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Treatment of Parkinson's disease with L-dopa:
A current appraisal

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Summary: Interest in L-dopa therapy for Parkinson's disease has been considerably enhanced since the recent release of this drug to all medical practitioners. Our experience in the use of L-dopa in 83 patients who have been treated during the past 22 months is presented to provide a practical approach to the administration of L-dopa. Many parkinsonian patients can be treated advantageously on an outpatient basis without the need for initial hospitalization. Some of the common side effects of L-dopa administration can be averted or controlled by a cautious and slow build-up to the optimal dosage level. In the majority (78%) of parkinsonian patients who had been carefully selected for treatment the drug had a beneficial effect on akinesia and rigidity. In the remainder, therapy had to be discontinued because of undesirable side effects or a limited response.

The object of this paper is to provide useful and practical guidance in the administration of L-dopa (L-3, 4-dihydroxyphenylalanine) for the treatment of Parkinson's disease. Interest in L-dopa therapy has been considerably enhanced following the recent release of this drug for use by all medical practitioners. Previously it had been restricted in Canada to three special investigators who had permission to carry out specific observations on L-dopa therapy in a limited number of parkinsonian patients. It is already evident that since the drug is now available on a commercial and unrestricted basis, many physicians are anxious to acquire confidence and experience in its administration. This should be possible after an initial consultation and possibly a follow-up discussion with a specialist experienced in this field. It is anticipated that in a short time L-dopa will be the most commonly used drug in the treatment of Parkinson's disease. It is likely to be given in various combinations with other previously known forms of therapy.

Within the past three years, L-dopa therapy has been the subject of several extensive reviews by investigators in various parts of the world.[1-6] The preliminary studies in both animals and humans date back to 1957[7] and the first clinical trials to 1960[8] and 1961.[9, 10] The latter were limited in scope and produced a few conflicting reports about the effectiveness of the drug.[11] Although Birkmayer and Hornykiewicz,[9] as well as Barbeau, Murphy and Sourkes,[10] had carried out encouraging clinical tests with L-dopa during the early 1960's, it was not until 1967, following the report of Cotzias, Van Woert and Schiffer[1] on 16 patients treated with D, L-dopa, that the medical world began to appreciate the potential implications of this form of therapy in parkinsonian patients. Subsequently a number of studies of increasingly large groups have satisfactorily demonstrated the advantages and limitations of this form of treatment. In addition there have been reports describing some of its associated problems. There is considerable evidence in both humans and animals to indicate that the cell loss in the substantia nigra in patients with Parkinson's disease is primarily responsible for the deficiency of dopamine. It is presumed that a specific deficiency of striatal dopamine is in turn related to the symptoms and signs of Parkinson's disease. L-dopa is capable of crossing the blood-brain barrier and subsequently, by means of decarboxylase, is converted into the active substance dopamine (Fig. 1). Both experimental and clinical studies have suggested that the depletion of dopamine can be corrected by the administration of L-dopa either orally or intravenously. In addition, with the collaboration of Hornykiewicz,[12] we ourselves have evaluated the levels of homovanillic acid (the main breakdown product of dopamine) in the cerebrospinal fluid of patients before and after the administration of oral L-dopa. Bernheimer, Birkmayer and Hornykiewicz[13] had previously shown in postmortem studies that there was a pronounced decrease in the concentration of homovanillic acid (HVA)

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in the substantia nigra and striatum of patients with Parkinson's disease. Furthermore, they demonstrated a substantial decrease in HVA in the cerebrospinal fluid of parkinsonian patients. This decrease was confirmed in the 15 of our patients in whom the HVA in the cerebrospinal fluid was determined. In each case the administration of L-dopa was associated with a pronounced rise in the HVA level which amounted to 10 to 50 times the initial level. This evidence suggested that there had been an increased perfusion of the brain tissue by homovanillic acid (and presumably dopamine) following L-dopa administration. Similar increases in CSF homovanillic acid levels have been reported by several authors since our unreported observations in early 1969.

