L-threo-3,4-dihydroxyphenylserine Treatment for Gait Apraxia in Parkinsonian Patients

MASAFUMI YOSHIDA, SHINJI NOGUCHI AND SHINKEN KURAMOTO

Department of Neurosurgery, Kurume University School of Medicine, Kurume, 830 Japan

Received for publication March 22, 1989

Summary: L-threo-3,4-dihydroxyphenylserine (L-DOPS) was administered to six parkinsonian patients for the treatment of gait related akinesia which was refractile to L-DOPA treatment. One responded with marked improvement and one with only mild improvement. Although number of patients who respond markedly to this noradrenaline precursor, L-DOPS, is limited, L-DOPS was felt to be the most effective treatment modality for L-DOPA refractile gait related akinesia and L-DOPA related orthostatic hypotension.

Key words: L-threo-3,4-dihydroxyphenylserine (L-DOPS) — parkinsonism — gait apraxia — freezing phenomenon — akinesia

Introduction

Since the introduction of L-DOPA for the treatment of parkinsonism (Cotzias et al. 1969), many patients have shown initially dramatic symptomatic improvement with this treatment. Although in some patients this symptomatic improvement lasts for many years, in many patients the effects of L-DOPA start to wear off in 3 to 5 years. In addition, the appearance of L-DOPA related side actions and complications further contributes to the symptomatic deterioration of patients undergoing long-term L-DOPA treatment (Sweet and McDowell, 1975; Barbeau, 1976; Markham and Diamond, 1981; Narabayashi and Nakamura, 1981; Farn and Bressman, 1984).

Basically, L-DOPA treatment is a replacement therapy; as experience accumulated, it became apparent that L-DOPA fails to halt the basic disease process of parkinsonism (Sweet and McDowell, 1975; Narabayashi, 1985). Therefore, although L-DOPA still remains a universally accepted main treatment modality, other adjunctive and/or palliative treatments are used to combat symptomatic deterioration of long-term parkinsonism (Fahn et al. 1979; Lieberman et al. 1980; Birkmayer and Riederer, 1984; Teychenne, 1984; Narabayashi, 1985; Pfeiffer et al. 1985).

Recent biochemical studies of autopsied material have revealed that the brain obtained from Parkinson's disease is deficient not only of dopamine, but also of other catecholamines especially noradrenaline (Riederer et al. 1977; Nagatsu et al. 1979 and 1982). Based on these findings, new agents to counteract each deficiency are now being introduced (Narabayashi et al. 1981; Narabayashi, 1985).

L-threo-3,4-dihydroxyphenylserine (L-DOPS) is a precursor of noradrenaline (Corrodi and Fuxe, 1967; Creveling et al.
Based on the possible link between noradrenaline deficient state in the central nervous system (CNS) and akinetic symptoms, L-DOPS can be expected to counteract particularly gait related akinesia such as gait apraxia, festination and retropulsion, and possibly other forms of akinesia, all of which are most often noted in patients who had long been on L-DOPA treatment and extremely difficult to control because they are usually refractile to L-DOPA treatment (Narabayashi and Nakamura, 1981). Initial reports on clinical trials of L-DOPS for gait related akinesia seem to be promising (Narabayashi et al. 1981, 1984 and 1986; Kondo, 1984; Ogawa et al. 1984; Suzuki et al. 1984a).

The authors report their experience with L-DOPS treatment of gait related akinesia or “freezing in gait” in parkinsonian patients.

Methods and Clinical Materials

L-DOPS, supplied in 100- or 200-mg capsules, was kindly provided by the Sumitomo Chemical Company, to be used for clinical trial of L-DOPS at the Parkinsonian Clinic of the Kurume University Hospital. Before starting L-DOPS, consent for entering the clinical trial study of L-DOPS treatment was obtained from patients and their family. Six patients entered this study. Their clinical profile is shown in Table 1. None had developed parkinsonism before the age of 40 years. Duration of L-DOPA treatment ranged from 1 to 14 years. All were receiving L-DOPA at the time of the L-DOPS trial. For the type of L-DOPA medication, combination of L-DOPA and decarboxylase inhibitor was given in all except two cases (Cases 2 and 5) in which L-DOPA alone was given. The dose of L-DOPA ranged from 1000 to 3000 mgm or its equivalent in cases L-DOPA was given with decarboxylase inhibitor. In addition to L-DOPA, anticholinergics, amantadine and bromocriptine were given as necessary. Neurologically gait disturbance was prominently noted as well as other symptoms of parkinsonism and therefore Yahr’s Grade III stage was registered in all but one case (Case 2) in which prominent symptoms were rigidity and tremor and only mild gait disturbance (festination) was noted.

