LEVODOPA AND RELIEF OF PARKINSONIAN SYMPTOMS

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It is not surprising that the discovery of L-DOPA (levodopa, L-3,4, dihydroxyphenylalanine) as an effective agent against the symptoms of parkinsonism has evoked such interest. Although the full range of its side effects and toxic reactions will become known only after wider use, there is no longer any serious doubt as to its efficacy when carefully and properly used. Many patients who have been severely incapacitated in spite of surgical procedures and extensive medication have been able to return to meaningful mobility, occupation and activities of living. It is not, however, the final answer or the cure. Some patients may be helped little, if at all, and others cannot tolerate the drug because of adverse reactions. Even in those patients who are markedly or significantly helped, dosage regulation is a continued long term problem requiring a close partnership with a skilled and knowledgeable physician.

In this paper, some of the background and rationale of this new therapy will be reviewed briefly and the results obtained thus far in the United States will be summarized from the reported series and from the patients treated at the University of Florida under the supervision of one of us (M. G.).

In the central nervous system many substances are found which are assumed to have roles in transmission or regulation of the nerve impulse. For the most, the precise action of each of these is unknown. The best known among these is acetylcholine which some consider to be uniquely involved with transmission at excitatory synapses. Others include gamma amino butyric acid, histamine, serotonin, norepinephrine and dopamine. Concentration of these substances varies in different parts of the nervous system. Thus, norepinephrine is present in high concentration in those anatomic structures related to autonomic function. The concentration of this catecholamine in the hypothalamus is at least ten times that found in the cerebral cortex [15]. Another major catecholamine fraction is dopamine which is found in high concentration in the corpus striatum. Concentration in the caudate nucleus is more than 50 times that of the cerebral cortex [15]. Although its precise role as a neurotransmitter is unknown, it is logical to hypothesize an important role in neuronal control of extrapyramidal motor activity.

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Deficiencies of dopamine in the corpus striatum of patients with parkinsonism was first noted in 1960 [7, 12] and subsequently a dopamine pathway was demonstrated between the substantia nigra and the corpus striatum by special histochemical technics [8]. Although the basic pathodynamic process remained unknown, this provided a potential link between the well-known degenerative changes and depigmentation of the substantia nigra and the altered physiology of the basal nuclei in parkinsonism.

Indirect studies of dopamine metabolism in parkinsonism gave conflicting results. Barbeau and colleagues found reduction of dopamine excretion in the urine of patients with parkinsonism [2], whereas one of the authors (M. G.) with Williams found no difference between patients with parkinsonism and control groups [11].

Early clinical trials of treatment with dopamine or its precursors were largely disappointing and gave few indications of the beneficial effects later noted [9, 13]. Dopamine itself does not cross the blood-brain barrier but its precursor, DOPA (3,4, dihydroxyphenylalanine) does. Cotzias and co-workers [6] were apparently the first to use the precursors of dopamine in sufficient doses orally over a long enough time to demonstrate the possible practicality of clinical treatment. In the initial study [6] the racemic form of DOPA was associated with granulocytopenia in a disturbing proportion of patients. Subsequently Cotzias et al. and others have used the levorotary isomer which has not been associated with significant hematologic changes. L-3,4, dihydroxyphenylalanine (L-DOPA, levodopa) does cross the blood-brain barrier and is decarboxlylated to dopamine by the enzyme dopa decarboxylase.

CLINICAL TREATMENT WITH L-DOPA

At the time of final review of this manuscript the announcement was made by the Food and Drug Administration of the United States of the approval of levodopa for more general use. Prior to this time distribution had been limited in the United States to physicians with approved investigational protocols. Experience has thus been gained with a large number of patients although many of the series are yet to be reported in the medical literature. Cotzias and co-workers have, perhaps, had the longest experience but not the largest number of patients [5, 6]. In his Wartenberg lecture delivered before the American Academy of Neurology in May 1970 [4], Cotzias reported upon 48 patients with parkinsonism, 14 with chronic manganese poisoning and upon several dystonics. Sustained therapeutic results were essentially confined to those with parkinsonism and those with manganese poisoning. He and his co-workers report fewer limiting side effects than do others, perhaps because of more gradual increase in dosage. Among the reports are those of Yahr et al. [16], Calne et al. [3], Godwin-Austen et al. [10] and McDowell et al. [14]. In our own institution, experience with levodopa began in January 1969 under the supervision of one of us (M.G.) and thus far approximately 120 patients have been started on treatment. Experience has been similar to that reported by others, both as to efficacy nd side effects but is too early to reach a definitive statement. Approximately 40% of the patients have had moderate or marked improvement and 40% definite though limited amelioration of symptoms. In the remainder, minimal or no improvement has been noted. Yahr et al. [16] in 38 patients noted complete amelioration of symptoms in one patient, marked improvement in 23, moderate in 4, and minimal or none in 10. In the series of 100 patients treated for six months or longer by McDowell et al. [14], 60 improved 50% or more and 33 of these improved 75 to 100%.

Only 15 improved less than 25% and there were but three who worsened. For scoring a weighted scale was used which included signs, symptoms and functional activities.

