Administration of Dihydroxyphenylalanine to Parkinsonian Patients

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ABSTRACT

Dihydroxyphenylalanine (dopa), the metabolic precursor of dopamine, was administered to 10 parkinsonian patients in oral doses of 1-5 g. and intravenous doses of 0.2-0.5 g. Increases in dopamine excretion of 100- to 1000-fold following the dopa administration indicated that dopa was being absorbed and metabolized. Only two of the 10 patients showed any objective improvement on this treatment. Although dopa did not show sufficient beneficial results in this study to be considered a useful therapeutic agent, its slight activity is consistent with other evidence suggesting that some extrapyramidal cells are sensitive to dopamine.

THE etiology of parkinsonism is as much a mystery today as when it was first described by James Parkinson in 1817. Although the disease is now classified into subtypes such as idiopathic, postencephalitic and arteriosclerotic, such a classification reflects special circumstances under which this clinical entity can occur, but does not suggest any specific etiological mechanism. The symptoms of the disease, however, indicate that a specific poisoning or degeneration of certain cells of the extrapyramidal system is involved; these cells must be peculiarly vulnerable, since other cells in the brain are relatively unaffected.

More specific suggestions regarding the basic causative process have developed from investigations of drug-induced parkinsonism. Drug-induced parkinsonism is a side effect of tranquillizer therapy, closely resembling other forms of parkinsonism both in symptomatology and in response to medication.

Carlsson[1] initially pointed out that reserpine, which is capable of producing a typical drug-induced parkinsonian state, depletes the caudate nucleus of its principle amine, dopamine. He suggested that dopamine, because of its high concentration in the corpus striatum, might well be important to extrapyramidal motor function. Certain phenothiazines also induce parkinsonism, and, while such phenothiazines do not deplete the corpus striatum of dopamine, they are potent blockers of physiological actions of this amine. Thus it can be argued that depletion or blockade of dopamine will impair the functioning of extrapyramidal cells in such a way as to produce parkinsonism.

The mechanism by which reserpine and the phenothiazines produce their major effect, tranquillization, is not proved. Most hypotheses, however, involve the undisputed fact that these agents are antagonistic not only to dopamine, but also to serotonin and noradrenaline.[1-4] These amines are widely distributed in the body, and in the brain are highly concentrated in the hypothalamus, septal region and brain stem,[5] in addition to the basal ganglia. Although the exact roles of these amines are not known, it is believed that they may be neurotransmitters or, at least, neuronal modulators of some sort, in the areas where they are concentrated. It is particularly noteworthy that the areas containing high concentrations of noradrenaline and serotonin are those areas widely believed to be important to emotional performance, while the closely related dopamine is concentrated in areas thought to be important to extrapyramidal function. It is therefore not surprising that extrapyramidal reactions should be a side effect of tranquillizer therapy.

Following the work of Carlsson, Barbeau[6] proposed that the fault in "naturally occurring" parkinsonism might be a deficiency in dopamine in the brain, a concept comparable to that postulated to explain reserpine-induced parkinsonism. Several lines of evidence were developed in support of this hypothesis. Barbeau, Murphy and Sourkes[7] reported less dopamine in the urines of patients with postencephalitic parkinsonism than in those of laboratory workers. Ehringer and Hornykiewicz[8] reported lower concentrations of dopamine in the neostriatum and hypothalamus of patients dying of Parkinson's disease than in similar brain areas of controls dying without neurological disorder. Finally, Barbeau,[9] Birkmayer and Hornykiewicz,[10] and Gerstenbrand and Pateisky[11] all reported substantial improvement in the clinical state of persons with Parkinson's disease treated with oral or intravenous doses of L-dihydroxyphenylalanine (dopa), the metabolic precursor of both dopamine and noradrenaline. Freidhoff *et al.*,[22] in a preliminary study on six parkinsonian patients, reported data "which suggest that dopa does in fact favourably reduce rigidity but does not produce striking differences in tremor amplitude or frequency". Greer and Williams,[12] however, found no change in two patients given dopa, and no difference between parkinsonian patients and controls in the excretion

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of homovanillic acid, the major metabolite of dopamine.

