Effect of entacapone, a peripherally acting catechol-O-methyltransferase inhibitor, on the motor response to acute treatment with levodopa in patients with Parkinson's disease

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Abstract

Catechol-O-methyltransferase (COMT) inhibitors may be useful in the treatment of Parkinson's disease by improving the bioavailability of levodopa and by prolonging its effects. Entacapone (OR-611), a novel COMT inhibitor, which does not cross the blood brain barrier, was assessed in 12 patients with Parkinson's disease and motor fluctuations in a randomised, double-blind, cross-over, single dose study. The magnitude and duration of the therapeutic response to a single dose of 200 mg levodopa/50 mg carbidopa was evaluated after concomitant placebo, or 200 or 800 mg entacapone. A significant increase in the duration of the motor response to levodopa was seen when 200 mg entacapone was given with levodopa/carbidopa. Plasma levodopa concentrations were increased with both doses of the COMT inhibitor. The latency to onset of motor response did not differ significantly between active drug and placebo. Entacapone may prove useful in prolonging the duration of the benefit obtained from individual doses of levodopa.

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Catechol-O-methyltransferase (COMT) is an important enzyme involved in the peripheral and central metabolism of dopamine.¹ In the central nervous system it is believed to exert its major action in the synaptic cleft.

When decarboxylation of levodopa is blocked by peripheral dopa decarboxylase inhibitors (DCIs), O-methylation becomes the most prominent pathway of levodopa catabolism² and leads to the accumulation of 3-O-methyldopa. It has been suggested that 3-O-methyldopa may impair the transport of levodopa across the blood brain barrier and compete with levodopa for decarboxylation within the brain.³⁻⁵ It has also been proposed that accumulation of 3-O-methyldopa may be a causal factor in the development of motor fluctuations in Parkinson's disease.⁶ This theory, however, has been challenged. The plasma concentrations of 3-O-methyldopa causing a deleterious effect on the clinical response to levodopa in parkinsonian patients are much higher than those found during long term levodopa decarboxylase inhibitor

treatment.⁷⁻¹⁰ The oral bioavailability of levodopa is low due to first pass metabolism which is at least partly due to the high activity of COMT in the gut and liver.^{11 12} The combination of a peripheral COMT inhibitor with levodopa/DCI therapy might therefore produce a smoother and more prolonged motor response in patients with Parkinson's disease.^{13 14} As early as in 1971 Ericsson¹⁵ reported beneficial effects with a COMT inhibitor with concomitant reduction in levodopa-induced dyskinesias. More recently, a new generation of COMT inhibitors have been developed, which are much more potent and specific.^{13 14 16-20} Fluorodopa positron emission tomography (PET) studies in monkeys and patients with Parkinson's disease have also shown that peripheral COMT inhibitors increase striatal fluorodopa uptake.²¹⁻²³

Entacapone (OR-611) is a highly selective and potent nitrocatechol-structured COMT inhibitor that penetrates the brain poorly, acting mainly in the gut. In animal models of Parkinson's disease, entacapone potentiated and prolonged the therapeutic effect of levodopa in a dose-dependent manner.^{24 25}

We have studied the motor response and pharmacokinetics of levodopa in 12 patients with Parkinson's disease and severe motor fluctuations after acute levodopa challenge alone or in combination with two different entacapone doses.

Materials and methods

Twelve patients from the Department of Neurology, University College and Middlesex Hospitals, London treated with levodopa (11 men and one woman, mean age 58.5 (range 46-71) years), mean duration of disease 14.7 (range 8-24) years), mean daily levodopa dose 1183 (range 300-4250) mg agreed to participate. The patients were informed about the objectives and design of the study, and informed consent was obtained. The study was approved by the Ethics Committee of the Faculty of Clinical Sciences, University College School of Medicine, London.

All patients fulfilled the United Kingdom Parkinson's Disease Brain Bank clinical diagnostic criteria for idiopathic Parkinson's disease²⁶ and had a clear response to an acute challenge with levodopa. Patients with secondary parkinsonism, severe dementia, unstable cardiac, renal, pulmonary, or gastrointestinal

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disease, and women of childbearing age were excluded. Those patients receiving drugs for treating parkinsonism other than levodopa continued on these unchanged throughout the study.

