Acta Medica Okayama

Volume 54, *Issue* 3 2000 *Article* 1

JUNE 2000

Factors affecting levodopa effects in Parkinson's disease.

Norio Ogawa*

*Okayama University,

Factors affecting levodopa effects in Parkinson's disease.*

Norio Ogawa

Abstract

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.

KEYWORDS: 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

---

*PMID: 10925733 [PubMed - indexed for MEDLINE]

ACTA MED OKAYAMA 2000; 54(3): 95-101

Review

Factors Affecting Levodopa Effects in Parkinson's Disease

Norio OGAWA*

Department of Neuroscience, Institute of Molecular and Cellular Medicine, Okayama University Medical School, Okayama 700-8558, Japan

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).

* To whom correspondence should be addressed.

Table I 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-*O*-methyldopa (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-*O*-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 performed 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, isoloicine, 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 flurorodoa 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 (Cmax) and in the area under the time-concentration curve (AUC) with decrease in the values of Tmax and T1/2) were significantly correlated. And, younger onset patients had a higher Cmax. 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.

References

1. Chase TN, Mouradian MM and Engber TM: Motor response complications and the function of striatal efferent systems. Neurology (1993) **43**, S23-S27.
2. Fahn S: Controversies in the therapy of Parkinson's disease. Adv Neurol (1996) **69**, 477-486.
3. Marsden CD and Parkes JD: "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. Lancet (1976) **1**, 292-296.
4. Lieberman A, Estey E, Gopinathan G, Ohashi T, Sauter A and Goldstein M: Comparative effectiveness of two extracerebral DOPA decarboxylase inhibitors in Parkinson disease. Neurology (1978) **28**, 964-968.
5. Pakkenberg H, Birket-Smith E, Dupont E, Hansen E, Mikkelsen B, Presthus J, Rautakorpi I, Riman E and Rinne UK: Parkinson's disease treated with Sinemet or Madopar: A controlled multicenter trial. Acta Neurol Scand (1976) **53**, 376-385.
6. Inoue N and Miyoshi S: Amelioration of wearing-off phenomenon by exchanging of levodopa-DCI drugs. Neurol Med (Tokyo) (1994) **40**, 313. (Japanese)
7. Metman LV, Hoff J, Mouradian MM and Chase TN: Fluctuations in plasma levodopa and motor responses with liquid and tablet levodopa/carbidopa. Mov Disord (1994) **9**, 463-465.
8. Pappert EJ, Goetz CG, Niederman F, Ling ZD, Stebbins GT and Carvey PM: Liquid levodopa/carbidopa produces significant improvement in motor function without dyskinesia exacerbation. Neurology (1996) **47**, 1493-1495.
9. Wade DN, Mearrick PT and Morris JL: Active transport of L-dopa in the intestine. Nature (1973) **242**, 463-465.
10. Mearrick PT, Wade DN, Birkett DJ and Morris J: Metoclopramide, gastric emptying and L-dopa absorption. Aust N Z J Med (1974) **4**, 144-148.
11. Djaldetti R, Koren M, Ziv I, Achiron A and Melamed E: Effect of cisapride on response fluctuations in Parkinson's disease. Mov Disord (1995) **10**, 81-84.
12. Neira WD, Sanchez V, Mena MA and de-Yebenes JG: The effects of cisapride on plasma L-dopa levels and clinical response in Parkinson's disease. Mov Disord (1995) **10**, 66-70.
13. Indo T and Ando K: Metoclopramide-induced Parkinsonism: Clinical characteristics on ten cases. Arch Neurol (1982) **39**, 494-496.
14. Champion MC: Domperidone. Gen Pharmacol (1988) **19**, 499-505.
15. Yazawa I, Terao Y, Sai I, Hashimoto K and Sakuta M: Gastric acid secretion and absorption of levodopa in patients with Parkinson's disease: The effect of supplement therapy to gastric acid. Clin Neurol (Tokyo) (1994) **34**, 264-266. (Japanese with English Abstract)
16. Mena I and Cotzias GC: Protein intake and treatment of Parkinson's disease with levodopa. N Engl J Med (1975) **292**, 181-184.
17. Riley D and Lang AE: Practical application of a low-protein diet for Parkinson's disease. Neurology (1988) **38**, 1026-1031.
18. Juncos JL, Fabbrini G, Mouradian MM, Serrati C and Chase TN: Dietary influences on the antiparkinsonian response to levodopa. Arch Neurol (1987) **44**, 1003-1005.
19. Kurlan R: Dietary therapy for motor fluctuations in Parkinson's disease. Arch Neurol (1987) **44**, 1119-1121.
20. Pincus JH and Barry K: Protein redistribution diet restores motor function in patients with dopa-resistant "off" periods. Neurology (1988) **38**, 481-483.
21. Berry EM, Growdon JH, Wurtman JJ, Caballero B and Wurtman RJ: A balanced carbohydrate: protein diet in the management of Parkinson's