For some time, this laboratory has been interested in the physiological roles played by central aromatic amines. Previously, we reported that oral DL-dopa is only weakly effective as an antidote for drug-induced parkinsonism caused by reserpine and certain phenothiazines. The relative ineffectiveness of dopa in these cases was attributed to the very strong antagonistic action towards the catecholamines of the tranquillizers being given.[13] In this communication, we report our experiences with the administration of dopa in cases of naturally occurring parkinsonism.

Materials and Methods

Ten patients took part in this study. Seven were chronic parkinsonian patients who had been followed up in the Vancouver General Hospital Outpatient Department for many years, were known to be reliable people, and were previously used in therapeutic trials of new agents for parkinsonism.[14] Two were relatively recent cases of parkinsonism who were not receiving other medication. The tenth was a patient with chronic parkinsonism who was given a long-term trial; he received approximately 3 g. per day of oral DL-dopa for nearly two years with no apparent ill effects.

Oral DL-dopa was administered as 250-mg. capsules in doses ranging from 1 to 5 g. per day and for periods ranging from a few days to almost two years. Placebo for oral dopa consisted of dextrose capsules indistinguishable in appearance from the dopa capsules. Capsules were increased by one per day (250 mg.) until the patient began to notice side effects. These invariably occurred on a dose of 5 g. per day. Intravenous dopa was infused as a 1 mg./ml. solution in saline, with saline alone serving as placebo.

Response to treatment was judged by a number of tests widely used in the assessment of parkinsonian patients. A digital counter was used to test finger, wrist and elbow mobility, and a peg board to test finger dexterity, as described by Burns and DeJong.[15] Speed of movement was assessed by the time taken to walk a given distance and the time taken to write a given number of words. Tremor was assessed by counting the deviations in a tracing made over a straight line. Balance and postural angles were measured in the usual way.

Baselines on the standard tests were established by repeated testing prior to dopa or placebo administration. There was generally a remarkable constancy of performance for control conditions. The response to dopa was scored as + if there was more than a 10% improvement on one or more of the tests of motor function, as ++ if there was 20-40% improvement, and as +++ for greater than 40% improvement. A positive subjective response was recorded if a patient stated that he felt more limber or more like undertaking activity.

Results

As can be seen from the summary of results in Table I, only two of the 10 patients showed any objective improvement on oral DL-dopa, and in one of these the improvement was maintained on placebo. One other patient who showed no objective change on oral DL-dopa showed slight improvement on both L- and DL-dopa given intravenously.

Chemical measurement by previously published methods[16] showed enormous changes in the urinary excretion of dopamine following the administration of dopa to these patients. Control excretions of dopamine were 0.2-0.4 μg./mg. of creatinine. In patients given 4 g./day of DL-dopa orally, the dopamine excretion increased to 300-600 μg./mg. of creatinine. Following intravenous infusions of 250 mg. of L-dopa, the dopamine excretion was 30-60 μg./mg. of creatinine in the first three hours, and 20-40 μg./mg. creatinine in the subsequent three hours. These increases in dopamine excretion of up to 1000-fold leave little doubt that absorption and metabolism of the dopa occurred, but there was, of course, no way of knowing to what extent dopamine levels in brain tissue were affected.

Side effects of dopa treatment were mild but consistent in pattern. Nausea, light-headedness and weakness were observed, in that order of frequency. No other side effects of any kind were observed. All side effects subsided quickly when dopa was withdrawn. Toleration of oral dopa varied. Approximately half of the patients reported some nausea on doses of 1-2½ g./day, while all noticed some effects at 5 g./day. All three patients who were given dopa intravenously experienced nausea when the rate of infusion was increased to 5 mg./min., but all tolerated infusion rates of 2 mg./min. with no noticeable side effects, except that one patient reported light-headedness immediately following the infusion.

Discussion

These results indicate that dopa has little to offer as a therapeutic agent in the treatment of parkinsonism. Established therapeutic regimens were obviously superior in some of the cases where withdrawal of standard drugs brought about a marked deterioration in motor control (Table I). In one case surgery brought about improvement far beyond that observed on a variety of medical regimens including the administration of dopa.