Until recently L-dopa has been cautiously administered under specific investigational circumstances. It has been the general impression that treatment with this drug is associated with considerable risk, and for this reason very close supervision in a special hospital setting has been required. It is now our opinion that the cautious administration of L-dopa can be initiated and continued in many patients on an outpatient basis without recourse to hospital. Careful clinical observation, as well as laboratory studies, will, of course, still be required. Moreover, a number of patients will still have to be admitted to hospital in view of the severity of their disability as well as the existence of other potentially complicating factors.

Our program was instituted over two years ago, in November 1968, and since then we have personally observed over 100 patients receiving L-dopa therapy. In the first group of 20 patients, treatment was started while they were under close surveillance in hospital for a period of four

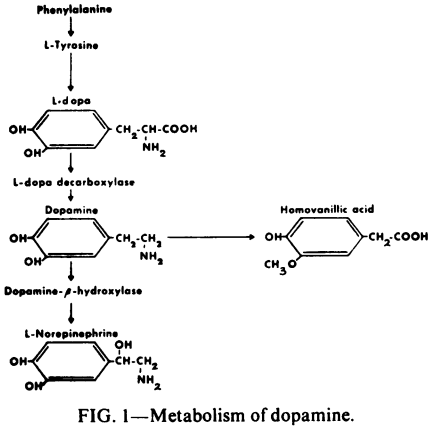

FIG. 1—Metabolism of dopamine.

to 16 weeks. In the last 15 months this has proved unnecessary, and the majority of the additional 80 patients we have treated have had therapy instituted entirely on an outpatient basis. It is to be noted, however, that about one-third of these 80 patients have been started on L-dopa while in hospital owing to a variety of medical and social reasons unrelated to the treatment itself. These have included severe disability and immobilization, as well as conditions such as hypertension, previous cardiac disease, etc., which have warranted particularly close supervision. In addition, many patients who have been referred from long distances have been treated in hospital; it has also been possible to manage some of these as outpatients.

Our institution and management of L-dopa treatment on an outpatient basis is not original, as this method had been used by the Miami group and by the Cornell group under the care of McDowell *et al.*[6] The advantages of outpatient therapy in terms of hospital usage, social and psychological adjustment, and the evaluation of drug effect in a normal non-hospital setting are obvious. In addition, more patients have had therapy available without prolonged and unnecessary delay in hospital admission. These factors will become increasingly important as the drug becomes more widely used.

Therapy should begin only after patients have had careful assessment in terms of the nature and seriousness of the disease. Blood pressure levels should be determined with the patient lying down and standing up. A general mental assessment should be made to rule out possible organic or psychotic factors. Pretreatment studies should include ECG, EEG, blood investigation (hemoglobin, leukocyte count, hematocrit, sedimentation rate, blood smear), biochemical tests (blood urea nitrogen, SGOT, SGPT, bilirubin, alkaline phosphatase, uric acid, blood sugar, Coombs' test) and urinalysis. It is particularly important to establish a base line for these laboratory tests because occasionally some of them appear to have been influenced by the administration of L-dopa.

Selection of patients

Patients who have indisputable evidence of Parkinson's disease without other disabling disease are to be considered for L-dopa treatment. The akinetic factor, i.e. the inability to initiate voluntary movements, is most likely to respond. Rigidity is affected favourably, and tremor may be influenced either beneficially or adversely. The severity of the disease appears to affect the result. Patients who have minimal evidence of Parkinson's disease are not really L-dopa candidates at this stage of our knowledge and experience. Only patients who have moderate or advanced disability should be considered for this form of treatment. It is conceivable that at some time in the future the slighter manifestations may be treated also with L-dopa, on the theoretical basis that such treatment will prevent progress of the disease. This has so far not been proved, although some of our clinical observations would support this contention; we have not observed advance of the disease in patients who are receiving and tolerating L-dopa therapy. However, one is not at present justified in treating early parkinsonian cases with L-dopa in view of its known side effects. L-dopa is not warranted in patients whose primary disability is tremor, with little bradykinesia or rigidity, although there have been a few exceptions to this dictum. In some advanced cases of the disease the response to L-dopa therapy may be minimal. This has been attributed to a presumed extreme degree of dopamine depletion. However, this observation is by no means a general indication to withhold therapy.

