ENTERIC COATED LEVODOPA FOR THE MEDICAL MANAGEMENT OF PARKINSONISM

MASAFUMI YOSHIDA AND SHINKEN KURAMOTO

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

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Enteric coated levodopa was administered to 6 parkinsonians who developed early and late complications of levodopa therapy in our clinic. Some of these complications were well controlled by enteric coated levodopa, which seemed to prove that at least part of the problems of levodopa treatment are of peripheral origin. Role of enteric coated levodopa in medical management of parkinsonism is discussed.

INTRODUCTION

Despite its initial enthusiasm and optimism (McDowell, et al., 1970), levodopa treatment of parkinsonism is not without problems especially when the patients are placed on long-term treatment (Ambani and Van Woert, 1973; Fahn, 1974; Sweet and McDowell, 1974, 1975). Even in the short-term treatment, although the vast majority of parkinsonians are benefited by levodopa treatment, there still remain quite a few patients who cannot enjoy this beneficial effects of levodopa simply because of intolerance to this medication (McDowell et al., 1970). Various modifications in the way of administration of levodopa have been tried in order to eliminate these long-term and short-term side effects (Sweet and McDowell, 1974). These include careful reduction of dose of levodopa and administration of levodopa combined with peripheral decarboxylase inhibitor (Sweet and McDowell, 1974). But there still remain some patients who continue to suffer from side effects. We administered enteric coated levodopa in such a group of patients with either acute or chronic side effects of levodopa and the role of this form of levodopa treatment in the medical management of this degenerative disease is discussed.

METHOD AND CLINICAL MATERIAL

During the course of the treatment of parkinsonians in our clinic with various combination of thalamotomy, levodopa with or without peripheral decarboxylase inhibitor and other anti-parkinsonian medications, we encountered patients who developed a state in which the effect of levodopa was not constant, i.e., the period of hypokinetic state after levodopa administration was followed by state of hypokinetic state before succeeding doses. And other patients complained of intolerance to levodopa from initiation of therapy. Enteric coated levodopa (Dopaston, S. E.) was administered to 6 patients who developed above complications and who were found to be difficult to be controlled by standard management in our clinic mentioned above. Some of these patients were evaluated by Cornell Weighted Scale (McDowell et al., 1970) before and after
initiation of enteric coated levodopa. In the presence of fluctuation of symptoms the scale was taken when medication was effective.

REPORT OF CASES

**Case 1.** 61-year-old male who has been suffering from parkinsonism since the age of 48 years was placed on enteric coated levodopa because of appearance of period of inadequate levodopa effect. This moderately disabled parkinsonian (Cornell Weight Scale 22 for physical examination score and 43 for functional disability score) has been treated with levodopa since 1971. The patients had been doing relatively well till March, 1978 when he noted involuntary nodding of the head. At that time he was on DIC 3T/day (One tablet of DIC contains 100 mgm of levodopa and 25 mgm of Ro 4-4602), levodopa 2,000 mgm/day and Artane 6 mgm/day in three divided doses. Various dosage of levodopa and DIC were tried and this involuntary movement disappeared when the patient was placed on DIC 1T q. d., levodopa 2,000 mgm/day and Artane 6 mgm/day in three divided doses. However, patient noted period of ineffectiveness of levodopa for 30 min. to 1 hr. before and after the doses at noon and in the evening manifested by increase in akinesia. Akinesia also noted in the morning lasted till about 1.5 hrs after morning dose.

Dopaston S. E. 1,800 mgm in three divided doses was started on November 30, 1978 and the dose was gradually increased to the maintenance dosage of 3,600 mgm/day and Artane 6 mgm/day in three divided doses. The period of ineffectiveness during the noon time and in the evening disappeared and the patient was doing well. Although slight worsening of akinesia was noted, there was no significant change in Cornell Weighted Scale before and during Dopaston S. E. treatment.

**Case 2.** 46-year-old female who has been suffering from parkinsonism since the age of 40 years was placed on enteric coated levodopa because of appearance of period of inadequate levodopa effect. This mildly disabled parkinsonian was treated with combination of Ro 4-4602 and levodopa since 1975.

In the course of treatment with combination of Ro 4-4602 and levodopa the patient gradually developed episodes of akinesia manifested by difficulty in writing and walking about 30 minutes after each medication which lasted for 2 and half hours followed by period of marked improvement in akinesia. The patient was placed on enteric coated levodopa 1,800 mgm/day in three divided dose on November 20, 1978 with disappearance of akinetic episode.

The patient was doing well till November 25, 1978 when she started suffering from nausea and vomiting and enteric coated levodopa was discontinued and combination of Ro 4-4602 and levodopa was resumed. Because of reappearance of fluctuation of symptoms enteric coated levodopa was again given on December 2, 1978 together with oral antiemetics. There was a delay in onset of effect of levodopa and for approximately 3 and half hours after each dose the patient noted some stiffness, but she subjectively felt much better on enteric coated levodopa. Cornell Weighted Scale was almost unchanged before and during treatment with enteric coated levodopa. The dose was subsequently increased to 2,000 mgm/day.

**Case 3.** 65-year-old female who has been suffering from parkinsonism since
the age of 59 years was referred to our clinic because of intolerance to levodopa manifested by severe anorexia and general malaise. Cornell Weighted Scale was done on November 20, 1978 and revealed physical examination scale to be 25 and functional disability scale to be 32. The patient was placed on enteric coated levodopa on the same day after evaluation and although she complained intermittently of anorexia and general malaise, she essentially torelated enteric coated levodopa 1,200 mgm/day in three divided doses and became able to perform part of her job as a housewife. Cornell Weighted Scale was unchanged on physical examination scale, but improved on functional disability scale (−10) during treatment.

