Effects of levodopa in parkinsonian patients with dementia

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■ The induction of confusional states, exacerbated dementias, deliria, anxiety states, elations, depressions, and frank psychoses by levodopa has been described by a number of authors. The reported incidence of such psychotic disturbances has varied widely—from 3.5%[1] to 55.5%.[2] Since levodopa has now been released for general use and is being given to large and constantly increasing numbers of parkinsonian patients, it is imperative to determine *which* patients are especially vulnerable to such disturbances. We have already noted, in preliminary communications, that postencephalitic[3-5] and demented[6] patients are especially at risk in this respect, a finding endorsed by the detailed studies of Celesia and Barr.[7] The effects of levodopa in postencephalitic patients, and in idiopathic patients with fully intact higher functions, have been described by us elsewhere.[8,9] The present communication is specifically concerned with the long-term effects of levodopa in parkinsonian patients with significant impairment of higher function and the ways in which concurrent dementia can modify reactions to levodopa.

Material

Of 72 institutionalized parkinsonian patients given long-term levodopa treatment, almost one-fifth (15 of 72) were considered to have significant impairment of higher functions. Of these 15 patients, 6 men and 9 women, 13 had idiopathic and 2 had postencephalitic disease. They ranged in age from 70 to 80 years and had exhibited parkinsonian symptoms for two to fifteen years and mental deterioration for one to ten years. The severity of parkinsonian and mental symptoms, prior to the administration of levodopa, is indicated in the table. In addition to parkinsonian symptoms, certain "semivoluntary" disturbances of tone and posture—paratonia, gegenhalten, catalepsy, etc.—could be demonstrated in some patients.

Conditions and methods

Most patients were observed for some weeks prior to the administration of levodopa to allow a detailed appraisal of their basal status by neurologists, internists, psychiatrists, speech pathologists, dentists, occupational and physical therapists, social workers, and nursing staff. During this preliminary period, visual and auditory recordings were made of the "starting situation," and parkinsonian symptoms and disabilities were assessed using the objective rating scales of Hoehn and Yahr. Assessment of higher functions was based partly on findings of intellectual and specific cortical deficits and partly on history of episodic confusion, disorientation, catastrophic reactions, etc. exhibited in response to stress. Patients who displayed intact capacities under optimal circumstances but had shown transient mental breakdowns under stress were considered to have minimal cortical damage or subclinical dementia (D1). Patients with clear-cut but not disabling impairments of recent memory, attention span, and "abstract attitude" were con-

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RESPONSES TO LEVODOPA IN PARKINSONIAN PATIENTS WITH DEMENTIA

Case No.	Before levodopa therapy: Mental status	Before levodopa therapy: Parkinsonian status	During levodopa therapy: Therapeutic effects	During levodopa therapy: Duration of benefit (weeks)	During levodopa therapy: Adverse effects: Chorea etc.	During levodopa therapy: Adverse effects: Akinesia etc.	During levodopa therapy: Adverse effects: Delirious psychosis	During levodopa therapy: Adverse effects: Stupor or coma	Problems after withdrawal: Duration of somnolence, stupor, or coma	Problems after withdrawal: Duration of confusional state or psychosis or both (months)	Mental status 6 months after withdrawal of levodopa
13	D1	Moderate	Moderate	1			2+	1+	1 week		D2
14	D2	Severe	Good	6	2+	3+	3+			>> 6	D3
15*	D3	Severe	Moderate	3		3+		3+	> 1 month		Unchanged
16	D2	Mild	Moderate	6	2+	1+	3+			>12	D3
17	D3	Severe	Moderate	2		2+	2+	3+	> 1 month	>> 6	D4
18	D1	Moderate	Mild	8	3+	2+	3+	3+	1 week	5	D2
19†	D2	Moderate	Mild	10	3+	2+	1+			>> 6	D5§
20	D3	Moderate	Mild	2	1+	2+	1+				D4
21	D1	Mild	Mild	8				3+	1 week		Unchanged
22	D2	Mild	Excellent	12	1+	1+	1+			< 1	Unchanged
23	D1	Moderate	Mild	6	2+	3+	3+	1+	2 weeks	>> 2	D4
24	D4	Severe	Mild	1	2+		3+	1+	2 weeks		D4
25*	D2	Moderate	Mild	15				3+	2 months	> 6	Unchanged
28‡	D1	Moderate	None	0	1+	2+		3+	2 weeks		Unchanged
51*‡	D2	Incapacitating	None	0			3+	3+	3 months	> 3	D5§

* Died during stupor or coma † Possible Jakob-Creutzfeldt disease ‡ Postencephalitic disease
§ Total dementia—decorticate reactions

sidered to have mild dementia (D2). Patients with severe impairments of memory and attention span, impoverishment of associations, and confusion were considered to have moderate dementia (D3). Patients who were completely disoriented, unable to recognize familiar places and persons, unable to act or speak coherently, and regressed to primitive perseverations, stereotypies, and automatisms were considered to have advanced dementia (D4). The conditions of institutional study allowed daily assessments of parkinsonian symptoms and mental status throughout the period of levodopa administration and for many months thereafter.

Administration of levodopa and other drugs

Levodopa of high purity (Nutritional Biochemicals Inc.) was freshly encapsulated from bulk powder kept in a watertight container. Patients were started on an initial dose of 100 mg. four times a day, existing medications (anticholinergic drugs etc.) having been discontinued before the start of the study. The 2 postencephalitic patients were started on one-fourth of this dose, 25 mg. four times a day. The dosage of levodopa was gradually raised over a period of six weeks until a satisfactory therapeutic response was achieved or, more commonly, until intolerable adverse effects resulted.

