

Review

Factors Affecting Levodopa Effects in Parkinson's Disease

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Levodopa is the gold standard for the treatment of Parkinson's disease (PD) because of its outstanding clinical efficacy. However, the majority of patients experience various adverse reactions, including the wearing-off phenomenon, the on-off phenomenon, dyskinesia and psychiatric symptoms. The response to levodopa depends not only on the intrinsic responsiveness of the patients, but also on various other important factors including the type of levodopa preparation, its absorption/metabolism, the blood-brain barrier, age at onset of disease and concomitant use of anti-parkinsonian drugs. This review summarizes factors which influence the effects of levodopa in PD. To minimize levodopa-induced adverse reactions and to relieve long-term parkinsonian symptoms, levodopa therapy should be conducted by taking these factors into consideration.

Key words: dopamine agonist, monoamine oxidase-B (MAO-B) inhibitor, catechol-*O*-methyltransferase (COMT) inhibitor, blood-brain barrier, age at onset, large neutral amino acids, gastric acidity

Thirty years after its clinical introduction, levodopa remains the most effective symptomatic treatment for Parkinson's disease (PD). However, within a few years of clinical treatment with levodopa, the majority of patients begin to experience various adverse reactions, including the wearing-off phenomenon, the on-off phenomenon, dyskinesia and psychiatric symptoms (1-3). The response of patients with PD to levodopa is not merely affected by intrinsic factors, but also by various factors including the type of levodopa preparation, its absorption/metabolism, the blood-brain barrier, age at

onset of disease and concomitant use of anti-parkinsonian drugs (Table 1). To minimize levodopa-induced adverse reactions and maximize therapeutic efficacy, levodopa therapy should be conducted by taking these factors into account.

I. Peripheral dopa decarboxylase inhibitors

Current levodopa therapy generally employs a combined levodopa/peripheral dopa decarboxylase inhibitor (DCI) preparation. There are 2 DCIs available: carbidopa (USA, Europe, and Japan) and benserazide (Europe and Japan).

In a study on the plasma levels of levodopa and dopamine following the administration of levodopa/DCI combinations, the levodopa/benserazide (200 mg/50 mg) combination produced a high plasma levodopa level and a low dopamine level, while the levodopa/carbidopa (250 mg/25 mg) combination produced a low plasma levodopa level and a high dopamine level (4). This suggests that levodopa underwent extensive peripheral metabolism to dopamine in the case of the levodopa/carbidopa combination.

Treatment with low doses of the levodopa/carbidopa (100/10) preparation available in Japan, which has a lower content of carbidopa than the combination used in western countries [levodopa/carbidopa (100/25)], may achieve a weak therapeutic response due to the inadequate DCI dose. Indeed, it has been reported that equal therapeutic effects were achieved by the levodopa/carbidopa (100/10) preparation and the levodopa/benserazide (100/25) preparation with 100% and 67% levodopa equivalent doses, respectively (5).

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Table 1 Factors affecting levodopa effects

1. Peripheral dopa decarboxylase inhibitor
2. Absorption of levodopa
1) type of preparation
2) gastrointestinal motility
3) gastric acidity
4) restriction of protein intake
3. Blood-brain barrier
1) large neutral amino acids
2) 3- <i>O</i> -methyl dopa (3-OMD)
4. Levodopa/dopamine metabolism
1) peripheral
2) central
5. Intrinsic responsiveness
1) pre-synaptic
2) post-synaptic (dopamine receptors)
6. Age at onset of disease
7. Concomitant use of anti-parkinsonian drugs
1) anticholinergics
2) dopamine agonists
3) monoamine oxidase-B (MAO-B) inhibitor
4) catechol- <i>O</i> -methyltransferase (COMT) inhibitor

II. Absorption of levodopa

1) Type of preparation

Treatment with levodopa will be ineffective if the drug is not absorbed. Indeed, failure of the levodopa/carbidopa combination to improve symptoms has been reported, with the cause being identified as the failure of the tablets to dissolve, and with subsequent change to the levodopa/benserazide combination resulting in improvement (6). This may be because benserazide is easily soluble in water and acid, while carbidopa is only slightly soluble. If necessary, levodopa/DCI tablets should be administered after conversion to a powder or liquid (7, 8).

