MEDICAL PRACTICE

Clinical Problems

Levodopa Therapy of Patients with Parkinsonism and Heart Disease

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Summary

Forty patients with Parkinsonism and heart disease were studied before and during the administration of levodopa. Patients with increasing angina, myocardial infarction within the previous year, pre-existing severe postural hypotension, or transient cerebral ischaemia were excluded. Thirty-eight patients showed no adverse effects; angina improved in one patient but later worsened; one patient died of myocardial infarction after a severe gastrointestinal haemorrhage. Therapy with levodopa appears to pose little increased hazard to patients with most forms of heart disease. Inpatient monitoring is recommended at the beginning of therapy, and antiarrhythmic agents should be used when required.

Introduction

In early clinical studies of the actions of levodopa in patients with Parkinsonism a high incidence of cardiovascular side effects was reported, including dysrhythmias, myocardial infarction, and alterations in blood pressure.¹⁻⁶ This is in keeping with the known pharmacological actions of levodopa and

dopamine on the heart.⁷⁻¹¹ Experience with greater numbers of patients suggested that the adverse cardiac effects of levodopa are less prevalent than was first thought. Both Parkinson's disease and heart disease are common afflictions of the elderly, and it is likely that in some cases their coexistence is coincidental.¹²⁻¹⁴

Because it had not been determined that the clinical effect of levodopa on the heart was significant enough to preclude its use in patients with heart disease, and because of the strong pleas by many of these patients to be given the drug, a prospective study was performed.

Patients and Methods

Patients with Parkinsonism referred to two urban neurological clinics for levodopa treatment were screened for cardiac disease. Those with "unstable" coronary disease, as indicated by increasing angina or by myocardial infarction within the previous year, were excluded, as were patients with transient cerebral ischaemia or pre-existing postural hypotension. Those with non-specific E.C.G. abnormalities, including right bundle-branch block, were treated in the same manner as patients with normal tracings and are not included in this study.

Forty patients with a history of heart disease or with significant E.C.G. abnormalities (arrhythmia, left bundle-branch block, or evidence of old infarction or ischaemia) were selected for treatment after study. Informed consent was obtained. There were 24 men and 16 women aged between 55 and 84 years (mean 71.46 years, S.E. of mean 1.04). They were all examined by a neurologist and a cardiologist and were admitted to a cardiac unit for baseline evaluation and institution of therapy with levodopa in a dose of 250 mg three times daily. Continuous E.C.G. monitoring was carried out at the start of treatment, and the dose of levodopa was increased by 250 mg every second or third day to the optimal

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TABLE I—Clinical Findings in 22 Patients with Arteriosclerotic Heart Disease

No. of Patients	Myocardial Infarction	Angina	Arrhythmia	Congestive Heart Failure	Other Findings	Course
4	+					
2	+	+				In one angina improved for nine months and then worsened
4	+		+		Left bundle-branch block in these, first-degree A-V block in another	
1	+			+		
2	+	+	+	+	Left bundle-branch block in one	In two-angina improved
2	+	+			First-degree A-V block in one	In one angina improved
2		+	+			
1		+	+		First-degree A-V block in one	
					Coronary atherosclerosis at necropsy	Died (see text)
22	15	12	9	3		

therapeutic level or to the maximum tolerated by the patient. The rate of increase was slower in some patients who became nauseated. Appropriate medications were prescribed for their other illnesses. The patients were examined daily and were discharged after several weeks to continue levodopa therapy as outpatients. When their cardiac state was shown to be stable they were seen by the neurologist alone at intervals of several months. Repeat E.C.G.s were obtained at the time of each return visit and chest radiographs and laboratory tests were ordered where appropriate. Patients with changes in their cardiac symptoms or in their E.C.G.s were re-examined by the cardiologist.

Parkinsonian disability was assessed by estimating and scoring postural stability, bradykinesia, finger dexterity, tremor, and rigidity on a 0-4 scale, as described previously by one of us.¹⁵

Results

The cardiac diagnosis and findings and the course of the heart disease during levodopa treatment are shown in Tables I to III. The commonest diagnosis was arteriosclerotic heart disease. Some patients with a history of myocardial infarction had active angina pectoris or arrhythmias; others were symptom-free. In two of the patients with previous myocardial infarction this had occurred within two years of starting levodopa therapy. Most of the patients with angina gave a history extending over a period of years. At the time of the first examination most patients with arrhythmias had chronic, frequent, premature atrial contractions (Table IV). Most of the patients with arrhythmias were not receiving antiarrhythmic drugs, but four patients were taking quinidine or procainamide and continued to do so during levodopa therapy.

The cardiac condition of two patients deteriorated while taking levodopa; in one angina improved for nine months

TABLE II—Findings in 13 Patients with Probable Arteriosclerotic Heart Disease

No. of Patients	Arrhythmia	Congestive Heart Failure	Other Findings
8	+		
3		+	
2			Intraventricular conduction defect in one
			Left bundle-branch block in one E.C.G. ischaemia alone in the other
13	8	3	

but later worsened, and the other died of myocardial infarction after a severe gastrointestinal haemorrhage. Details of the latter case are given below.