Case 4. This is 48-year-old female who has been suffering from parkinsonism since the age of 41 years. This mildly disabled parkinsonian has been treated with levodopa since 1973. In the course of levodopa treatment the patient noted delay in onset and shortening of duration of effectiveness of levodopa. Enteric coated levodopa 2,400 mgm/day in three divided doses was started of February 8, 1979 and subsequently increased to 3,000 mgm/day with resultant disappearence of fluctuation of symptoms. However, the control of the symptoms was not quite optimal and slight to moderate akinesia was noted and the patient suffered from intermittent nausea and vomiting.

On March 5, 1979 the patient suddenly developed chills, flushing of body and perspiration and became severely akinetic. She was not able to turn over in the bed and was speechless with freezing of the upper limbs in flexion posture. The dosage was decreased, but no improvement was noted. Medication was changed to combination of peripheral decarboxylase inhibitor and levodopa, on which regimen the patient became able to care herself, but no house keeping was possible.

Case 5. This is 45-year-old female who has been suffering from parkinsonism since the age of 43 years. She had been treated with levodopa 1,200 mgm, but because of cardiovascular and gastrointestinal side effects, enteric coated levodopa was started on December 7, 1978. When the dosage was increased to 1,800 mgm/day in three divided doses, the patient complained of discomfort in epigastrium and palpitation which became manifest about two hours after each dose and lasted for about 30 minutes. Enteric coated levodopa 2,000 mgm/day was given in 5 divided doses and palpitation and epigastric discomfort disappeared. The parkinsonian symptoms improved markedly and she became able to conduct almost normal life.

Case 6. This is 46-year-old female who has been suffering from parkinsonism since the age of 42 years. She has been treated with levodopa since 1974 and with combination of levodopa and Ro 4-4602 since 1976.

There was a delay in onset of effect of levodopa after the 1st dose of the day for about 2 hours and appearence of slight akinesia shortly before evening dose. Akinesia in the morning was slightly improved by giving extradose of 200 mgm of levodopa in the morning when she woke-up, and the dosage was given in 5 divided doses. However, the effect of levodopa appeared about 2 hours after each dose and lasted less than 2 hours. While levodopa was effective the patient was symptom free, but otherwise the patient was akinetic and suffered from gait apraxia. Enteric coated levodopa 1,800 mgm/day in
three divided doses was started and during the period of 3 weeks the dosage was gradually increased up to 3,000 mgm/day. However, no satisfactory control of parkinsonian symptoms was noted and the patient refused to continue on enteric coated levodopa. Combination of levodopa and Ro 4-4602 was resumed and the patient continued to suffer from the same problem.

DISCUSSION

Levodopa for the treatment of parkinsonians who are deficient in dopaminergic nigrostriatal system (Hornykiewicz, 1963) is theoretically rationale and its clinical beneficial effects are well documented. However, true mechanism of its beneficial and adverse effects is not well understood (Wurtzmann, et al., 1970; Weiss, et al., 1969). Rinne and Sonninen (1973) measured catecholamine and their metabolites in autopsied brain from parkinsonian patients and from the control group and suggested exogenous levodopa can increase the metabolism of dopamine in the parkinsonian brain by increasing dopamine metabolism of surviving dopaminergic substantia nigra neurons. However, they could not find relationship between concentration of the catecholamine in the brain and clinical response.

For mechanism of "akinesia paradoxica" formation of dopa metabolites from gut flora acting as a false transmitter (Sandler, 1973), condensation products of levodopa metabolites competing with dopamine for its receptors (Hornykiewicz, 1973), competition between levodopa and other large neutral amino acids for transport across both the intestine and the blood-brain barrier (Cotzias, 1973) are postulated. Determination of plasma dopa and its metabolites revealed that patients generally were more likely to be hyperkinetic when plasma levels of dopa were rising or higher than 10 μM and akinetic with falling levels or levels less than 9 μM (Fahn, 1974), however, this relationship was not definite (Sweet and McDowell, 1974). No correlation was found with plasma levels of HVA, OMD or 5HIAA (Sweet and McDowell, 1974). Sweet and McDowell (1974) suggested that at least part of the problem may lie peripheral to the brain, i.e., absorption from gut, metabolism in the liver or sequestration in sites unknown (Fahn, 1974).

Our experience with enteric coated levodopa showed that this medication was partly useful when the patient encountered intolerance to levodopa with gastrointestinal or cardiovascular symptoms or developed disabling fluctuation of symptoms on levodopa therapy. Combination of decarboxylase inhibitor and levodopa was reported to be effective in these situations (Sweet and McDowell, 1974). However, Fahn (1974) noted no effect on fluctuation of plasma levodopa level and on the "on-off" phenomenon in parkinsonians when the patients received this combination, which is in contrary to Tissot et al. (1969) and Dunner et al. (1971) who noted plasma levels of dopa to be higher and remained high longer when peripheral decarboxylase inhibitor was given than otherwise. The fluctuation of effectiveness of levodopa when the patient was given a combination of levodopa and decarboxylase inhibitor which we noted in our cases (Okada, et al., 1979) was relatively well controlled in our cases by enteric coated levodopa. Enteric coated levodopa by slow absorption from the gut seemed to maintain the plasma levodopa level not causing various complications, but satisfactory for its action in the central
nervous system without much fluctuation.

Although this measure is only partly helpful for reversal of acute and chronic complications of levodopa therapy, maintenance of minimal effective concentration of levodopa without much fluctuation at its site of action seems to be optimal for long-term levodopa therapy in selected parkinsonian patients and might lead to prevention of chronic complications if such are due to over optimal levodopa concentration within the central nervous system.

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REFERENCES