2) Gastrointestinal motility

Since levodopa is absorbed from the small intestine (9), the use of metoclopramide has been reported to increase gastrointestinal motility, leading to an increase in absorption of levodopa from the small intestine (10). Even in recent years, the concomitant use of cisapride, which increases gastrointestinal motility, has been reported to increase the plasma levodopa level and enhance the improvement of symptoms (11, 12). However, benzamides have the pharmacological nature of dopamine receptor antagonists and can themselves induce parkinsonism (13), so such combination therapy must be per-

formed under close observation. Another gastrointestinal motility stimulating agent, domperidone, which does not cross the blood-brain barrier (14), has been reported to induce parkinsonism. When we administered domperidone to PD patients, symptoms improved or remained unchanged in 14 out of 15 cases, and the patients who achieved improvement were those who had been changed from metoclopramide to domperidone. This may be because metoclopramide is a dopamine receptor antagonist that easily crosses the blood-brain barrier, while domperidone is believed to be unable to cross this barrier. In one case, however, domperidone resulted in deteriorated symptoms. This probably indicates that domperidone has difficulty crossing the blood-brain barrier, but that trace amounts may pass through.

3) Gastric acidity

Because levodopa is easily soluble in acid, its absorption varies with gastric acidity. Accordingly, Yazawa *et al.* (15) showed that, in patients with gastric hyposecretion, symptoms may be improved and plasma levodopa levels increased by administration of levodopa plus lemon juice. These authors also emphasized that improvement of symptoms is well correlated with plasma levodopa levels, indicating that maintenance of a high plasma levodopa level is the most critical factor in achieving therapeutic effects. Although this phenomenon has been attributed to the difference in gastric acidity, considering that absorption of levodopa occurs in the duodenum, the possibility of gastrointestinal motility being promoted by an increase in gastric acidity cannot be ruled out.

4) Restriction of protein intake

Since the 1975 report by Mena and Cotzias (16) that restriction of protein intake alleviates the wearing-off of levodopa effects, several studies on this method have been published (17-20). Although there is no clear agreement regarding the appropriate level of protein intake restriction, restriction to the smallest possible protein intake at breakfast and lunch leads to relief from the wearing-off phenomenon and allows a reduction of the levodopa dose (20). However, long-term treatment requires milder restriction, while racial differences and different eating habits should also be taken into consideration. In the USA, efforts have been made to put this therapy to practical use by altering the dietary protein and carbohydrate balance (21). We recommend that Japanese patients restrict their total protein intake at breakfast and

lunch to 7.5 g for the first 2 weeks and to 12.5 g from the third week, with 45–50 g being taken at dinner to ensure the necessary protein intake for health. Levodopa competes with such large neutral amino acids as valine, leucine, isoleucine, tyrosine, tryptophan and phenylalanine, since levodopa and these amino acids depend on the same transport system during absorption from the intestinal tract and crossing of the blood-brain barrier (21, 22). Therefore, although the mechanism by which the protein-restricted diet works is not known in detail, it may be related to the following known actions of large neutral amino acids: (i) inhibition of the absorption of levodopa from the intestines, (ii) competitive inhibition of levodopa at the blood-brain barrier, and (iii) inhibition of uptake and metabolism by brain tissue as well as inhibition at the receptor level (9, 23–25). In our study, there was no relapse of symptoms for at least three days after returning to a normal diet, so factors (i) and (ii) alone cannot explain the mechanism, suggesting the involvement of factor (iii). Protein-restricted diet therapy cannot be recommended for all patients, since strong willpower is required to continue it for a long period and psychiatric symptoms may become worse in some patients.

III. Blood-brain barrier

In connection with the protein-restricted diet therapy described above, there have been a number of reports that large neutral amino acids competitively inhibit levodopa from crossing the blood-brain barrier (23, 24). When levodopa undergoes peripheral metabolism by catechol-*O*-methyltransferase (COMT), 3-*O*-methyldopa (3-OMD) is formed, which competitively inhibits levodopa from crossing the blood-brain barrier. Accordingly, efforts are now ongoing to develop COMT inhibitors, as will be described later. However, the hypothesis that 3-OMD competitively inhibits levodopa at the blood-brain barrier (26, 27) has been contradicted in recent reports, which revealed that 3-OMD did not alter fluorodopa transport into brain and did not alter the alleviation of parkinsonian symptoms (28, 29).