Methods of administration — Our schedule has called for an initial dose of levodopa of 250 mg. four times a day, increasing in increments of 500 mg. every two or three days to a maximum of eight grams daily. In many, early side effects limit this to smaller amounts and smaller increments spread over a longer period of time. Symptoms such as nausea and vomiting, agitation, insomnia or confusion are frequently limiting in terms of initial dosages and of rapidity of increase. In such patients one may obviate or minimize the difficulty by decreasing initial doses as low as 50 to 100 mg. three times a day and similarly reduce increments of increase. Cotzias and co-workers [4, 5] start with much lower doses, increase more gradually. It is, perhaps, for this reason that they appear to have less difficulty with dose-limiting side effects than have others and have been able to treat successfully some patients who had unsuccessfully used the drug before.

The total dose required or tolerated varies from patient to patient and cannot be predicted with certainty. Furthermore dosage is subject to reduction or change with the passage of time because of induced transitory dyskinesias or other side effects. A reduction in dose requirement for sustained improvement has also been noted. Thus, a patient may reach a total dosage of six grams a day for maximum relief within tolerance. After several months because of limiting side-effects such as dyskínesia this might be reduced to three to four grams a day with continued relief to extent greater than that noted previously on the same amount of drug. In the University of Florida series there has been a disappointing regression in approximately half of the patients who were over 70 years of age or who had very severe disability. Increasing or reducing dosage has not been associated with significant change in these patients.

Levodopa may be associated with improvement of all of the manifestations of parkinsonism. Initial effects appear to be principally a lessening of rigidity and amelioration of bradykinesia. Patients and famlies report an increased mobility, clearer speech and a quickening of mental processes. Depressive symptoms may be markedly reduced. Treatment has appeared to be more effective against bradykinesia and rigidity than against tremor, *per se*.

Side effects — Side-effects may be dose limiting and thus interfere with effective therapy. Using smaller initial doses and smaller increments of increase may reduce the severity of those which limit treatment. Among the side effects frequently observed are nausea or vomiting, anorexia, mental changes including confusion and agitation, postural hypotension, episodic hypertension, flushing, dyskinesia and cardiac arrhythmias. Cotzias and colleagues [15] have noted episodes of immobility which may be corrected, in part, by redistribution of time of administration. Such symptoms may be associated with eating a heavy meal.

Involuntary movements may appear after the patient has been under a stable dosage for several months. Most commonly these are dyskinetic movements about the mouth and are analogous to those observed with phenothiazine drugs. On only rare occasions are severe dyskinesias such as opisthotonic spasms or myoclonic jerks observed. These dyskinesias are reversible and may require reduction in dosage. At times, there may be a balance between the symptoms of parkinsonism and drug-induced involuntary movements, with the former being more disabling than the latter. The patient may be unaware of these involuntary movements in spite of the fact that they are readily observed by others.

Postural hypotension is usually asymptomatic but occasionally leads to fainting or light-headedness in the erect posture. Cardiac disturbances are usually limited to ventricular premature contractions but one patient of McDowell et al. [14] had

electrocardiographic evidence of transient subendocardial ischemia with premature contractions while receiving 2.0 g per day of levodopa. There were no other episodes in spite of continued treatment.

Serious toxic reactions have been few. In the McDowell series ten patients had elevations of serum glutamic-oxalacetic and glutamic-pyruvic transaminase levels. These returned to normal in spite of continued treatment. Serious hematologic or renal toxicity has not been a problem.

DISCUSSION

Experience thus far has largely confirmed the beneficial effects of treatment of parkinsonism with dopamine precursors but the basic problem of pathogenesis of the disease remains unsolved. Furthermore, evidence has not yet been forthcoming to indicate that the progressive course of the disease process has been altered. Treatment with levodopa does offer sustained and significant relief of symptoms for many patients but often at the expense of annoying side effects produced by the drug which may, at times, seriously limit effective therapy. It is only in the exceptional patient, usually with relatively mild symptoms, that amelioration is complete. It is as yet too early to assess long-term effects. What will be the fate of these patients five or ten ears from now is not known. Also, with expanded clinical experience obtained with large numbers of patients throughout the world, other toxic reactions may be observed. Such has been the case with other drugs which appeared "safe" on initial clinical trials.

On the more encouraging side, the discovery of the beneficial effect of levodopa may be looked upon as a first step toward a more effective treatment. As an example, Cotzias and co-workers [4, 5] have been investigating the effects of a dopa decarboxylase inhibitor D-L alpha-methyldopa hydrazine (MK-485) which blocks the formation of dopamine from dopa. This does not act within the nervous system because it does not cross the blood-brain barrier. Therapeutic doses of levodopa thus may be greatly decreased by effectively limiting the necessity of flooding all body tissue to obtain a concentration in the nervous system.

It should further be observed that the use of dopa in therapy was not a chance discovery but resulted ultimately from intelligent application of basic scientific research on the nervous system. Continuation of basic scientific investigation of nervous system function may lead to further information which can be translated ultimately into practical clinical terms.

SUMMARY

This paper has presented a brief review of the treatment of parkinsonism with levodopa. Although there are problems in the utilization of this amino acid in practical therapy, significant amelioration of the symptoms and signs of parkinsonism can be obtained and sustained over long periods of time. It is as yet too early to detect any potential of alteration in the basic progressive course of the disease.

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