Generally speaking, age is not an important factor in the selection of patients. Our series includes one patient aged 16 years. This is of particular interest in view of the rarity of juvenile Parkinson's disease without evidence of previous encephalitis. This patient showed typical features of moderately advanced Parkinson's disease with akinesia, rigidity and tremor. There was an overall distinctly favourable response to L-dopa given in a daily dosage of 4.5 g. The cause of the parkinsonian state in this lad is not yet clear but may be related to previous treatment of leukemia with methotrexate. A more detailed case report of this patient will be published shortly by Dr. B. Laski.

Several patients were in the fifth decade and two were in the ninth; the average age was 62 years. Younger patients have an advantage in that they may have increased tolerance for L-dopa. There is some evidence that patients with post-encephalitic parkinsonism do not respond as favour-

ably as those with idiopathic Parkinson's disease. The effect of L-dopa may be less in drug-induced forms of the disease; with rare exceptions these patients will improve when the causative agent, e.g. phenothiazine, reserpine, is discontinued.

Patients with severe cardiac, hepatic or cerebrovascular disease should not receive L-dopa. Active peptic ulcer is also a contraindication because of the gastrointestinal irritation that can ensue. Patients who have a tendency to psychosis generally tolerate the medication poorly, and sometimes L-dopa enhances the manifestations of these underlying mental disorders. Patients with marked dementia generally respond unfavourably. Diabetic patients can be treated satisfactorily but require close supervision. Moderate hypertension is not a contraindication; indeed, L-dopa may have a beneficial effect, since it is known sometimes to produce hypotension, although occasionally a hypertensive episode has been noted.

Methods

There are many ways of instituting treatment with L-dopa, and the various series that have been reported to date lack uniformity. The 250-mg. capsule or tablet is the most practical for both the initial and continued treatment. Larodopa (Roche) is presently being produced only as a scored 500-mg. tablet, twice the dosage used in most investigational series, so that half-tablet dosage is necessary.

When the patient is hospitalized, dosage can be increased rapidly, from 250 mg. on the first day, given immediately after breakfast, with increments of 250 mg. daily within the limit of the patient's tolerance. This means that within a 20-day period the patient will reach a level of approximately 5 g. daily (five 250-mg. capsules or tablets four times daily, generally taken immediately after meals and at bedtime). The medication should be taken with food at all times because it frequently tends to produce nausea or vomiting.

If the patient shows intolerance by lack of appetite, nausea, vomiting or other possible side effects, the dosage is lowered or else is maintained and the increments are delayed. This is a matter where variation is optional. Generally a level of 3 to 5 g. can be reached without too much difficulty, but some patients develop troublesome side effects at much lower levels (1 to 2 g. daily). The usual maintenance level is 3 to 5 g. per day, but sometimes as little as 1.5 to 2 g. daily will produce a favourable response. At times it is advantageous to administer the drug in divided doses five to six times daily to prevent some of the adverse effects, particularly nausea. While in hospital, blood pressure levels should be taken twice daily and biochemical studies should be repeated once a week.

On an outpatient basis the administration of L-dopa should be more cautious, and we have found that 250 mg. on the first day with a 250-mg. increase every three days to a maximum of approximately 20 capsules (5 g.) or occasionally more, is the most satisfactory. This dosage has averted most of the known side effects although nausea and loss of appetite still may occur. The patient is watched carefully at repeat visits in one, three, six, 10 and 14 weeks, and the dosage level can be adjusted according to tolerance. The laboratory tests, blood pressure, etc. are taken at each visit.

Other drugs that have been useful in Parkinson's disease (anticholinergic agents, antihistamines, etc.) can be continued in conjunction with L-dopa therapy and the combination has proved to have considerable advantage for prolonged periods. At a later stage in treatment one may consider cautiously reducing or discontinuing the other medications. L-dopa should not be administered along with monoamine oxidase inhibitors because of a potential and unpredictable hypertensive reaction. Other antidepressants do not have this effect, but tricyclic antidepressants, i.e. imipramine (Tofranil) and amphetamines, should be used only with caution. Patients receiving L-dopa therapy should not take vitamin products that contain pyridoxine (vitamin B_6) as this can detract from the beneficial effects. Phenothiazines, rauwolfia alkaloids (reserpine) and butyrophones (haloperidol) which are known to produce parkinsonian features are potentially antagonistic to L-dopa and should not be used in combination therapy.

