Augmenting the action of levodopa

S. K. RAO
M.B., M.R.C.P. (Lond. & Glas.)

S. D. VAKIL
M.B., M.R.C.P.

D. B. CALNE
D.M., M.R.C.P.

*Department of Medicine, The Royal Postgraduate Medical School
and Hammersmith Hospital, London, W.12*

A. HILSON
M.B., M.R.C.P.

Department of Neurology, The Royal Free Hospital, London, W.C.1

Summary

Various pharmacological approaches to potentiate the therapeutic actions of levodopa and reduce side-effects are reviewed.

Of currently available drugs, anticholinergic agents and amantadine have been studied extensively. Inhibition of extracerebral decarboxylase appears to be the most promising new area of investigation, though experience is at present limited.

Other methods discussed include inhibition of enzymes catechol-O-methyl transferase, monoamine oxidase and dopamine beta hydroxylase. Conflicting evidence on 3-O-methyldopa is discussed.

THERE is severe depletion of dopamine in the brain of Parkinsonian patients (Hornykiewicz, 1966). Levodopa is now a well established treatment for Parkinsonism but its therapeutic action is often associated with prominent unwanted side-effects. Most of the side-effects are dose-dependent.

We review here the various theoretical and practical ways of modifying levodopa treatment in order to minimize side-effects without reduction in therapeutic efficacy.

Anticholinergic drugs

Before the advent of levodopa therapy for Parkinsonism, anticholinergic drugs were the mainstay of treatment and invariably patients were on one or more of these drugs. It seemed logical to withdraw these when levodopa came to be the effective treatment. Hughes *et al.* (1971) investigated gradual and sudden withdrawal of anticholinergic drugs in a group of patients receiving a stable dose of levodopa for Parkinsonism. They found that only eleven out

of thirty-four patients were able to tolerate either gradual or sudden withdrawal for more than eight weeks. They suggest that synergism seems to exist between anticholinergic drugs and levodopa and this may be due either to inhibition of dopamine inactivation or a primary central anticholinergic effect. Conversely, it would appear from their results that the introduction of anticholinergic drugs in patients treated initially with levodopa is likely to produce additional benefit.

Amantadine

Amantadine hydrochloride, a drug recently introduced for Parkinsonism (Schwab *et al.*, 1969) has been found to release dopamine and other catecholamines from neuronal storage sites in dogs (Grelak *et al.*, 1970). In mice, the actions of levodopa are potentiated by amantadine (Svensson & Strömberg, 1970). The reported efficacy of amantadine in Parkinsonism may be due to the release of dopamine, but reports of synergism with levodopa have been conflicting (Godwin-Austen *et al.*, 1970; Hunter *et al.*, 1970a; Parkes *et al.*, 1971; Sacks, Schwartz & Messeloff, 1971).

Inhibition of catechol-O-methyl transferase

Catechol-O-methyl transferase (COMT) is an enzyme which contributes to the breakdown of levodopa, dopamine and other monoamine metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxymandelic acid (DOMA).

If O-methylated derivatives of levodopa and dopamine play any part in producing the adverse effects of levodopa, benefit might come from blocking the action of COMT by suitable inhibitors. Pyrogallol is

a COMT inhibitor, but it has proved to be too toxic for human use (Braham, 1970). Ericsson (1971) has conducted a clinical trial with *N*-butylgallate (GPA 1714), a drug which inhibits COMT *in vivo* and *in vitro*. He noted alleviation of Parkinsonian features and was able to reduce the dose of levodopa. There was a reduction of nausea, vomiting and involuntary movements.

Inhibition of dopamine beta hydroxylase

Theoretically, another way to increase the concentration of cerebral dopamine is to block its conversion to noradrenaline by inhibiting the enzyme dopamine beta hydroxylase. In animals disulfiram, a beta hydroxylase inhibitor, was found to increase the concentration of dopamine in the caudate nucleus, hypothalamus and brain stem with a corresponding reduction of noradrenaline (Goldstein & Nakajima, 1967). Clinically, however, Braham (1970) found no improvement after addition of disulfiram to levodopa therapy.

Fusaric acid, another inhibitor of dopamine beta hydroxylase, has also been investigated in Parkinsonism. When administered in combination with levodopa, a better therapeutic result was achieved than that obtainable with either drug (Hidaka, 1971). Mena, Court & Cotzias (1971) found that fusaric acid caused neither improvement nor worsening of signs or symptoms of Parkinsonism but they reported that this drug alleviated the involuntary movements produced by levodopa. They suggested that noradrenaline formed from dopamine causes the involuntary movements which occur with levodopa therapy.

Alkalinization of gastric contents

In six patients who had failed to respond to high doses of levodopa, Rivera-Calimlim *et al.* (1970) found increased gastric acidity and prolonged emptying time. Fractionation of the gastric juice showed significant quantities of levodopa metabolites, suggesting destruction of administered levodopa in the stomach. Addition of an antacid (magnesium and aluminium hydroxide) resulted in increased levodopa levels in the blood and clinical improvement. An antacid given half an hour before the dose of levodopa may thus prove useful in some patients.

Dopamine agonists

Apomorphine, a dopaminergic stimulant, is therapeutically active in Parkinsonism and augments the effects of levodopa. However, it causes severe nausea; it has to be injected; and its effects are only brief (Duby, Dahl & Cotzias, 1971).

