TREATMENT OF SEVERE PARKINSONISM WITH L-DOPA*

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SUMMARY

The beneficial effect of L-dopa in the treatment of Parkinson's disease is confirmed, although the success rate was slightly lower than reported in other studies. This can be explained by the fact that only elderly and very severely disabled patients were treated. Akinesia and rigidity were the symptoms which responded best to this form of treatment. Tremor responded poorly and most of the therapeutic failures were in patients where tremor was the major complaint. It is possible that this symptom may respond to very much larger doses.

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James Parkinson first described the condition which today bears his name in 1817. He had a sceptical attitude towards the medicinal treatment of the disease, but current research has given hope of providing more effective drug therapy. A fruitful approach has been the treatment of parkinsonism by stereotactic surgery but recently, with the advent of L-dopa, a dramatic advance has been made in the medical treatment of the 'shaking palsy'.

The history of the development of this new form of treatment starts in 1959 when Sano *et al.*[1] and Carlsson[2] showed that the normal corpus striatum had the highest level of dopamine concentration in the brain. Carlsson[2]

also showed that in rabbits, when the brain was depleted of catecholamines by reserpine L-dopa could reverse this process. In 1960, Ehringer and Hornykiewicz[3] showed that in disease states affecting the corpus striatum, this organ showed a decreased concentration of dopamine. In 1961 Barbeau *et al.*[4] demonstrated a lower urinary excretion of dopamine in patients with parkinsonism as compared with normal subjects. Barolin *et al.*[5] published a very important case report of predominantly right-sided parkinsonism, showing a lower dopamine content in the left corpus striatum as compared with the right. Poirier and Sourks[6] showed that electrocoagulation of the substantia nigra in the monkey caused a fall in dopamine and noradrenaline content in the striatum on the same side while anomalies of movement developed on the contralateral side.

The first attempts at using L-dopa as a therapeutic agent in parkinsonism were by Barbeau[7] and Birkmayer and Hornykiewicz.[8] However, it was only in 1967 that Cotzias *et al.*[9] published reports on the first large series of patients treated with L-dopa, and showed that this compound was remarkably effective in alleviating the symptoms of parkinsonism. These results have been confirmed in several published reports.

Tyrosine, an amino acid derived from protein in the diet, is converted in the body to adrenaline by a rather complicated pathway:

Tyrosine
↓ oxidation
L-dihydroxyphenylalanine (L-dopa)
↓ decarboxylation
Dopamine
↓ oxidation
Noradrenaline
↓ methylation
Adrenaline

It would appear that in at least some cases of parkinsonism there is a biochemical disorder in the brain leading to a decreased amount of dopamine in the corpus striatum. Attempts at correcting this by the administration of dopamine were not successful because this substance does not cross the blood-brain barrier. Administering the precursor of dopamine, i.e. L-dopa, appears to be effective.

Previous studies have investigated the efficacy of L-dopa in all grades of Parkinson's disease. The object of our trial was to investigate the efficacy of the drug only in very severely disabled patients.

METHOD AND MATERIAL

Twenty-four very severely disabled patients were selected for the trial of L-dopa therapy. In each case at least 75% of the symptoms fell within grade 3 on the Webster scale rating. All had failed to respond, or continued to deteriorate, on conventional drug therapy with physiotherapy. Two patients had to stop treatment with L-dopa. One developed severe recurrent hypotension at the beginning of the trial when we did not appreciate the degree of resistance patients could acquire to the hypotensive effects of the drug. The second patient developed a relapse of a chronic paranoid-depressive illness soon after admission to hospital. Cessation of treatment had no effect on the mental illness.

The aetiology of the parkinsonism in the remaining 22 patients appeared to be either idiopathic (paralysis agitans) or arteriosclerotic in origin. As far as could be ascertained there were no cases of postencephalitic parkinsonism.