Results

The results of treatment with L-dopa in our patients are essentially similar to those of several of the more favourable series that have been reported during the past 18 months.[2-6] Of our group of 100 patients, 83 have had treatment and observation for a period of three to 22 months, which can be considered adequate for assessment. (The results in the other 17 treated patients cannot be properly evaluated at this early stage.) In 64 patients (78%) the degree of clinical improvement justifies the continued use of L-dopa therapy. This implies a subjective and objective total functional improvement of 30% or more with reference to akinesia, rigidity and, occasionally, tremor (Table I). It is well known that not all of these features are necessarily improved; the least predictable is tremor, although at times this has been strikingly reduced. There may be some improvement of the mask-like facies, seborrhea, and sometimes sialorrhea, but these responses are less dramatic than the more striking effect of L-dopa therapy on akinesia and rigidity. The benefit to post-thalamotomy patients was comparable to the response of the unoperated group. It is to be noted that L-dopa was discontinued in 19 patients (22%) because of failure of response or inadequate response, or because of serious or intractable side effects.

TABLE I
Results of L-dopa therapy (83 patients treated for 3 to 22 months)

Degree of total functional improvement	*No. of patients*	*%*
Marked	15	18
Moderate	49	60
Discontinued:		
(a) mild or no response	12	14
(b) due to side effects	7	8

All of the patients who have responded favourably to L-dopa therapy have achieved an obviously increased independence in terms of their self-care and social adjustment. Several who had been essentially chronic bed patients were able to move about independently and improved to a degree which allowed their discharge from chronic hospital or nursing home and their return to relatively independent home facilities. Many have been able to undertake household responsibilities, such as cooking and gardening, which previously had been beyond their capacity. Several patients who had been markedly restricted in their work activity have been able to improve their efficiency, sometimes to a striking degree. Three patients have been able to participate in active sports, such as

tennis and golf, from which they had earlier been compelled to withdraw. One improved patient was faced with the problem of returning to work after seven years of financial support from a total disability pension.

Complications

Adverse reactions are common and are listed in Table II. It is to be noted that loss of appetite, nausea and vomiting are the commonest undesirable manifestations and can be satisfactorily dealt with only by dosage reduction or by the more frequent administration of smaller quantities of L-dopa. Generally we have not found specific diets, antacids or antinauseants of significant value, although at times dimenhydrinate (Gravol) or cyclazine (Marzine) 50 mg. prior to L-dopa administration may be of limited benefit. One patient developed recurrent vomiting after ingesting a single capsule of L-dopa; the same reaction followed rectal administration of the drug and its use had to be abandoned.

TABLE II
Common side effects of L-dopa (83 patients)

Side effects	*No.*	*%*
Nausea, vomiting, anorexia.	32	40
Involuntary movements....	28	34
Psychic changes.....	10	12
Hypotension.....	5	6
Cardiac irregularities.....	3	4

The problem of associated involuntary movements is of major importance and occurs in approximately one-third of the patients treated with L-dopa. The involuntary movements are entirely dose-dependent and will generally subside after reduction of dosage although their disappearance may be delayed. Sometimes they are incapacitating and unpleasant, and may distress the relatives as well as the patient. Frequently they take a bizarre form such as facial and tongue dystonia, spasms, irregular breathing patterns, and various combinations and forms of chorea, dystonia and dyskinesia affecting the extremities. We have attempted to counteract these involuntary movements by the use of trifluoperazine (Stelazine) or methyldopa (Aldomet)[14] which, in theory, should act as an antagonist to L-dopa, but our observations suggest that when these drugs are helpful, the improvement is at the expense of some of the beneficial effects of L-dopa. There was a distinct impression that in a small number of patients the involuntary movements were controlled by these additional agents without prejudice to the relief conferred by L-dopa, but this was by no means the rule. Certainly, further study in this respect is warranted. Sometimes it is necessary to reduce the dosage markedly (from 4 g. to 2 g. daily) before the movement disorder ceases, and then one can gradually increase the medication to a level of approximately 3 g. without their recurrence. The individual tolerance varies considerably and requires close personal adjustment, as the rules are not absolute with the general exception of relative dose-dependency in each individual. Not infrequently the dyskinesia may not appear until treatment has continued at an apparent optimum dosage for a period of two months or longer.