Monoamine oxidase inhibitors

These drugs potentiate the actions of levodopa by

blocking the breakdown of dopamine and noradrenaline. Unfortunately, toxic effects are augmented in addition to the therapeutic action (Barbeau, 1961, 1962). Dangerous hypertension has been reported following administration of levodopa with monoamine oxidase inhibitors (Hunter *et al.*, 1970b).

Extracerebral decarboxylase inhibitors

The most satisfactory method, at present, to potentiate the action of levodopa, is selective blockade of extracerebral decarboxylase as first suggested by Bartholini *et al.* (1967). Levodopa is avidly decarboxylated to dopamine by the enzyme L-aromatic amino acid decarboxylase in the blood and tissues. Dopamine formed outside the central nervous system does not readily cross the blood-brain barrier. Because L-aromatic amino acid decarboxylase is so widespread, large doses of levodopa must be given to generate a therapeutic blood level. The large intake of levodopa may produce unwanted effects by peripheral adrenergic activity. Drugs are available which inhibit L-aromatic amino acid decarboxylase but are unable to penetrate the blood-brain barrier. The use of extracerebral decarboxylase inhibitors prevents the conversion of levodopa to dopamine in the gut, blood and peripheral tissues, thus enabling a larger proportion of the administered levodopa to cross the blood-brain barrier and there be converted to dopamine.

Initial reports with extracerebral decarboxylase inhibitors, such as L-alpha methyl dopahydrazine and seryltri hydroxybenzylhydrazine, are encouraging (Cotzias, Papavasiliou & Gellene, 1969; Bartholini *et al.*, 1969; Barbeau, 1969; Siegfried *et al.*, 1969; Calne *et al.*, 1971). We now report six patients with idiopathic Parkinsonism, treated with lower doses of L-alpha methyl dopahydrazine than have previously been employed.

The patients were treated in a double-blind, randomized cross-over comparison of levodopa with and without L-alpha methyl dopahydrazine. Regimen A comprised L-alpha methyl dopahydrazine, 100 mg a day in four divided doses, plus maximum tolerated dosage of levodopa. Regimen B comprised levodopa alone in maximum tolerated dosage. Each drug regimen was administered over a period of 6 weeks.

Clinical features were evaluated according to an arbitrary scoring protocol from 0 (normal) to 4 (severe disability). The results are summarized in Table 1. The maximum tolerated doses of levodopa are shown in Table 2. The effects of treatment on nausea (Fig. 1) and blood pressure (Fig. 2) are shown by linked scattergrams.

There were no obvious differences in the therapeutic responses on the two regimens, but nausea was less troublesome when patients were receiving L-

TABLE 1. Mean scores for individual therapeutic effects

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	A	B	A	B	A	B	A	B	A	B	A	B
Tremor	2.75	1.75	0	0	1	1	0	0.75	0	0	0	0
Rigidity	1.25	0	1	1	0	0	1	1	0	0	0.75	1.75
Speech disorder	0	0.25	0.5	1	0	0	0.5	0.5	1	0.5	1	1.5
Facial expression	1	0.5	2.25	2	0.75	0.25	1	1	2	1.5	1.25	1.75
Arising from chair	1	0.75	0.75	0.5	0	0	0	0.25	1	0	0.75	0.75
Balance	2	2	0.5	0.25	0	0	0.5	2	2	1	0.25	0
Finger dexterity	2.5	1	0.25	0.25	0	0	0	1	2	0.67	3	3
Drooling saliva	0	0	2	2	0	0	0.5	0.25	2	1.75	2	2
Sweating	0.75	0.25	0.5	1	0	0	0.25	1	1	0.75	0.25	0.75
Gait	1	1	0.75	0.25	0	0	0	0	1	0	1	1
Posture	1	1	0.75	0	0	0	1	1	1	1	2	2
Dressing	1	1	1	1	0	0.5	1	1	2.5	3	1	1.25
Washing	1	1	0	0.25	0	0	1	1.5	2	2	1	1.25
Eating	1	1	1	0.25	0	0	1	1	2	2	1	1.25
Writing	2	1.25	0.25	0.5	0	0	1	2	2	3.75	1	1
Timed tests (sec)												
Paper folding	5.62	4.85	11.67	10.12	9.2	10.2*	8.3	10†	Patient too confused to assess		13.3	14.3
Peg test	7.25	8.6	10.27	8.67	12.8	11.5*	13.3	13.1‡			9.9	14.4
Walking	33.62	28.27	20.67	20.07	15.7	14.4*	15	14†			17	17.5
Writing	26.4	22.97	16.85	17.1	17.1	17.3*	14.2	15‡			18.7*	22

A and B, regimens

* Mean of three assessments

† Mean of two assessments

‡ On one occasion only

FIG. 1. Nausea scores on each regimen.

FIG. 2. Blood pressures on each regimen. ----, supine; —, erect.

TABLE 2. Mean maximum tolerated doses of levodopa (g)

Patient	Regimen A	Regimen B
1	0.15	0.18
2	0.3	1.93
3	0.35	3
4	0.3	2.6
5	0.35	2
6	0.45	4
Means	0.32	2.4

alpha methyl dopahydrazine. By elevating the blood pressure slightly, inhibition of extracerebral decarboxylase militated against the mild hypotension commonly induced by levodopa. Although similar therapeutic effects were achieved on each regimen, the dose of levodopa was substantially lower when given in combination with L-alpha methyl dopahydrazine.

The overall results are very similar to those obtained with three times the dose of L-alpha methyl dopahydrazine (Calne *et al.*, 1971).

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