Before L-DOPS trial, Cases 3 and 6 had undergone unilateral stereotaxic thalamotomy and Case 5 bilateral thalamotomy. Cases 2 and 3 underwent bilateral and contralateral thalamotomy, respectively, following the initiation of L-DOPS treat-

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Age at Onset</th>
<th>Duration of L-DOPA Therapy (yrs)</th>
<th>Maximal Dose of L-DOPA (mg)</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>68</td>
<td>61</td>
<td>(&gt;3)</td>
<td>100</td>
<td>n. a.</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>58</td>
<td>56</td>
<td>1</td>
<td>300</td>
<td>mild</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>62</td>
<td>57</td>
<td>5</td>
<td>600</td>
<td>marked</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>74</td>
<td>67</td>
<td>3</td>
<td>800</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>68</td>
<td>60</td>
<td>3</td>
<td>800</td>
<td>temporary</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>67</td>
<td>49</td>
<td>14</td>
<td>600</td>
<td>n. a.</td>
</tr>
</tbody>
</table>

In Case 1 precise duration of L-DOPA treatment could not be assessed.

n. a.: not applicable, i.e., L-DOPS was discontinued because of side effect.
L-DOPS THERAPY FOR GAIT APRAXIA

69

As associated conditions, the following were noted: Case 3 had diabetes mellitus and low back pain due to herniated lumbar disc; Case 1 had bilateral subdural hematoma which required burr hole evacuation on several occasions and manic-depressive psychosis which required appropriate medications at the psychiatry clinic.

For pre- and post-treatment clinical evaluation, the same protocol as used in the Phase II Open Trial Study (Narabayashi et al. 1986) was utilized. In this protocol physical findings and functional disabilities, including petit pas, festination, retropulsion, freezing in gait, freezing in speech and dysdiadochokinesis, were scored using five rating scale (0 to 4: 0 being none and 4 markedly present) at each clinical visit. For each items effect of L-DOPS was rated by change of the score into five categories at the end of the study: 1) marked improvement, 2) moderate improvement, 3) mild improvement, 4) no effect and 5) worsening. For the final rating of improvement for an individual patient same rating for improvement categories described above was used and the patient was rated based on improvement in gait related akinesia. All ill effects noted after administration of L-DOPS was registered as complication(s) related to L-DOPS unless clinical situation positively identified other causes. All of these evaluation was done by one of the authors (MY).

L-DOPS was started at an initial dose of 100 mg per day, and increased as tolerated, with the increment rate of 100 mg every 1 to 7 days, reaching as much as 800 mg per day, until clinical improvement was noted. The patients were evaluated at least once every two weeks until optimal dose was determined, after which the patients were followed once a month, excepting in case clinical situation required more frequent evaluation.

Patients who showed no clinical improvement when L-DOPS was increased to 800 mg per day were classified as non-responders. L-DOPS was discontinued in the case of non-responders and patients who exhibited L-DOPS related side action. For the responders L-DOPS was continued, and the dose was adjusted as necessary.

Results

Two (Cases 2 and 3) responded to L-DOPS treatment, one of which (Case 3) dramatically. Two (Cases 4 and 5) showed no improvement. In two cases (Cases 1 and 6), adverse effects attributed to L-DOPS were noted; these included abdominal cramping pain (Case 6) and worsening of manic-depressive psychosis (Case 1). For these two cases, L-DOPS had to be discontinued before the intended maximum dose was reached. An adverse effect was also noted in Case 2, in which development of palpitation prohibited the further increase of L-DOPS. In one patient (Case 2) improvement in the orthostatic hypotension was noted. No apparent improvement was noted in any of the other signs or symptoms of parkinsonism.

Illustrative Cases:

Case 3: This 62-year-old woman who had right V. im. (nucleus ventralis intermedius thalami) thalamotomy 2 years prior to admission entered the Kurume University Hospital for left thalamotomy. Besides right sided parkinsonian symptoms, she was suffering from severe gait disturbance consisting of marked festination, retropulsion and gait apraxia. After L-DOPS was started, her gait improved dramatically and no festination, retropulsion, or gait apraxia was noted when the dose reached 600 mg per day. Three days before surgery all medication including L-DOPS was discontinued. The left V. im. thalamotomy was performed without incidence. Postoperatively, despite
discontinuation of L-DOPS, no gait disturbance was noted except moderate retropulsion until one month after surgery, when her gait gradually deteriorated. Two months after surgery, L-DOPS treatment, 300 mg per day, was resumed. The dose was increased to 600 mg per day over a period of three weeks; however, only mild improvement was noted. Although the patient had been on L-DOPS treatment, further worsening of her gait was noticed beginning 8 months after surgery, and therefore 2 months later L-DOPS dose was gradually increased during the next two months. However, only slight improvement of gait was noted at the end of this time period, at which time she was receiving 900 mg of L-DOPS daily.