Case Report.—An 82-year-old woman with premature atrial contractions and Parkinson's disease manifested by bradykinesia, rigidity, and severely impaired balance was given levodopa. The

TABLE III—Diagnoses in 5 Patients with Heart Disease other than Arteriosclerosis

No. of Patients	Diagnosis	Course
3	Calcific aortic stenosis. Possible Stokes-Adams attacks in one, arrhythmia in another	
1	Lown-Genong-Levine syndrome	
1	Paroxysmal atrial tachycardia, unknown aetiology	One self-limited episode after seven months of levodopa

TABLE IV—Types of Arrhythmia (All Aetiologies) in 20 Patients

Premature atrial contractions	..	..	..	..	..	..	..	2
Premature ventricular contractions	..	..	..	..	..	..	..	10
Premature atrial and ventricular contractions	..	..	..	..	..	..	..	4
Paroxysmal atrial tachycardia	..	..	..	..	..	..	..	2
Atrial fibrillation and ectopic ventricular contractions	..	..	..	..	..	..	..	2

dosage was reduced from 2.5 g to 1.5 g a day to alleviate severe dyskinesias, but she continued to benefit from this dose, and balance especially was improved. Fourteen months later she developed anginal pain, which was relieved by glyceryl trinitrate, and minor E.C.G. changes. Seventeen months later she was admitted to another hospital with melaena and was transfused. Two weeks later she bled again, developed pulmonary oedema, and died. Necropsy showed severe ulceration of the gastric and duodenal mucosa and haemorrhagic diverticulitis of the colon. Thrombosis was present in the circumflex branch of the left coronary artery with myocardial changes of recent infarction. There was also severe atheroma in the other coronary arteries and the aorta, diffuse myocardial fibrosis, fibrinoid pericarditis, and a sclerotic aortic valve.

In the other 38 patients cardiac symptoms and signs remained unchanged or, in a few instances, showed coincidental improvement during the period of follow-up.

Only one out of more than 350 patients with Parkinsonism who had no initial clinical or E.C.G. evidence of heart disease and who received levodopa therapy concurrently with the cardiac group developed arrhythmia. This patient was a 69-year-old man who developed atrial flutter with a 2:1 ventricular response after he had taken levodopa for 10 months. Normal rhythm was restored by cardioversion without withdrawal of levodopa, and his heart remained in normal rhythm for more than a year on a combination of levodopa and quinidine.

Parkinsonian disability was greatly relieved in 29 of the 40 patients with heart disease, eight showed slight to moderate improvement, and three showed no improvement.

Discussion

It has been established that dopamine, the decarboxylation product of levodopa, increases the contractile force of the heart in animals⁷⁻¹⁰ and in man¹¹ and produces arrhythmia in cats.⁹ Parks, Watanabe, and Kopin¹⁶ showed that levodopa

infusion in dogs anaesthetized with halothane resulted in the accumulation of catecholamines in the heart and kidneys and the development of cardiac arrhythmias, which could be prevented by pretreatment with dopadecarboxylase inhibitors.

Cardiac dysrhythmias¹⁻⁵ and myocardial infarction^{2,4,6,14} have been reported in patients receiving levodopa, and the dangers of unaccustomed exertion have been noted.⁴ Premature ventricular contractions may increase in some but not all patients receiving levodopa.^{17,18} β -adrenergic blocking drugs such as propranolol,^{17,19} antiarrhythmic agents such as quinidine,¹⁷ or decarboxylase inhibitors such as alpha-methyl-dopa hydrazine¹⁸ may reduce the number of premature ventricular contractions occurring in patients treated with levodopa. Patients appear to develop a tolerance to the cardiac effects of levodopa^{17,19} and it has not been necessary to give other drugs prophylactically to patients with heart disease whose rhythms do not change.

Goldberg and Whitsett¹⁹ pointed out that dopamine acts on three different receptors: β -adrenergic, which stimulate the heart; α -adrenergic, which cause vasoconstriction; and dopaminergic, which cause renal and mesenteric vasodilatation. They adduced experimental evidence of an inotropic effect of levodopa in man, with loss of this effect after three or more months of treatment.

Cardiac arrhythmias are common in the age group in which Parkinsonism appears, since patients of this age also show a relatively high incidence of coronary artery disease. Mones, Elizan, and Siegel¹⁴ reported that arrhythmias were present before or at the time of the initial examination in 40 out of 152 patients with Parkinsonism. Young and Downie¹² suggested that anticholinergic drugs may promote the occurrence of abnormal cardiac rhythms; Freeman¹³ examined the routine E.C.G.s of 45 patients under treatment for Parkinsonism before the introduction of levodopa and found that 10 (22%) showed various arrhythmias.

Further clinical observations of the effects of levodopa on patients with Parkinsonism and heart disease are needed, but in the present series of 40 such patients there was no cardiac deterioration in 38. In the remaining two deterioration was compatible with the natural course of the disease and appeared to be coincidental to treatment with levodopa. The patient who died did not develop cardiac symptoms during 14 months of levodopa therapy despite severe, generalized coronary atheroma. Her angina was relieved by glyceryl trinitrate and she suffered an acute myocardial infarction three months later after a profound fall in blood pressure due to blood loss. These facts tend to strengthen rather than weaken the im-

pression that levodopa is not unduly dangerous to patients with heart disease.

In the early phase of our study we were prepared to withdraw levodopa if angina or arrhythmias worsened or if there was E.C.G. deterioration, but in no case did this prove necessary. With our present experience we feel that patients with such changes should be treated in the usual way without withdrawing levodopa unless the changes appear early in treatment while the dose is being increased. We continue to watch for the appearance of hypotension, which may be hazardous to patients with coronary artery disease. Our findings are consistent with those of Hunter, Laurence, Hollman, and Stern²⁰ in 20 patients.

We conclude that levodopa may be used safely in patients with heart disease (1) if those with severe postural hypotension or unstable coronary disease are excluded, (2) if inpatient monitoring is used during the early days of increase in dosage, and (3) if antiarrhythmic agents are administered when indicated. The presence of heart disease in these patients does not influence the therapeutic effect of levodopa on their Parkinsonism.

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