Journal of Neurology, Neurosurgery, and Psychiatry, 1973, **36**, 10–14

Treatment of Parkinson's disease with levodopa combined with L-alpha-methyldopahydrazine, an inhibitor of extracerebral DOPA decarboxylase

C. D. MARSDEN, P. E. BARRY, J. D. PARKES, K. J. ZILKHA

From the University Department of Neurology, Institute of Psychiatry, and King's College Hospital, London

SUMMARY Thirty patients with Parkinson's disease were treated for four weeks with levodopa combined with an inhibitor of extracerebral dopa decarboxylase, L-alpha-methyldopahydrazine (MK 486). The therapeutic results were compared with the effects of treatment of a group of 40 patients with levodopa alone. Patients treated with the combined therapy improved more rapidly, had less nausea and vomiting, and required a much smaller dose of levodopa than patients treated with levodopa by itself.

Levodopa is the best treatment available for Parkinson's disease, but it takes weeks or months of treatment to achieve the maximum improvement and about one quarter of patients gain no benefit or cannot tolerate the drug. Dose limiting side-effects are common, occurring in about 75% of patients. Nausea and vomiting, involuntary movements, psychiatric disturbances, postural hypotension, and cardiac arrhythmias often limit or prohibit effective treatment.

The therapeutic effect of levodopa is thought to be due to its conversion to dopamine in the brain, thus reversing the depletion of this catecholamine in the corpus striatum of patients with Parkinson's disease. Dopamine given parenterally does not enter the brain; most of an oral dose of levodopa does not reach the brain parenchyma, for it is converted into dopamine and other metabolites outside the brain. This extracerebral formation of dopamine and other catecholamines may be responsible for some of the side-effects of levodopa treatment and considerably reduces the amount of levodopa available to the brain cell.

The enzyme dopa decarboxylase is responsible for the conversion of levodopa to dopamine both in the brain and in extracerebral tissues such as gut wall, heart, kidney, and cerebral capillaries. Drugs that preferentially inhibit extracerebral decarboxylase have been developed (Udenfriend, Zaltman-Nirenberg, Gordon, and Spector, 1966; Bartholini, Burkard, Pletscher, and Bates, 1967) and used in an attempt to improve the therapeutic response to levodopa (Birkmayer, 1969; Siegfried, Ziegler, Regli, Fischer, Kaufmann, and Perret, 1969; Tissot, Gaillard, Guggisberg, Gauthier, and Ajuriaguerra, 1969; Barbeau, Gillo-Joffrey, and Mars, 1971; Calne, Reid, Vakil, Rao, Petrio, Pallis, Gawler, Thomas, and Hilson, 1971). As these drugs do not readily enter the brain, their inhibitory action is mainly peripheral and they do not significantly affect intracerebral dopamine formation from levodopa.

We report here our experience of the use of a combination of levodopa and the extracerebral decarboxylase inhibitor L-alpha-methyldopahydrazine (MK 486; Porter, Watson, Titus, Totaro, and Byer, 1962) in a group of patients with Parkinson's disease and compare the results with those achieved by treatment with levodopa alone.

METHODS

PATIENTS Thirty patients with Parkinsonism (28 idiopathic and two postencephalitic; 19 male and 11

female; aged 49–74 years) were treated with both levodopa and MK 486. The results obtained were compared with those achieved by treatment with levodopa alone in a group of 40 patients (38 idiopathic and two postencephalitic; 18 male and 22 female; aged 51–75 years).

TREATMENT *Levodopa and MK 486* Each patient was admitted to hospital to start treatment. Eighteen had taken levodopa alone previously; this was stopped 48 hours before starting MK 486. Most patients were taking other anti-Parkinsonism drugs (anticholinergics in 19; amantadine in 20) and these were continued unaltered.

MK 486 was given in a dose of 200 mg per day throughout the trial. The effect of one week's treatment with MK 486 by itself was assessed in 16 patients. Levodopa was then started at 125 mg thrice daily, and increased by 125 mg each day until side-effects prevented any further increase, or a dose of 3 g/day was reached.

Levodopa alone The treatment of this group of patients was described in detail by Parkes, Baxter, Curzon, Knill-Jones, Knott, Marsden, Tattersall, and Vollum (1971).

ASSESSMENT The severity of diability was scored as described by Parkes *et al.* (1971), with minor modifications. Patients treated with combined levodopa and MK 486 therapy were assessed before treatment and at weekly intervals thereafter until a stable dose of dopa was reached, which took four weeks on average (range three to seven weeks). The results after four weeks of treatment are presented. Patients treated with levodopa alone were assessed before treatment and at intervals of three, six, and nine months after starting levodopa. The effects of treatment on scores for total disability, functional disability, akinesia, tremor, rigidity, and posture were analysed.