disease. Neurology (1991) **41**, 1295–1297.
22. Leenders KL, Palmer AJ, Quinn N, Clark JC, Firnau G, Garnett ES, Nahmias C, Jones T and Marsden CD: Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. J Neurol Neurosurg Psychiatry (1986) **49**, 853–860.
23. Tsui JK, Ross S, Poulin K, Douglas J, Postnikoff D, Calne S, Woodward W and Calne DB: The effect of dietary protein on the efficacy of L-dopa: A double-blind study. Neurology (1989) **39**, 549–552.
24. Nutt JG, Woodward WR, Hammerstad JP, Carter JH and Anderson JL: The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N Engl J Med (1984) **310**, 483–488.
25. Baruzzi A, Contin M, Riva R, Procaccianti G, Albani F, Tonello C, Zoni E and Martinelli P: Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. Clin Neuropharmacol (1987) **10**, 527–537.
26. Fabbrini G, Mouradian MM, Juncos JL, Schlegel J, Mohr E and Chase TN: Motor fluctuations in Parkinson's disease: Central pathophysiological mechanisms, Part I. Ann Neurol (1988) **24**, 366–371.
27. Nutt JG, Woodward WR, Gancher ST and Merrick D: 3-*O*-methyldopa and the response to levodopa in Parkinson's disease. Ann Neurol (1987) **21**, 584–588.
28. Guttman M, Leger G, Cedarbaum JM, Reches A, Woodward W, Evans A, Diksic M and Gjedde A: 3-*O*-Methyldopa administration does not alter fluorodopa transport into brain. Ann Neurol (1992) **31**, 638–643.
29. Schuh LA and Bennett JP Jr: Suppression of dyskinesias in advanced Parkinson's disease. I. Continuous intravenous levodopa shifts dose response for production of dyskinesias but not for relief of parkinsonism in patients with advanced Parkinson's disease. Neurology (1993) **43**, 1545–1550.
30. Alexander GM, Schwartzman RJ, Grothusen JR and Gordon SW: Effects of plasma levels of large neutral amino acids and degree of parkinsonism on the blood-to-brain transport of levodopa in naive and MPTP parkinsonian monkeys. Neurology (1994) **44**, 1491–1499.
31. Roberts JW, Cora-Locatelli G, Bravi D, Amantea MA, Mouradian MM and Chase TN: Catechol-*O*-methyltransferase inhibitor tolcapone prolongs levodopa/carbidopa action in parkinsonian patients. Neurology (1993) **43**, 2685–2688.
32. Kurth MC, Adler CH, Hilaire MS, Singer C, Waters C, LeWitt P, Chernik DA, Dorflinger EE and Yoo K: Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: A multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology (1997) **48**, 81–87.
33. Kaakkola S, Teravainen H, Ahtila S, Rita H and Gordin A: Effect of entacapone, a COMT inhibitor, on clinical disability and levodopa metabolism in parkinsonian patients. Neurology (1994) **44**, 77–80.
34. Nutt JG, Woodward WR, Beckner RM, Stone CK, Berggren K, Carter JH, Gancher ST, Hammerstad JP and Gordin A: Effect of peripheral catechol-*O*-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology (1994) **44**, 913–919.
35. Ahtila S, Kaakkola S, Gordin A, Korpela K, Heinavaara S, Karlsson M, Wikberg T, Toumainen P and Mannisto PT: Effect of entacapone, a COMT inhibitor, on the pharmacokinetics and metabolism of levodopa after administration of controlled-release levodopa-carbidopa in volunteers. Clin Neuropharmacol (1995) **18**, 46–57.
36. The Parkinson Study Group: Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med (1993) **328**, 176–183.
37. Heikkila RE, Cabbat FS, Manzino L and Duvoisin RC: Potentiation by deprenil of l-dopa induced circuling in nigral-lesioned rats. Pharmacol Biochem Behav (1981) **15**, 75–79.
38. Riederer P and Youdim MB: Monoamine oxidase activity and monoamine metabolism in brains of parkinsonian patients treated with l-deprenyl. J Neurochem (1986) **46**, 1359–1365.
39. LeWitt RA: Levodopa therapeutics: New treatment strategies. Neurology (1993) **43**, S31–S37.
40. Mouradian MM, Juncos JL, Fabbrini G, Schlegel J, Bartko JJ and Chase TN: Motor fluctuations in Parkinson's disease: Central pathophysiological mechanisms, Part II. Ann Neurol (1988) **24**, 372–378.