The emotional and mental effects may prove to be a source of considerable concern. There may be agitation, insomnia, confusion, depression, hallucinations, paranoia, psychotic episodes, euphoria and even suicidal tendencies. If any of these features already exist or are latent they may be enhanced during L-dopa therapy. Patients who develop these disorders may prove to be unsatisfactory candidates for continued L-dopa therapy. Patients who have gross EEG irregularities often prove to have a limited tolerance for L-dopa. A small minority of patients have a very definite increase in libido while receiving L-dopa. In our series, two female patients and one male patient were aware of such changes. In the majority of patients with Parkinson's disease, sexual function has ceased for a prolonged period and their state in this regard is generally not altered by L-dopa therapy.

A variety of biochemical abnormalities have been observed during L-dopa administration, but with the rare exception these do not have clinical manifestations and are reversible spontaneously during continued therapy or upon reduction of dosage. In our experience, elevations of serum uric acid and alkaline phosphatase are occasionally seen. Elevations of SGOT, blood urea nitrogen and bilirubin and a positive direct Coombs' test are less common. One patient had a rise in BSP excretion to 30% in conjunction with an elevation of SGOT and alkaline phosphatase; however, these liver function tests returned to normal shortly after discontinuing L-dopa. A liver biopsy was taken by means of peritoneoscopy shortly after the drug was stopped. The gross appearance of the liver suggested a subacute form of hepatitis and the presence of fibrin on the surface that the process was a recent one. The histology revealed mild fatty metamorphosis.

Occasional hypotensive episodes with a decrease in both systolic and diastolic pressures of at least 20 mm. Hg have been noted. Although generally these are asymptomatic, they may be associated with clinical manifestations. If the patient complains of lightheadedness or dizzy spells, one must be careful to check for postural hypotension as this may account for such symptoms. In these cases dosage reduction is essential. If a hypotensive state is produced, there is the theoretical possibility that coronary or cerebral artery thrombosis may be induced, although such occurrences have been rare. One of our patients who had been treated with L-dopa for over one year developed coronary thrombosis without apparent hypotension; following recovery from the acute phase he has been able to continue effective L-dopa therapy on a slightly reduced level. Another patient developed acute coronary artery insufficiency shortly after taking a single capsule of L-dopa (250 mg.); hypotension was not detected but may have been transient. L-dopa therapy was not continued following this episode.

Discussion

It is apparent that L-dopa therapy is often remarkably effective and has resulted in a high degree of objective and subjective improvement in the majority of patients with Parkinson's disease who have significant akinesia and rigidity. The variation in response to therapy is considerable. Treatment is generally more effective in patients who have not reached the advanced stages of the disease. Some patients who have been totally disabled have returned to useful activity beyond one's most fanciful dreams. This, unfortunately, is not always the situation. Other cases have been somewhat disappointing in spite of the fact that the dosage levels have been increased to 6 or 7 g. daily over a prolonged period of several months. In some patients the degree of improvement is not sufficient to warrant continued treatment, particularly if

there are any undesirable side effects such as nausea, loss of appetite, etc. In these circumstances L-dopa can be discontinued and then a decision may be reached as to whether the treatment was of any real value. There seems to be little harm in stopping the drug rather abruptly, and it can subsequently be slowly reinstituted. General surgical procedures can be carried out during L-dopa therapy without increased risk. The dosage level should not be changed and the medication omitted only immediately before and after the operation. The anesthetist should pay particular attention to the blood pressure levels. Tolerance to L-dopa does not seem to be induced by prolonged usage or by re-administration of the drug. After a period of treatment the dosage will sometimes have to be increased to obtain the full beneficial effects that had been noted previously from a smaller dosage. On the other hand, one can sometimes reduce the dosage below the optimal level that had been required previously. One cannot really establish the optimal dosage until the patient has been on treatment for at least three to four months. We have had several patients in whom a favourable response was anticipated judging from the usual criteria for selection, but, in effect, few or no beneficial results were observed, even in cases of overt akinesia and rigidity. The explanation for this is not forthcoming, but this relatively small group of patients must be recognized.