Intraperitoneal administration of β -adrenergic agonists was reported to facilitate crossing of the blood-brain barrier by levodopa in monkeys with parkinsonism induced by 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) (30).

IV. Levodopa/dopamine metabolism

Levodopa becomes unable to cross the blood-brain barrier after it undergoes peripheral metabolism to dopamine by L-amino acid aromatic decarboxylase, but this can be prevented by concurrent use of a DCI. However, if levodopa is converted to 3-OMD by peripheral COMT, the 3-OMD competitively inhibits levodopa's penetration of the blood-brain barrier and thereby reduces the response to levodopa therapy. The use of a COMT inhibitor, entacapone or tolcapone, with levodopa/DCI combinations markedly inhibits 3-OMD production and increases the amount of levodopa crossing the blood-brain barrier (31–35). Although 3-OMD once attracted attention as a cause of motor fluctuations, the on-off phenomenon and dyskinesia (26, 27), most recent reports have been negative in this regard (28, 29).

Selegiline (deprenyl) inhibits monoamine oxidase-B (MAO-B), another important enzyme for dopamine metabolism. Because it is known to prevent MPTP-induced dopamine neurotoxicity, selegiline was tested for possible prophylaxis of the progression of neural degeneration in the DETATOP Study (36), but no convincing evidence of inhibition of progression was obtained. It is now generally recognized that the effectiveness of levodopa is enhanced and prolonged by selegiline owing to the suppression of dopamine metabolism in the brain (37, 38). In other words, selegiline can be seen as an economizer for levodopa.

Accordingly, the concomitant use of levodopa/DCI combinations, MAO-B inhibitors, and COMT inhibitors is being considered for the future. However, there have been no reports on long-term combination therapy with these 3 enzyme inhibitors, so neither the influence on levodopa metabolism nor the systematic effects are known.

V. Intrinsic responsiveness

It is generally thought that levodopa is converted to dopamine in the brain before acting on dopamine receptors. When PD has progressed until the number of dopamine nerve terminals, or conversion sites, has markedly decreased, conversion of levodopa to dopamine may be impaired, and the therapeutic response will diminish. In general, the dopamine pool is small and dopamine metabolism is accelerated in the brains of PD patients (39). With regard to the mechanism of symptoms known

as motor fluctuations during long-term levodopa therapy, it is now generally considered that wearing-off is caused by presynaptic degeneration of the dopaminergic system, and that the on-off phenomenon is a postsynaptic disorder that probably develops at the receptor level (40).

In general, persistently low presynaptic levels of neurotransmitters cause an increase in postsynaptic receptor levels known as denervation supersensitivity. A study on the postmortem changes of brain dopamine receptor levels in untreated PD patients showed that the affinity of D1 and D2 receptors in the caudate nucleus and globus pallidus was increased, and this affinity was reduced by treatment with levodopa (41).

A study of the D2 receptor in PD patients using positron emission tomography (PET) and single photon emission computed tomography (SPECT) showed that D2 receptor expression was unchanged or increased (42-44), but that it was down regulated by levodopa therapy (43, 44). Another SPECT study of the D2 receptor revealed that patients responsive to dopaminergic agents had high receptor levels (45), indicating that maintenance of an adequate D2 receptor level is important for drug efficacy. Reduced D2 receptor affinity induced by varying the stimulation of the receptor with levodopa is generally considered to account for development of the wearing-off phenomenon during chronic levodopa treatment (26, 46).

At least 5 different dopamine receptors (D1-D5) are known to exist. However, there are no ligands that selectively bind to each receptor subtype, so a 2-family classification (D1 and D2 receptor families) is still used in pharmacotherapy (47). Although a therapeutic effect on PD is produced via the D2 receptor, prior stimulation of the D1 receptor is known to augment the response to D2 receptor stimulation (48, 49). Dopamine derived from levodopa stimulates both receptor families and has an excellent therapeutic effect, but the dosage of levodopa needs to be minimized because of various problems created by long-term treatment. Thus, the following approach would currently appear to be optimal for use in standard pharmacotherapy: after stimulation of both D1 and D2 receptors with a low dose of levodopa, dopamine agonists should be given concomitantly to further stimulate D2 receptors (50).

It has been reported that idiopathic PD and parkinsonism can be distinguished by the response to subcutaneous injection of a dopamine agonist, apomorphine (45, 51). Patients responsive to apomorphine show high D2

receptor levels on SPECT (45), reconfirming that the response to dopamine supplementation therapy is dependent on the D2 receptor.