Dosage

All previous drugs and physical therapy were continued without change. The initial dose of L-dopa in all patients was 125 mg *t.d.s.* This was increased by 125 mg daily and from the second day the drug was administered 4 times a day after each meal and at bedtime. Increase in dosage was always started with the evening dose. When hypotension or gastro-intestinal disturbances proved troublesome at the beginning of therapy the drug was temporarily discontinued and then restarted with 62·5 mg *b.d.*, gradually increasing as before. The maximum dosage administered was 6 g per day. This figure was determined largely by the cost and availability of the drug at the time and the fact that in other trials most of the therapeutic responses were obtained at this dosage level.

All patients were admitted to hospital for the first 2 weeks of the trial and thereafter treated as outpatients. Before admission all serious diseases other than parkinsonism were excluded. In particular, renal, hepatic, cardiac and haematological disorders were looked for.

During their stay in hospital all patients had their blood pressure measured every 4 hours, day and night. During the day this was done in the erect and supine positions. After each dose of L-dopa they were required to stay in bed for at least 1 hour until we were sure that there was no hypotension, especially after assuming the erect position. Before starting treatment a full blood count, blood urea, Coombs and liver function tests were carried out in each case. These were repeated after 2 weeks and thereafter every 6 weeks.

RESULTS

All those patients who appeared to benefit from this treatment began to show improvement between the second and sixth weeks. Assessment at the end of 6 months' trial showed dramatic improvement in 6 patients, moderate improvement in 6 patients, only slight improvement in 3 patients, and 7 patients were considered unchanged.

In the 12 patients who showed significant improvement, the most striking feature was the improvement in akinesia and rigidity. Akinesia was usually the first symptom to respond and this occurred as early as the second week of treatment. Tremor responded poorly. Of the 10 patients who showed slight or no improvement, 7 presented with severe tremor as their main complaint with little or no akinesia and rigidity. Five patients in this series had previously undergone surgical treatment for parkinsonism.

At the end of 12 months' therapy only 2 patients who initially showed a good response had relapsed and did not respond to an increase in dosage to 8 g per day. The following case records illustrate the degree of improvement in 2 patients.

Case 1. A 63-year-old male had parkinsonism for 8 years. On admission the patient was emaciated, bedridden, incontinent of urine and faeces, and aphonic. He could not even whisper. He was unable to do anything for himself. His whole body was rigid and tremor was present in both upper limbs. The severest possible degree of physical disability was present. Six weeks later, on 4 g of L-dopa per day, there was a tremendous change. He was able to walk unaided. His voice was clearly audible and speech was reasonably clear. He was able to feed himself and had gained weight. There was full control of bladder and bowels. A significant degree of akinesia was still present but he could get in and out of a chair unaided and could dress and undress himself except for closing and opening buttons.

Case 2. A 64-year-old female suffered from parkinsonism for 6 years, and had been using a wheelchair for the previous few months. The whole body was rigid, with little tremor. Akinesia was severe and she could not walk or stand without support. She could not turn over by herself in bed, or get out of a chair without assistance and she was unable to feed or dress herself. Voice volume was still fairly good. Three months after starting treatment consisting of 3 g L-dopa a day there was dramatic improvement. She could walk with good balance and was able to climb and go down stairs without assistance. She could get in and out of a chair with ease and had no difficulty turning over in bed. She could feed and dress herself and was doing some of her own housework.

SIDE-EFFECTS

In the first 3 months of the trial the only side-effect which proved troublesome was postural hypotension. In one patient this was so severe that the treatment was abandoned. In 12 other patients who developed this complaint reduction of dosage and the avoidance of sudden changes of posture made continuation of therapy possible. Lying in bed for at least 1 hour after each dose of L-dopa during the first 2 - 4 weeks of treatment, appeared to be the best prophylactic measure.

Five patients complained of severe nausea after each dose of L-dopa. This was controlled by ensuring that the drug was taken on a full stomach together with the administration of an antacid mixture. The complaint eventually cleared in all the affected patients. Three patients complained of insomnia during the first few weeks of treatment. No patient showed any haematological change, disturbance of blood urea or liver function tests. The patient who relapsed into chronic mental illness at the beginning of therapy, did so after taking only 375 mg of L-dopa. Stopping treatment had no effect on the psychotic symptoms so that it is possible that the L-dopa was not responsible for the relapse.