Comment: This case showed long lasting gait improvement even after the discontinuation of L-DOPS. However, when her gait apraxia recurred one month after left V. im. thalamotomy, tolerance to L-DOPS was noted.

Case 2: This 58-year-old woman was admitted to the Kurume University Hospital for right thalamotomy. Besides left-dominant parkinsonian symptomatology, she was suffering from mild gait disturbance, primarily due to festination. L-DOPS treatment was started. When the dose was increased to 300 mg per day, mild improvement in gait disturbance was noted. However, at this dose, the patient complained of occasional palpitation which prohibited further dose increase. Three days before surgery, all medication including L-DOPS was discontinued. The right V. im. thalamotomy was performed. Her gait remained moderately improved until four months later when festination recurred and dizziness on standing was noted. L-DOPS treatment was then resumed. These symptoms responded to 200 mg per day of L-DOPS treatment. Fourteen months after the first thalamotomy, the patient underwent left V. im. thalamotomy. Postoperatively she did well. Her medications, including L-DOPA and L-DOPS, which were discontinued a few days prior to the second thalamotomy, were not resumed postoperatively. On follow-up two months after the second thalamotomy, she did not show any signs of festination.

Comment: This case also showed a long lasting effect of L-DOPS on gait improvement. Although only a low dose of L-DOPS could be tolerated, the benefits obtained from improvement of gait and orthostatic hypotension were gratifying for this patient to perform daily activities. Whether or not the bilateral thalamotomy also helped to "cure" the gait apraxia and orthostatic hypotension remains moot.

Discussion

It is generally accepted that the fundamental neurochemical abnormality encountered in parkinsonism is decreased tyrosine hydroxylase activity with consequent dopaminergic deficiency in the central nervous system (Ehringer and Hornykiewicz, 1960; Bernheimer et al. 1963). However, recent neuropharmacological and neuroanatomical studies have revealed that the parkinsonian brain is also deficient in noradrenergic neurons, dopamine beta hydroxylase, and phenylethanolamine-N-methyl transferase (PNMT); noradrenaline receptor abnormality was also noted (Riederer et al. 1977; Nagatsu et al. 1979 and 1982). This noradrenergic abnormality of parkinsonism seems to appear relatively late in the course of L-DOPA treatment. In fact, decrease in CSF dopamine beta hydroxylase activity is more often noted in patients who have received L-DOPA treatment for more than 5 years than in those on L-DOPA treatment for shorter period of
L-DOPS THERAPY FOR GAIT APRAXIA

Clinically, the type of akinesia often noted after long-term L-DOPA treatment is predominated by freezing phenomena with respect to gait, speech and writing (Narabayashi, 1983). Freezing phenomenon is characterized by failure to perform quick repetitive movement and freezing or convergence of such movement to a certain fixed frequency usually of 5-5.5 Hz range although very slow repetitive movement may be conducted. This phenomenon is often noted at initiation of repetitive movement (start hesitation). Therefore, this phenomenon is a peculiar type of akinesia and may well be called the "fourth motor symptom of parkinsonism" (Nakamura et al. 1976; Narabayashi and Nakamura, 1981). These symptoms usually do not respond to a further increase in L-DOPA dosage and for those patients in this situation freezing of gait among other symptoms is often times the most disabling in conducting daily life.