41. Seeman P and Niznik HB: Dopamine receptors and transporters in Parkinson's disease and schizophrenia. FASEB J (1990) **4**, 2737–2744.
42. Antonini A, Leenders KL, Meier D, Oertel WH, Boesiger P and Anliker M: T2 relaxation time in patients with Parkinson's disease. Neurology (1993) **43**, 697–700.
43. Brooks DJ, Ibanez V, Sawle GV, Playford ED, Quinn N, Mathias CJ, Lees AJ, Marsden CD, Bannister R and Frackowiak RS: Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supranuclear palsy, measured with ^{11}C-raclopride and positron emission tomography. Ann Neurol (1992) **31**, 184–92.
44. Brucke T, Wenger S, Asenbaum S, Fertl E, Pfafflmeyer N, Muller C, Podreka I and Angelberger P: Dopamine D2 receptor imaging and measurement with SPECT. Adv Neurol (1993) **60**, 494–500.
45. Schelosky L, Hierholzer J, Wissel J, Cordes M and Poewe W: Correlation of clinical response in apomorphine test with D2-receptors status as demonstrated by ^{123}I IBZM-SPECT. Mov Disord (1993) **8**, 453–458.
46. Chase TN, Baronti F, Fabbrini G, Heuser IJ, Juncos JL and Mouradian MM: Rationale for continuous dopaminomimetic therapy of Parkinson's disease. Neurology (1989) **39**, S7–S10.
47. Ogawa N: Molecular and chemical neuropharmacology of dopamine receptor subtypes. Acta Med Okayama (1995) **49**, 1–11.
48. Ahlskog JE, Muenter MD, Bailey PA and Stevens PM: Dopamine agonist treatment of fluctuating parkinsonism. D-2 (controlled-release MK-458) vs combined D-1 and D-2 (pergolide). Arch Neurol (1992) **49**, 560–568.
49. Robertson HA, Peterson MR and Worth GG: Synergistic and persistent interaction between the D2 agonist, bromocriptine, and the D1 selective agonist, CY 208-243. Brain Res (1992) **593**, 332–334.
50. Ogawa N: Levodopa and dopamine agonists in the treatment of Parkinson's disease: Advantages and disadvantages. Eur Neurol (1994) **34**, S20–S28.
51. Bonuccelli U, Piccini P, DelDotto P, Rossi G, Corsini GU and Muratorio A: Apomorphine test for dopaminergic responsiveness: A dose assesment study. Mov Disord (1993) **8**, 158–164.
52. Cedarbaum JM: Pharmacokinetic and pharmacodynamic considerations in manegement of motor response fluctuations in Parkinson's disease. Neurol Clinics (1990) **8**, 31–49.
53. Nutt JG, Carter JH, Woodward W, Hammerstad JP and Gancher ST: Dose tolerance develop to levodopa? Comparison of 2- and 21-H levodopa infusions. Mov Disord (1993) **8**, 139–143.
54. Febbrini G, Juncos JL, Mouradian MM, Serrati C and Chase TN: 3-*O*-methyldopa and motor fluctuations in Parkinson's disease. Neurology (1987) **37**, 856–859.
55. Murata M and Kanazawa I: Repeated L-dopa administration reduces the ability of dopamine storage and abolishes the supersensitivity of dopamine receptors in the striatum of intact rat. Neurosci Res (1993) **16**, 15–23.
56. Bravi D, Mouradiam MM, Roberts JW, Davis TL, Sohn YH and Chase

TN: Wearing-off fluctuations in Parkinson's disease: Contribution of postsynaptic mechanisms. Ann Neurol (1994) **36**, 27–31.
57. Murata M, Mizusawa H, Yamanouchi H and Kanazawa I: Chronic levodopa therapy enhances dopa absorption: Contribution to wearing-off. J Neural Transm (1996) **103**, 1177–1185.
58. Lee CS, Schulzer M, Mak EK, Snow BJ, Tsui JK, Calne S, Hammerstad J and Calne DB: Clinical observation on the rate of progression of idiopathic parkinsonism. Brain (1994) **117**, 501–507.
59. Murata M and Kanazawa I: Effects of chronic levodopa therapy on dopa pharmacokinetics. Eur Neurol (1997) **38**, S50–S55.
60. Roos RA, Vredevoogd CB and van der Valde EA: Response fluctuations in Parkinson's disease. Neurology (1990) **40**, 1344–1346.
61. Ogawa N, Tanaka K and Asanuma M: Bromocriptine markedly suppress levodpa-induced abnormal increase of dopamine turnover in the parkinsonian striatum. Neurochem Res (2000) **25**, 755–758.

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