TOXICITY STUDIES The following were determined before and after one month's treatment with levodopa and MK 486 to detect any toxic effects; haemoglobin, leucocyte count, erythrocyte sedimentation rate (Westergren), blood urea nitrogen, glucose, calcium, phosphate, alkaline phosphatase, uric acid, cholesterol, total protein, albumin, globulin, bilirubin, glutamic-oxaloacetic-transaminase, lactic dehydrogenase, indirect Coomb's test, electrocardiogram, and urine specimen for cells, protein, and sugar.

RESULTS

EFFECT OF MK 486 ALONE (16 PATIENTS) MK 486 had no effect on the severity of disability in the 16 patients treated with the drug for one week. The mean total disability score was 46·5 before treatment, and 44·5 after MK 486; functional disability, akinesia, tremor, rigidity, and posture scores were unaltered.

EFFECT OF LEVODOPA COMBINED WITH MK 486 (30 PATIENTS) All parameters of the patients' disability improved (Table 1). The improvement was rapid in onset and on some occasions dramatic. The majority of patients had both subjective and objective improvement within 14 days of starting treatment (Figure). There was no significant difference between the response at two and four weeks of treatment.

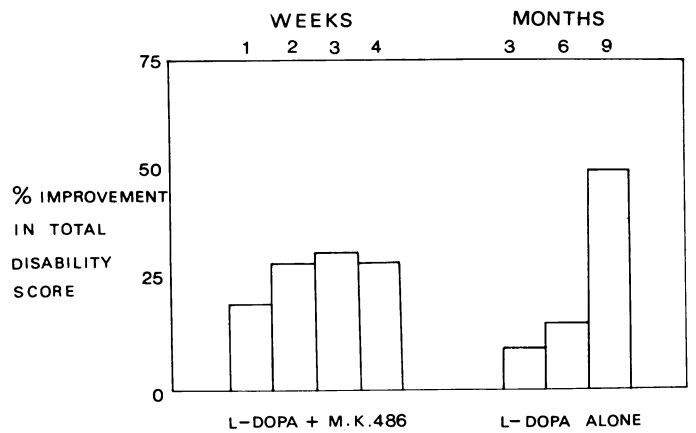

FIGURE *The effect of treatment of 30 patients with Parkinson's disease with MK 486 and levodopa, compared with treatment of 40 patients with levodopa alone. Mean total disability scores before the treatment are compared with scores after one, two, three, and four weeks combined therapy, and three, six, and nine months of levodopa therapy; the results are expressed as percent improvement from pretreatment scores.*

TABLE 1

RESPONSE TO COMBINED TREATMENT WITH LEVODOPA AND MK 486

	Mean score before treatment (±1 SD)	*Mean score after 4 weeks' treatment* (±1 SD)	*Significance of difference*
Total disability (123)	49·4 (±16·4)	35·2 (±16·2)	P<0·001
Functional disability (45)	20·3 (±7·7)	14·3 (±8·0)	P<0·001
Akinesia (18)	8·6 (±2·7)	7·4 (±2·8)	P<0·02
Tremor (15)	3·7 (±3·3)	2·5 (±2·6)	P<0·02
Rigidity (15)	6·9 (±2·4)	5·3 (±2·5)	P<0·01
Posture (24)	8·8 (±3·9)	5·3 (±3·6)	P<0·001

The maximum possible score is given in parentheses.
The significance of the mean of the differences between paired scores was assessed by Student's *t* test.

TABLE 2

COMPARISON OF COMBINED THERAPY AND LEVODOPA ALONE (TOTAL DISABILITY SCORES)

	Levodopa + MK 486 at 1 month (*30 patients*)	*Levodopa alone at 3 months* (*40 patients*)	*Levodopa alone at 9 months* (*40 patients*)
% Improvement	Number of patients		
0–19	8	20	7
20–49	18	15	7
50–79	3	5	18
80–100	1	0	8
Side-effects			
Nausea and vomiting	13 (43%)	32 (80%)	
Involuntary movements	13 (43%)	18 (45%)	
Hallucinations	6 (20%)	6 (15%)	

FACTORS GOVERNING RESPONSE TO COMBINED THERAPY There was no significant relationship between duration of disease, degree of disability, age, sex, or previous thalamolysis and the response to combined levodopa and MK 486 treatment. Both slightly and severely disabled patients showed improvement. Four of six mildly disabled patients (pretreatment total disability score less than 35) improved by 20% or more; 12 of 15 moderately disabled patients (pretreatment total disability score 35–59) improved by 20% or more; six of nine severely disabled patients (pretreatment total disability score 60 or more) improved by 20% or more. Four of the six patients who had had previous unilateral or bilateral thalamolysis improved by 20% or more.