As a precursor of noradrenaline, L-DOPS was introduced to counteract noradrenaline deficiency and thus to improve symptoms presumably related to this state. Initial experience with L-DOPS treatment which was initiated for the improvement of gait apraxia was promising (Narabayashi et al. 1981, 1984 and 1986; Kondo, 1984; Ogawa et al. 1984; Suzuki et al. 1984a). In addition, L-DOPS was found to be effective for disease conditions other than parkinsonism and for symptoms other than gait apraxia, such as: juvenile form of parkinsonism (Narabayashi et al. 1981 and 1984); familial amyloid polyneuropathy (Suzuki et al. 1980, 1981 and 1982); pure akinesia (Itouji et al. 1984; Yamamoto and Ujike, 1985; Narabayashi et al. 1986); Shy-Drager's syndrome (Sakoda et al. 1985) and neoplasm in the caudate head (Suzuki et al. 1984b). Symptoms which responded to L-DOPS include; gait apraxia; freezing of speech and writing; depressive state; orthostatic hypertension (Suzuki et al. 1981; Birkmayer et al. 1983; Sakoda et al. 1985); up and down phenomenon; L-DOPA induced apraxia and other symptoms of parkinsonism (Kondo, 1984). Drug-induced dyskinesia, however, seems to be worsened by L-DOPS (Kondo, 1984).

Our experience with L-DOPS treatment was too limited to draw any definite conclusions. However, some aspects of our study warrant attention.

In our cases, none of the signs or symptoms listed above other than gait apraxia and orthostatic hypotension showed apparent improvement. However, L-DOPS seemed to be effective in only a small portion of parkinsonian patients presenting with gait apraxia. The neuropharmacological states in which gait apraxia can be observed include: 1) dopamine deficiency in the striatum, for which L-DOPA is effective, 2) non-dopamine deficiency exhibiting normal dopamine metabolites in biological fluid, for which L-DOPA is not effective, 3) side effects of long-term L-DOPA treatment (Narabayashi, 1983; Tanaka and Nishino, 1985). All of our patients most likely belong to category 3 although inclusion of patients in category 2 can not be excluded. Our response rate is similar to that noted in the Cooperative Phase II Study on L-DOPS (Narabayashi, 1985; Narabayashi et al. 1986) in which approximately 20-30% of patients had marked or moderate improvement and additional one third only slight improvement. Kondo (1984) reported that the response to L-DOPS was not related to either duration of illness or that of L-DOPA treatment.

There is a possibility that appropriate amount of L-DOPS or noradrenaline could not reach the strategic site(s) of action. Moreover, since in this study the maximum dose was designed to be 800 mg per day, some of the cases who did not respond to a lower dose might have re-
sponded to higher doses of L-DOPS. Nevertheless, since only one third of patients with gait related akinesia are benefited by L-DOPS treatment, it may be speculated that, as gait apraxia may result from many different biochemical states, cause-effect relationship between noradrenaline deficiency and gait apraxia may be present in only a small portion of patients with apraxia. Clinically, it has so far been impossible to select a group of patients who respond to L-DOPS.

It is of interest that in our two responders (Cases 2 and 3), effect of L-DOPS lasted for 4 and 1 months, respectively, after discontinuation of the drug. Both of them underwent thalamotomy which usually has little effect on akinesia (Kelly and Gillingham, 1980). Therefore, if the effect of surgery (Narabayashi, 1983) can be excluded, this unusually long lasting effect suggests an extremely slow turnover or metabolism of L-DOPS (Corrodi and Fuxe, 1967), or an indirect action via some other mechanism.

In one of the two responders (Case 3) tolerance of the L-DOPS effect was noted. Whether or not the bilateral thalamotomy is related to this phenomenon is not known. Nevertheless, it may be speculated that a neurophysiological alteration at receptor site similar to that observed with long-term L-DOPA treatment might be responsible for this phenomenon.

Altogether, although the response rate was low, L-DOPS appears from this study to be a useful therapeutic measure for L-DOPA non-responsive gait apraxia which so far did not seem to respond to any therapeutic modality. No clue for selecting patients who will benefit by L-DOPS treatment is known. Therefore, further understanding of the biochemical mode of L-DOPS action on gait apraxia is needed.

The administration of L-DOPS in parkinsonism should be primarily aimed at the improvement of gait apraxia, and possibly used as treatment for orthostatic hypotension.

Acknowledgment: The authors are grateful to the Sumitomo Chemical Co. Ltd. for providing the L-DOPS.

References

CORRODI, H. and FUXE, K. (1967). The effect of catecholamine precursors and monoamine oxidase inhibition on the amine levels of central catecholamine neurons after reserpine treatment or tyrosine hydroxylase inhibition. Life Sci. 6, 1345-1350.
EDWARDS, D.J. and SEDLOCK, M.L. (1982). Increased brain concentration of homovanillic
L-DOPS THERAPY FOR GAIT APRAXIA

acid in rats treated with threo-3, 4-dihydroxyphenylserine. J. Pharm. Pharmacol. 34, 685-686.


YOSHIDA, ET AL.


