to levodopa (oral *v* parenteral treatment, brief *v* prolonged infusions, high *v* low doses). Moreover, the evaluation of motor responses in mildly disabled untreated patients is not easy and it may vary considerably from one examiner to another. Despite this, our findings with apomorphine confirm the importance of pharmacodynamic receptor modifications in determining the shortening of motor response and contributing to the onset of motor fluctuations. A modest down regulation of striatal dopamine receptors in parkinsonian patients on long term levodopa treatment has been shown by in vivo[17 18] and neurochemical pathological studies.[19]

We also found that the onset of a levodopa effect occurred earlier in fluctuating patients, in agreement with two other studies,[8 20] but by contrast with another clinical report, which reported a delayed "start up" time in fluctuating patients.[21] The decreased response latency to levodopa in patients with advanced Parkinson's disease may be related to the compensatory acceleration in dopamine synthesis and turnover due to the progressive loss of nigrostriatal dopaminergic neurons.[20] The development of tolerance to the inhibitory effect of levodopa on gastric emptying is another possible explanation for its more rapid absorption (and effect) after chronic use.[22]

Although the mean duration of the motor effect to a single dose of levodopa decreases with progression of disease, the mean difference is not great, and there is considerable overlap between groups at different stages of disease. The widening response amplitude and increasing *off* phase disability occurring during disease progression is therefore probably a critical factor in determining the appearance of motor fluctuations. The presence of a clear short duration response to both apomorphine and levodopa in most untreated patients with Parkinson's disease might indicate that motor fluctuations are present from the beginning of

treatment, but because the amplitude of motor response is relatively small at this stage it may escape notice by the patient and physician[7]: disease progression would then render fluctuations more evident over time. Support for this comes from the finding that in the same cohort of patients followed over time there is relatively little reduction in the response duration to levodopa[23] and that fluctuations appear early in patients with parkinsonism induced by 1-methyl-4-phenyl, 1, 2, 3, 6 tetrahydropyridine (MPTP) and postencephalitic parkinsonism when the onset is acute and the disease is severe from the beginning.[24 25]

In conclusion, the progressive shortening of motor response after both apomorphine and levodopa suggests that pharmacodynamic factors play a major part in determining duration of motor response and argue against altered central pharmacokinetics of levodopa as being the main event responsible for the fluctuating response. Our finding also emphasises the role of a widening response amplitude and increasing *off* phase disability during disease progression. These findings raise the possibility that the use of continuous as opposed to pulsatile waking day dopaminergic stimulation might avoid some of the long term pharmacodynamic effects seen with oral levodopa treatment.[26 27]

CC was funded by the European Science Foundation, AJH by the UK Parkinson's Disease Society. We are indebted to M Fiorelli for his statistical advice.

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