COMPARISON OF COMBINED LEVODOPA AND MK 486 TREATMENT WITH TREATMENT WITH LEVODOPA ALONE Treatment with levodopa alone produced a gradual improvement; after three months 50% of patients had improved by 20% or more, while after nine months of treatment 82% of patients had improved by 20% or more. The response to combined treatment with levodopa and MK 486 was more rapid; after one month of combined therapy 73% of patients had improved by 20% or more (Table 2; Figure).

The final mean dose of levodopa when given with MK 486 was 1·0 g per day (range 0·15–2·5 g per day). The final mean dose of levodopa when given by itself was 2·1 g per day (range 0·5–5·0 g per day).

SIDE-EFFECTS (Table 2) The incidence of nausea and vomiting in patients treated with levodopa and MK 486 was half that in patients treated with levodopa alone. Involuntary movements (orofacial dyskinesia, myoclonic jerks, chorea, and dystonic movements of trunk and limbs) were the single most important side-effects limiting levodopa dosage when combined with MK 486, while nausea and vomiting was the most important dose-limiting side-effect when levodopa was given by itself. Hallucinations occasionally proved troublesome in both groups of patients.

No patient developed symptoms of postural hypotension in either group, nor were cardiac arrhythmias encountered. No new side-effects that could be attributed to MK 486 were encountered.

COMPARISON OF TWO TREATMENT REGIMES IN SAME PATIENT Eighteen patients who were given combined therapy with MK 486 had been previously treated with levodopa alone. Four of these patients had not responded to levodopa but had no side-effects. The remaining 14 patients were given combined therapy because of intolerable side-effects which prevented adequate levodopa therapy (Table 3). On combined levodopa and MK 486 treatment, nausea and vomiting improved or disappeared in seven patients, but involuntary movements and hallucinations persisted on combined therapy.

Thirteen of these 18 patients had taken levodopa for a month or longer (the remaining five patients did not tolerate a single dose). In these

TABLE 3

REASON FOR CHANGE OF THERAPY IN 14 PATIENTS PREVIOUSLY TAKING LEVODOPA ALONE

	Levodopa alone (*no.*)	*Levodopa + MK 486* (*no.*)
Nausea and vomiting	7	Improved in 3 Disappeared in 4
Postural hypotension	4	Disappeared in 4
Involuntary movements	3	No change
Hallucinations	2	No change

Two patients complained of more than one side-effect.

13 patients the mean dose of levodopa was 2·9 g per day; when MK 486 was given in addition, the mean levodopa dosage fell to 1·0 g per day.

TOXICITY OF LEVODOPA AND MK 486 There was no significant change in any of the parameters measured in the 30 patients treated with levodopa and MK 486.

DISCUSSION

These results with combined levodopa and MK 486 therapy are comparable with those reported previously by Cotzias, Papavasiliou and Gellene, 1969; Calne *et al.*, 1971; Yahr, Duvoisin, Mendoza, Schear, and Barrett, 1971. Similar results have also been obtained by combining levodopa with the different extracerebral decarboxylase inhibitor N^1-(DL-seryl)-N^2-(2,3,4,-trihydroxybenzyl)-hydrazine (RO4-4602) (Birkmayer, 1969; Siegfried *et al.*, 1969; Tissot *et al.*, 1969; Barbeau *et al.*, 1971). Combined treatment with levodopa and MK 486 seems to achieve the same therapeutic response as levodopa alone, but improvement is much more rapid in onset with marked reduction in nausea and vomiting. There is also a considerable reduction in the dose of levodopa required for maximum benefit. It is not known whether anticholinergic drugs and amantadine have an additive effect when given with dopa decarboxylase inhibitors and levodopa, but these additional drugs have also been used in many patients in the trials referred to. Decrease of the incidence of nausea and vomiting is a significant gain to the patient and the initial period of levodopa treatment is rendered much more tolerable. Combined therapy, however, does not seem to influence the occurrence of involuntary movements or hallucinations which still prove troublesome in many patients.

Levodopa, due to a peripheral action of its metabolites, carries some risk of inducing cardiac arrhythmias in patients with heart disease. Combined treatment with MK 486 may reduce the peripheral formation of levodopa metabolites and reduce the risk of cardiac arrhythmias. Similarly, there may be a reduction in the incidence of severe postural hypotension, although there is some evidence to suggest this is due to a central, rather than peripheral action of levodopa (Watanabe, Chase, and Cardon, 1970).