Results

All patients, with the exception of the 2 postencephalitic patients, showed clear-cut theraupeutic responses to levodopa. These consisted of reduction in akinesia, rigidity, tremor, festination, "freezing," and postural impairments. These therapeutic responses were achieved at dose levels of 1 to 4 gm. of levodopa daily and were completed in all cases within two weeks of the first visible response to levodopa. The intensity of therapeutic response showed no consistent relationship to the severity of the original parkinsonian status (see table). The duration of uncomplicated therapeutic response was only one to fifteen weeks in this group as opposed to four to fifty weeks of unqualified benefit obtained by our "intact" idiopathic patients.

These therapeutic responses were followed in all 15 cases by the appearance of adverse

responses, taking the form of excitement and hyperkinesia in 11 and somnolence and akinesia in 4. In contrast to our intact patients who showed relatively simple movement disorders of the choreiform type, the excited patients with dementia showed rather complex and bizarre movement disorders—pressure and precipitancy of voluntary movement, sudden tics and impulsions, and a variety of perseverating and stereotyped movements such as picking, tapping, banging, moaning, repeating words, verbigerating, etc. This "driven" state was peculiarly distressing to them and led to increasingly severe behavioral disturbances.

Within a few days or, at most, two weeks of the onset of such pressured, hyperkinetic states, indications of breakdown in higher function appeared. These occurred as very excited confusional states, associated with incessant hallucinations of sight and hearing, and abortive impulses immediately forgotten. Thus, these patients were precipitated into a functional disorganization resembling an advanced dementia coupled with a peculiar motility and busyness reminiscent of an "occupation delirium"—a state quite different from the well-organized motility psychoses sometimes induced by levodopa in parkinsonian patients with intact mental functions. Although brief outbursts of hilarity, fear, and anger occasionally occurred, it could not be said that any consistent affect accompanied these extraordinarily disorganized and incoherent states.

In 4 of 15 patients, adverse reactions to levodopa assumed the form of recurrent akinesia, peculiar bemused or trance-like states, perseverations of posture and passive movement (catalepsy and echokinesis), increasing inaccessibility, and deepening somnolence. These akinetic patients gradually moved toward states of stupor and coma and showed no signs of the delirious and disorganized states exhibited in the hyperkinetic group. Two patients (Cases 18 and 51) showed striking and sudden *oscillations* of hyperkinetic-delirious and akinetic-somnolent states at the height of their reaction to levodopa.

These alarming states steadily increased in severity if levodopa administration was maintained. Attempts to control them by systematic manipulations of drug dosage were unavailing. Once such pathological reactions had become established, it was no longer possible to retrieve the original, uncomplicated, therapeutic response; complete withdrawal of levodopa was necessitated. This, in itself, gave rise to "withdrawal syndromes" characterized by exacerbated parkinsonism, somnolence, and sometimes stupor.

In contrast to our intact idiopathic and post-encephalitic patients who showed a relatively rapid and complete *restitutio ad integrum* following withdrawal of levodopa, demented patients who had passed through periods of gross disorganization and delirium exhibited very persistent deteriorations of basal mental status with intermittent confusion, psychosis, perseverative behavior, and verbigeration for prolonged periods following the withdrawal of levodopa (see table).

Conclusions

Two years ago we published a preliminary communication that concerned the reactions of three demented parkinsonian patients to levodopa. In our original communication we suggested that the reactions of such patients, though alarming in the extreme, were wholly reversible. Our subsequent experience has shown that this was too optimistic a view.

It is evident that the reactions of parkinsonian patients with dementia are both qualitatively and quantitatively different from those of intact parkinsonian patients. Their reactions are similar in regard to the initial therapeutic response and the subsequent development of chorea, synkinesis, and hypotonia (the "anti-Parkinsonian state," in Duvoisin's term) but radically different in regard to the development of perseverative and compulsive behavior, i.e., catatonia-like states, and disintegration of higher functions.

It seems probable that these specific reactions reflect specific susceptibilities and predispositions characteristic of demented patients, i.e., their pre-existing tendencies to compulsive and perseverative behavior and their known instability of higher (cortical) functions.

In 1970 we expressed the hope that suboptimal doses of levodopa might procure a useful diminution of parkinsonian disability in demented patients without producing catastrophic "side effects." Our endeavors to achieve this have been frustrated by the finding that

any dose of levodopa sufficient to procure therapeutic activation invariably leads to a profound and sometimes persistent disorganization of higher functions. We therefore consider it unsafe to administer levodopa to parkinsonian patients with dementia because they cannot tolerate the dosage required.

Summary

L-dopa was administered to 15 institutionalized parkinsonian patients with significant impairment or instability of higher cortical functions. All of these patients save 2 with postencephalitic disease showed substantial reduction of parkinsonian symptoms and disabilities; however, within one to fifteen weeks, they developed crippling adverse reactions with the continued administration of L-dopa. In 11 of 15 patients these reactions took the form of confusional or hallucinatory states of abrupt onset and great severity, associated with chorea and akathisia and followed by the development of stupor or coma; 4 patients moved at once into stuporous or comatose states without preceding periods of excitement. All patients who had experienced severe delirious disorganization showed exacerbated intellectual deficits many months after the withdrawal of L-dopa. It is concluded that parkinsonian patients with dementia may suffer prolonged and perhaps permanent disorganization of higher functions from the administration of L-dopa and should be given this drug only with the utmost caution.

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