The group studied was small, but it represented such a range of circumstances for Parkinson's disease that any striking benefit of dopa should have become evident. Patients with recent onset of the disease as well as those with chronic, stabilized conditions were tried. Dopa was given alone and as an adjunct to other medical therapy. Different etiological types of parkinsonism were included. Oral and intravenous therapy and both the L- and DL- forms of dopa were tried. Three of the patients had surgical intervention prior to dopa testing, and

TABLE I.

Age and sex of patient	*Presumed type of parkinsonism*	*Duration of illness*	*Basic medication**	*Experimental treatment (g. dopa/day)*	*Response subjective*	*Response objective*	*Side effects*	*Remarks*
58 M	Postencephalitic	9 years	2, 3, 4	Oral DL-dopa —4 g.	+	++	Slight nausea	No improvement with surgery carried out following dopa treatment
				I.V. L-dopa —250 mg.	+	++	Light-headedness	
62 M	Idiopathic	10 years	1, 2, 3, 4	Oral DL-dopa —2 g.	0	0	Weakness in legs	Discontinued medication because of side effects
55 F	Idiopathic	4 years	5	Oral DL-dopa —2 g.	0	0	Slight nausea	
62 F	Postencephalitic	7 years	2, 3, 4	Oral DL-dopa —1½ g.	0	0	Nausea	Severe deterioration when standard medication reduced
45 F	Idiopathic	11 years	1, 3	Oral DL-dopa —1 g.	+	++	None	Improvement maintained on placebo
68 M	Idiopathic	5 years	none	Oral DL-dopa —2½ g.	0	0	None	
52 M	Idiopathic	8 years	1, 2, 3	Oral DL-dopa —4 g.	0	0	None	No deterioration when Drugs 2 and 3 were removed
52 M	Idiopathic	8 years	1, 2, 3, 4	Oral DL-dopa —5 g. I.V. L-dopa —250 mg.	+	0	Slight nausea	Severe deterioration when standard medication cut back. Subjective improvement maintained on placebo. +++ improvement from thalamotomy
56 M	Postencephalitic	39 years	1, 2, 3	Oral DL-dopa —5 g.	0	0	None	
				I.V. L-dopa —250 mg.	+	++		
				I.V. DL-dopa —500 mg.	+	+		
67 M	Arteriosclerotic	8 years	1	Oral DL-dopa —3 g.	+		None	Maintained for two years on DL-dopa with no side effects

*1 = Trihexyphenidyl hydrochloride (Artane).
2 = Diphenhydramine plus hyoscine (Benacine).
3 = Chlorphenoxamine (Phenoxene).
4 = Cycrimine hydrochloride (Pagitane).
5 = Biperiden hydrochloride (Akineton).

in two cases surgical treatment was carried out subsequent to the experiment.

It is disappointing in view of the interesting ideas put forward regarding a possible biochemical lesion in Parkinson's disease that dopa should not be more effective as a therapeutic agent. These disappointing results, however, in no way challenge the possibility that dopamine may be a neurohormone for certain cells of the extrapyramidal system. Microscopically, in parkinsonism, one sees round cell infiltration, swelling of cells and dropping out of cells in the basal ganglia and in areas of the brain stem.[17] In view of such pathological changes, it is not surprising that Hornykiewicz and colleagues[8, 18, 23] should find decreased amounts of dopamine and serotonin in these same brain areas. Such a finding is a suitable adjunct to the already established pathology in this condition. The slight therapeutic effect of dopa is explainable also on the basis of this known pathology. There is not a complete destruction of extrapyramidal cells in parkinsonism, and it is conceivable that elevated levels of dopamine, brought about by large doses of its precursor, dopa, could enhance the excitability of those cells still able to function.

This view of parkinsonism—that amine metabolism is affected only in certain cells of the nervous system, and then only as a secondary effect—is not consistent with the finding of a decrease in urinary excretion of amines and their metabolites reported by Barbeau and colleagues,[7, 9, 19] but is consistent with the conflicting data of Greer and Williams[12] and Resnick *et al.*[20] who found no difference between parkinsonian patients and controls in such excretory levels. Only a tiny fraction of the total metabolism of the amines could pass through extrapyramidal cells, the major part being carried out in the gut, lungs, heart, adrenal medulla and other non-nervous tissues. Therefore, impairment of cells of the extrapyramidal system should not by itself noticeably affect the total excretion of amines or their metabolites.