Barbeau[5] has claimed that R04-4602, an experimental decarboxylase inhibitor which can be used to advantage in parkinsonian patients in conjunction with much smaller quantities of L-dopa, has reduced some of the peripheral side effects such as nausea, vomiting and hypotension. The toxicity of this substance is being investigated and it is not available for general use.

Since the predominant beneficial effects of L-dopa are related to akinesia and rigidity, one might theorize that thalamotomy which primarily reduces tremor would be usefully combined with L-dopa administration in some patients. From our limited experience we have established a firm conclusion that no patient should have a thalamotomy performed before there has been a more prolonged assessment of L-dopa. Cooper[15] has stated that many patients referred to him for surgical treatment of Parkinson's disease have been found to respond extremely well to L-dopa. When they are offered operation for appreciable residual tremor, they will frequently decline because the tremor is no longer the handicap that it was prior to L-dopa therapy. This is presumably because of the beneficial effects on muscle tone and rigidity, and the consequent improvement of limb function in spite of the residual tremor. Some of these features warrant further observation before permanent conclusions can be drawn.

There appears to be no improvement in the mental status of patients with senile or pre-senile dementia who have received L-dopa therapy primarily for their parkinsonism. We have treated two patients with progressive supranuclear palsy with L-dopa and in neither case was there the satisfactory response occasionally reported in the literature.[16]

Conclusions

L-dopa therapy has proved to be the most useful medication available to date for the treatment of Parkinson's disease; it is of particular benefit for the akinesia and rigidity of the condition. Many patients can be treated entirely on an outpatient basis.

There is considerable variation in the response to L-dopa, but generally a level of 4 to 6 g. daily is useful although at times we have found that as little as 1 to 3 g. is satisfactory. Its combination with other drugs hitherto employed in parkinsonism has proved to be most useful and is better than the administration of L-dopa alone.

Side effects, particularly gastrointestinal upset and involuntary muscular movements (dyskinesia), occur in over 50% of the treated patients. The majority of these are reversible and dose-dependent. Careful individual adjustment of dosage is required in order to prevent or alleviate these undesirable features.

The cautious and slow build-up of dosage level is preferred, as this will frequently avoid some of the known side effects and allow the patient to take levels of the medication that would not be tolerated if the amount were rapidly increased. Careful follow-up at repeated intervals is essential and includes the recording of blood pressure and performance of biochemical tests.

It is our expectation that L-dopa therapy will prove to be the most commonly used drug in the treatment of Parkinson's disease. Facility in the use of this medication will develop with time and experience, although constant caution must be exercised in view of the known side effects. It is probable that a satisfactory means will be found of preventing these side effects by combining L-dopa with other therapy.

It is conceivable that in the future all patients with Parkinson's disease, even at an early phase, will be treated with L-dopa on the theoretical basis that this will prevent further development of the disease. At present such a conclusion is unjustified and early cases are generally not considered for L-dopa therapy.

Résumé

Le traitement au L-dopa de la maladie de Parkinson: évaluation récente

L'intérêt du L-dopa comme traitement de la maladie de Parkinson s'est considérablement accru depuis que ce médicament est à la portée de tous les médecins praticiens. Nous présentons ici notre expérience personnelle avec ce produit dans 83 cas qui ont été traités au cours des 22 derniers mois, dans l'espoir que ceci pourra constituer un guide pratique de son administration. Grâce au L-dopa, nombre de parkinsoniens prevent être traités facilement en service externe sans qu'il soit nécessaire de les hospitaliser au préalable.

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