The magnitude and duration of the therapeutic response of a single dose of 200 mg levodopa in combination with 50 mg carbidopa (two tablets of Sinemet plus, Merck, Sharp, and Dohme) were evaluated after concomitant administration of placebo, or 200 or 800 mg entacapone (Orion Pharmaceutica, Espoo, Finland). The pharmacokinetics and metabolism of levodopa were also studied. The study followed a double-blind, cross-over design and the order of medication was randomised.

The single doses of levodopa/carbidopa and study drugs (entacapone/placebo) were given simultaneously at 8.00 am in the fasting state after an overnight drug holiday.

Clinical scoring was carried out at 15–30 minute intervals from 7.30 am to noon. If the drug effect persisted after the noon rating, assessments were continued at 30-minute intervals until motor scores had returned to baseline. The motor function was assessed by (1) a tapping test—the number of times the patient could alternately tap two laboratory counters 20 cm apart in 30 s with the more severely affected hand; (2) a walking test—the time required to rise from an armless chair, walk 6 m, turn, and sit down (cut off time 30 s); (3) a 5-point dyskinesia scale; and (4) an overall global score (−4 = severe, disabling symptoms to 0 = normal to +4 = severe disabling dyskinesia). The criteria used to assess the duration of response and the time to “switch off” have been previously described.²⁷

Plasma concentrations of levodopa, 3-O-methyldopa, and the dopamine metabolites dihydroxyphenyl acetic acid and homovanillic acid were measured by high performance liquid chromatography (HPLC).²⁸

STATISTICS

For each clinical variable, the mean duration of the difference of the means and the mean of the maximum values for each patient in each treatment sequence were compared by

the Wilcoxon rank test. Statistical analysis of the plasma concentrations was carried out with analysis of variance and the Newman-Keuls test.

Results

CLINICAL RESPONSE

The latency to peak motor response was not significantly different between the three trial days, but the duration of effect when entacapone was administered with levodopa was increased by a mean of 34.5 minutes (200 mg) and 39 minutes (800 mg), respectively, compared with the placebo day (table). The difference in the duration between the placebo and 200 mg days was statistically significant ($p < 0.05$) by paired t test, but significance was not quite reached between the placebo and 800 mg day due to a larger variation in response (table). When 200 mg of entacapone was used, the overall scores for tapping ($p < 0.05$), dyskinesias ($p < 0.005$), and global score ($p < 0.05$) were significantly higher and the walking time significantly lower ($p < 0.05$) than on the placebo day (figs 1a and b). The global score with 200 mg of entacapone was also higher ($p < 0.05$) than with 800 mg, but no statistically significant differences were found between the placebo day and the 800 mg day when maximum values were compared (fig 1b). The 800 mg dose of entacapone gave a higher peak score for dyskinesias than placebo ($p < 0.05$). The maximum tapping score with 200 mg entacapone was significantly higher than with 800 mg ($p < 0.05$; fig 1a).

Two patients showed a biphasic motor response when they received 800 mg entacapone (table). Pronounced waning of the motor response was followed in these patients by a second spontaneous motor improvement lasting 45 to 60 minutes. These findings are not included in the statistics. Patient 6 did not “switch on” at all either with placebo or with 800 mg of entacapone. Patient 7 also failed to “switch on” with 800 mg of entacapone. These patients are not included in the calculation of the latency and duration of the motor response to levodopa. By contrast, all the patients on 200 mg entacapone

Table Motor response (time in minutes)

Placebo	Entacapone					
	200 mg		800 mg			
Patient	Latency	Duration	Latency	Duration	Latency	Duration
1	105	120	45	195	30	360
2	105	105	75	120	60	150
3	60	165	60	240	45	105
4	45	165	45	180	60	270
5	45	165	45	225	90	90
6†	NR	NR	60	60	NR	NR
7†	45	90	120	45	NR	NR
8	30	150	45	180	75	210
9	75	105	30	60	120	105
10	30	180	45	225	30	210
11	105	30	90	60	105	60
12	60	105	60	150	90	120
Mean (SD)	66 (30.17)	129 (45.39)	54 (17.61)	163.5 (65.36)*	70.5 (30.86)	168 (93.75)

* $p < 0.01$ v placebo.

†These patients are not included in the statistical analysis.

NR = No response.

Figure 1 Curves of the means of different clinical variables in 12 patients after acute administration of levodopa plus placebo or 200 or 800 mg entacapone. (A) Number of taps in 30 s with the more disabled hand; (B) global score. (□) placebo; (△) entacapone 200 mg; (○) entacapone 800 mg.