The combination of levodopa and MK 486 may influence the activity of certain hepatic microsomal enzyme systems for it delays the plasma clearance of antipyrine (Vessell, Ng, Passananti, and Chase, 1971). The possibility that MK 486 alters the metabolism of other drugs given concurrently thus needs to be explored further and the long-term effects of MK 486 determined.

There are patients who cannot tolerate adequate therapeutic doses of levodopa alone, but who respond satisfactorily to combined treatment with MK 486. In addition, many patients suffer distressing nausea and vomiting to gain the therapeutic benefits of levodopa and in these patients a more acceptable form of therapy is combined treatment with a dopa decarboxylase inhibitor. However, there remain limitations even to such combined treatment, for a significant proportion of patients still fail to improve and involuntary movements remain the most common dose-limiting side-effect.

We thank Dr. S. K. Rao and Merck Sharp and Dohme Limited who supplied the levodopa and MK 486.

REFERENCES

Barbeau, A., Gillo-Joffroy, L., and Mars, H. (1971). Treatment of Parkinson's disease with levodopa and Ro 4-4602. *Clinical Pharmacology and Therapeutics*, **12**, 353–359.

Bartholini, G., Burkard, W. P., Pletscher, A., and Bates, H. M. (1967). Increase of cerebral catecholamines caused by 3,4-dihydroxyphenylalanine after inhibition of peripheral decarboxylase. *Nature*, **215**, 852–853.

Birkmayer, W. (1969). Experimentelle Ergebnisse über die Kombinationsbehandlung des Parkinson-Syndroms mit L-DOPA und einem Decarboxylasehemmer (Ro 4-4602). *Wiener klinische Wochenschrift*, **81**, 677–679.

Calne, D. B., Reid, J. L., Vakil, S. D., Rao, S., Petrie, A., Pallis, C. A., Gawler, J., Thomas, P. K., and Hilson, A. (1971). Idiopathic Parkinsonism treated with an extracerebral decarboxylase inhibitor in combination with levodopa. *British Medical Journal*, **3**, 729–732.

Cotzias, G. C., Papavasiliou, P. S., and Gellene, R. (1969). Modification of Parkinsonism—chronic treatment with L-dopa. *New England Journal of Medicine*, **280**, 337–345.

Parkes, J. D., Baxter, R. C. H., Curzon, G., Knill-Jones, R. P., Knott, P. J., Marsden, C. D., Tattersall, R., and Vollum, D. (1971). Treatment of Parkinson's disease with amantadine and levodopa. A one-year study. *Lancet*, **1**, 1083–1087.

Porter, C. C., Watson, L. S., Titus, D. C., Totaro, J. A., and Byer, S. S. (1962). Inhibition of DOPA decarboxylase by the hydrazine analog of methyldopa. *Biochemical Pharmacology*, **11**, 1067–1077.

Siegfried, J., Ziegler, W. H., Regli, F., Fischer, C., Kaufmann, W., and Perret, E. (1969). Treatment of Parkinsonism with L-DOPA in association with the decarboxylase inhibitor. First objective results. *Pharmacologia Clinica*, **2**, 23–26.

Tissot, R., Gaillard, J.-M., Guggisberg, M., Gauthier, G., and Ajuriaguerra, J. de (1969). Thérapeutique du syndrome de Parkinson par la L-dopa 'per os' associée à un inhibiteur de la décarboxylase (Ro IV 46.02). *Presse Médicale*, **77**, 619–622.

Udenfriend, S., Zaltzman-Nirenberg, P., Gordon, R., and Spector, S. (1966). Evaluation of the biochemical effects produced *in vivo* by inhibitors of the three enzymes involved in norepinephrine biosynthesis. *Molecular Pharmacology*, **2**, 95–105.

Watanabe, A. M., Chase, T. N., and Cardon, P. V. (1970). Effect of L-dopa alone and in combination with an extracerebral decarboxylase inhibitor on blood pressure and some cardiovascular reflexes. *Clinical Pharmacology and Therapeutics*, **11**, 740–746.

Vessell, E. S., Ng, L., Passananti, G. T., and Chase, T. N. (1971). Inhibition of drug metabolism by levodopa in combination with a dopa-decarboxylase inhibitor. *Lancet*, **2**, 370.

Yahr, M. D., Duvoisin, R. C., Mendoza, M. R., Schear, M. J., and Barrett, R. E. (1971). Modification of L-dopa therapy of Parkinsonism by alpha-methyldopa hydrazine (MK-486). *Transactions of the American Neurological Association*, **96**, 55–58.