Greer and Williams studied the homovanillic acid excretion in parkinsonian patients and in controls matched for age and diet, with and without a dopa load.[12] They found no difference between the two groups in the excretion of this major metabolite of dopamine. Barbeau and colleagues found a decreased dopamine excretion[7] and a decreased ability to metabolize a dopa load,[9] using laboratory workers as a control group.[7]

It is widely believed that the same enzyme, dopa decarboxylase, which converts dopa to dopamine, also converts 5-hydroxytryptophan to serotonin, which is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA). On the basis of their findings with dopamine excretion, Barbeau, Jasmin and Duchastel[19] expected a decreased 5-HIAA excretion in parkinsonian patients, which they reported finding. However, Resnick *et al.*[20] found no difference in 5-HIAA excretion in parkinsonian vs. non-parkinsonian patients, with or without a 5-hydroxytryptophan load. Significantly, the reported excretions of 5-HIAA by parkinsonian patients were almost identical in the studies of Barbeau and Resnick; the difference lay only in the higher values for controls found by Barbeau. Resnick *et al.* used, as controls, patients on the same neurological ward as the parkinsonian patients, and stated that some degree of control over the diet and exercise of the two groups was possible.

All the factors which contribute to the metabolism of the amines in question are by no means known; nevertheless, age, degree of activity and diet may all be important. Certainly, such factors need careful evaluation before the full range of normal values is established and before the reported decrease in excretion of the various amines and their metabolites in parkinsonian patients could be considered to have a primary link with the disease process.

There remains the strong evidence from drug-induced parkinsonism that some extrapyramidal cells are dependent on dopamine and possibly on other amines for normal functioning. There must, however, be other cells of this system, not sensitive to dopamine, which act as some sort of a balancing force. Treatment of parkinsonism, whether drug-induced or naturally occurring, is most effective when anticholinergic and antihistaminic drugs are used. These agents may possess antagonistic action towards cells which depend upon acetylcholine and histamine for normal function, and which are presumably unaffected by the disease process.[21]

SUMMARY

Dihydroxyphenylalanine (dopa) was administered to 10 parkinsonian patients. Doses of 1 to 5 g. were used orally and 250 to 500 mg. intravenously. Response of the patients was evaluated by means of a number of tests widely used in the assessment of parkinsonian patients.

Only two of the 10 patients showed any objective improvement on oral DL-dopa, and in one of these improvement was maintained on placebo. One other patient, not showing any response to oral DL-dopa, showed a detectable improvement on L-dopa and DL-dopa administered intravenously.

The improvements noted were not striking. On the other hand, severe deterioration was observed in two of three patients taken off their standard medication. Side effects of dopa treatment were mild, consisting of nausea and light-headedness.

In this study, dopa gave no indication of being a practical adjunct to therapy in Parkinson's disease. However, the detectable response to dopa in some patients is of theoretical interest in view of experimental evidence suggesting that certain extrapyramidal cells may depend upon dopamine, a metabolic product of dopa, for normal function.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE FAME OF WEIR MITCHELL

With the death of Weir Mitchell one of the most notable figures in American medicine has passed away. In the later years of his life Dr. Mitchell attained to so great a celebrity in the world of letters that his fame as a physician was over-shadowed. He was a very great physician, and established a tradition which he acquired from his father and handed down to his son. His practice was based upon research at a time when the empirical method held full sway, and he had the rare quality of combining in himself the attributes of the scientist and the practitioner. To writers he was a writer, and to physicians, a physician. He has now a place beside Holmes in the public mind; and in the course of human events one other name will be added to the short but impressive list, namely, that of Sir William Osler. These three will constitute a trinity which any profession and any country might well contemplate with satisfaction.—Editorial, *Canad. Med. Ass. J.*, 4: 135, 1914.