Figure 2 Means of the plasma concentrations for (A) levodopa and (B) homovanillic acid (HVA). (○) placebo; (■) entacapone 200 mg; (□) entacapone 800 mg.

showed clinical benefit and 10 out of 12 patients given 200 mg entacapone had a duration of motor response longer than that found with placebo.

SAFETY

Routine clinical haematological and biochemical variables did not change significantly during the study. No adverse events were reported but a transient strong orange colouration to the urine was seen in many patients, probably due to entacapone.

PHARMACOKINETIC ANALYSIS

Entacapone significantly delayed the fall in plasma levodopa concentrations ($p < 0.05$). The higher dose also delayed the attainment of peak plasma levodopa concentrations but neither 200 nor 800 mg entacapone increased the magnitude of the levodopa peak (fig 2a). The plasma dihydroxyphenyl acetic acid concentrations were significantly increased and the homovanillic acid concentrations reduced ($p < 0.01$) with 800 mg of entacapone, but not with 200 mg (fig 2b). Plasma 3-O-methyldopa concentrations were not significantly different during the three days of the trial.

Discussion

Levodopa pharmacokinetics play an important part in determining the duration of the motor response in Parkinson's disease.^{2,9,28,29} Peripherally acting COMT inhibitors, by preventing conversion of levodopa to 3-O-methyldopa, might therefore provide a means of extending the duration of motor benefit from individual levodopa doses. The two novel peripherally acting COMT inhibitors do not significantly alter striatal COMT activity in animal studies.^{16,25} They also seem to be much less toxic than the first generation COMT inhibitors (Gallates, Tropolone, U-0521).^{13-15,30} The first studies in normal healthy subjects indicate that nitecapone and entacapone should be safe.^{19,20,31-34} At the present time it is unclear whether a COMT inhibitor with both peripheral and central effects would confer any greater therapeutic benefit, or whether it could be safely used in combination with monoamine oxidase inhibitors.³⁵

The mean increase of about 30% in the duration of motor response (129 minutes to 163 and 169 minutes) after entacapone intake is appreciable when compared with that reported for selegiline³⁶ or sustained release levodopa formulations in acute dose studies.³⁷ If these findings could be reproduced with chronic repeated dosing of entacapone, a further 30 minute motor improvement from each levodopa dose could result in up to two to four hours more waking mobility each day in parkinsonian patients. This may also permit a reduction in the requirement in the total daily dose of levodopa.

Patients receiving entacapone had somewhat more dyskinesias indicating increased bioavailability of levodopa to the brain and providing clinical support for the PET studies, which have shown increased striatal fluorodopa uptake.²¹⁻²³

In previous studies we have found that patients "switched off" when plasma levodopa concentrations fell to around half the peak values in an individual patient.²⁸ If this is applied to the present study, however, a somewhat greater prolongation of motor response with entacapone would have been predicted than that found. The recorded motor response and the plasma levodopa

concentrations correlated closely. No difference in peak plasma concentrations of levodopa were found between placebo and entacapone, but the slopes of the curves were more gradual and at four hours after giving levodopa plasma concentrations were significantly higher with 200 and 800 mg of entacapone. This is in accordance with results in animals and healthy volunteers.^{20 25 34 38} The delay in the attainment of peak plasma levodopa concentrations with 800 mg entacapone might be explained by interference with levodopa absorption in the gut.

The two patients who failed to "switch on" with placebo or 800 mg entacapone normally took 500 mg levodopa in the morning instead of the standard 200 mg dose used in this study. The fact that 200 mg entacapone with 200 mg levodopa "switched them on" might indicate possible levodopa sparing effects. Both patients had very high 3-O-methyldopa concentrations.

The lower concentrations of the O-methylated and deaminated catabolite of dopamine, homovanillic acid, on both entacapone days and the increased production of the deaminated metabolite, dihydroxyphenyl acetic acid, provide confirmatory evidence that entacapone systematically reduces COMT activity. The finding that these effects were greater with 800 than with 200 mg entacapone implies that COMT inhibition was dose related, even if the improvement in motor response to levodopa was not.

The plasma concentrations of 3-O-methyldopa in patients on chronic levodopa DCI therapy are very high and the half life of 3-O-methyldopa is long (15–16 hours) compared with levodopa (one hour).² Therefore plasma concentrations of 3-O-methyldopa should not be reduced by a single dose of entacapone. To reduce the plasma concentrations of 3-O-methyldopa chronic COMT inhibition would be required.

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