Continuous infusion of levodopa has been reported to achieve sustained dopamine receptor stimulation and to control motor fluctuations (52), but this strong and continuous receptor-stimulation method has also been reported to induce tolerance to levodopa and the prolongation of dyskinesia (53). Sustained mild stimulation of dopamine receptors by means of a sustained-release preparation of levodopa (for example Sinemet CR) or by dopamine agonists may effectively relieve motor fluctuations over the long term.

VI. Age at onset of disease

Levodopa therapy generally produces various adverse reactions, including the wearing-off phenomenon, dyskinesia and psychiatric symptoms, and candidate factors for the development of wearing-off include a decrease in striatal dopamine storage, a modification of postsynaptic receptors and a change in peripheral pharmacokinetics (24). Although there is supporting evidence that the former 2 factors play a role in the wearing-off phenomenon (54-56), the contribution made by the peripheral pharmacokinetics of levodopa is controversial. Recently, Murata *et al.* reported that long-term levodopa therapy accelerates the absorption of levodopa (57). They showed that duration of levodopa treatment and peripheral pharmacokinetic features of levodopa (increases in the values of the peak levodopa concentration (C_{max}) and in the area under the time-concentration curve (AUC) with decrease in the values of T_{max} and $T_{1/2}$) were significantly correlated. And, younger onset patients had a higher C_{max} . The natural history of PD is quite valuable, and it is notable that PD progresses more slowly in younger than in older patients with the disease (58), indicating that younger onset patients receive levodopa therapy for longer periods. These findings may explain why the wearing-off phenomenon occurs so frequently after levodopa therapy in the younger onset group. On the other hand, although long-term levodopa therapy steepened the pattern of the levodopa time-concentration curve in the middle-age-onset PD patients, the slope of the curve did not change even after long-term levodopa therapy in the senile-onset group (59). This may explain why the senile-onset PD patients scarcely experience the wearing-off phenomenon even after long-term levodopa therapy (60).

VII. Concomitant use anti-parkinsonian drugs

Problems associated with the levodopa preparations themselves were discussed in the previous sections. However, the influence of concomitant drug use should also be considered, since PD is often treated by coadministration of several anti-parkinsonian agents. PD patients have intestinal hypomotility and the concurrent use of anticholinergic agents can markedly suppress intestinal motility, possibly inhibiting the absorption of various drugs including levodopa.

Dopamine agonists such as bromocriptine are commonly used in combination with levodopa for the treatment of PD. We previously examined the effects of bromocriptine administered alone or in combination with levodopa on dopamine turnover in the striatum of rats with hemi-parkinsonism (61). The parkinsonian striatum showed a 3.4-fold increase of dopamine turnover relative to the control striatum, as often observed in the brain of PD patients (39). Levodopa therapy more markedly increased dopamine turnover in the parkinsonian striatum (a 53-fold increase over the control level) than in the control striatum (a 5-fold increase over the control level). However, bromocriptine specifically and markedly suppressed the levodopa-induced abnormal activation of dopamine turnover in the parkinsonian striatum (61). This indicates that dopamine agonists should be used during long-term levodopa therapy.

Another approach to ameliorate motor fluctuations is the use of drugs that interfere with the catabolism of levodopa and/or dopamine. Irreversible and reversible MAO-B inhibitors such as selegiline (deprenyl) and lazabemide inhibit the metabolic breakdown of dopamine in the striatum. Alternatively, COMT inhibitors (entacapone and tolcapone) interfere with the peripheral breakdown of levodopa, leading to the prolongation of the antiparkinson effect of levodopa and allowing a reduction of its daily dose (31-35). As described in the section on levodopa and dopamine metabolism, if dopamine metabolism is suppressed by treatment with MAO-B inhibitors or COMT inhibitors, the dopamine derived from levodopa will remain in the brain for longer periods, thereby enhancing the effectiveness of levodopa.

Acknowledgments. This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas and Scientific Research (C) from the Japanese Ministry of Education, Science, Sports and Culture, and by Grants-in-Aid for Research on Brain Science, Comprehensive Research on Aging and Health, and Research on CNS Degenerative Diseases from the

Japanese Ministry of Health and Welfare.

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Received November 15, 1999; accepted January 7, 2000.