About 3 months after starting the trial the complaint of dyskinesia was first noted and so far 6 patients have presented with this side-effect. This usually takes the form of facial grimacing or chewing movements and the patient may not be aware of his involuntary movements. Those who are aware of the chewing movements usually attribute them to dryness of the mouth. In 2 cases these movements were accompanied by twitching of the neck and shoulder muscles. In all cases these involuntary movements responded rapidly to a reduction in dosage but in 1 patient this was accompanied by a significant return of akinesia and rigidity. This patient finds his involuntary movements less of a burden than parkinsonism.

We did not observe any of the other side-effects reported in the literature. These include rashes, tachycardia, palpitations, extrasystoles, psychic symptoms, e.g. confusional states, agitation, dyspnoea, hypertension (temporary) and more severe involuntary movements, chorea and hemiballismus. Biochemical and haematological changes have been reported but these are uncommon when the maximum daily dose does not exceed 4 - 8 g per day. Neutropenia, thrombocytopenia and haemolytic anaemia are the most serious blood dyscrasias which may occur and routine blood counts are essential while the drug is being administered. A temporary rise in blood urea has been reported in elderly patients.

DISCUSSION

The treatment of Parkinson's disease with laevodopa represents one of the most dramatic advances in the therapy of neurological disorders. Unfortunately laevodopa does not 'cure' the disease but only produces relief from symptoms and decreased disability. It is as if the clock was turned back in the patient's disease process. The signs and symptoms of Parkinson's disease are still all present but to a much lesser degree. We cannot at present explain why some patients fail to respond and why some respond better than others. It is our impression that those patients who did not show any evidence of significant intellectual or personality deterioration responded best.

Fewer side-effects were encountered in this trial than have been previously reported. This could possibly be attributed to our much smaller starting dose, the more gradual increase to a therapeutic level and the absence of patients suffering from postencephalitic parkinsonism. The usual recommended starting dose is 0·5 - 1 g per day. Our experience before this trial suggested that severely disabled, frail patients could not tolerate this dose to begin with. Although our usual starting dose was 125 mg *t.d.s.*, in 5 patients this had to be reduced by half because of nausea and vomiting (3) and hypotension (2). In order to avoid side-effects the increase in dosage must be very gradual and it took 4 - 6 weeks to reach a total dose of 4 g per day. During this period it is essential that the patient be kept under very close medical supervision. Most of the side-effects reported so far appear to be dose-dependent and respond to reduction in dosage and more gradual increase thereafter.

Our observation that hypokinesia and rigidity responded better than tremor has been confirmed in other trials.[11] It is possible that with much larger doses laevodopa will also ameliorate tremor as reported by Cotzias *et al.*[12] Increased availability of the drug and decreased cost will make such treatment possible. We noted in a few patients a temporary aggravation of the tremor when rigidity was

relieved, but this soon passed off.

When a therapeutic response has been obtained it is nearly always possible to reduce the total daily dose to a lower maintenance level without clinical deterioration. We have found that maintenance doses as low as 1·5 g per day may be adequate. This reduction in dosage should be attempted after about 6 months' therapy and must be carried out under very careful supervision. The rate of decrease should be as carefully controlled as the mode of increase to a therapeutic level at the beginning of treatment. Three of our patients who suddenly stopped treatment for 2 days did not appear to suffer any ill-effects, but one patient who stopped for 5 days suffered a severe relapse of his parkinsonism.

There are few contraindications to therapy with L-dopa. Caution should be exercised in the presence of renal, hepatic and cardiac disease and the drug should not be administered concurrently with MAO inhibitors or within 1 month of taking such preparations.[13] It has been shown that failure to observe this precaution may result in very severe degrees of hypertension or the development of psychotic symptoms. It has also been reported that pyridoxine hydrochloride renders L-dopa ineffective so that this vitamin should not be administered to patients taking L-dopa.

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