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The relationship between the distinct ratios of benserazide and carbidopa to levodopa and motor complications in Parkinson's disease: A retrospective cohort study

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ABSTRACT

Background: In Japan, only two medications of immediate-release levodopa with distinct ratios of decarboxylase inhibitor (DCI), namely levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg, are available for the treatment of Parkinson's disease (PD). The relationship between the difference in the DCI to levodopa ratio and the development of motor complications in long-term administration of levodopa is unknown.
Purpose: We assessed the duration from initiation of levodopa/DCI to the emergence of motor fluctuations in patients with PD treated with levodopa/benserazide and levodopa/carbidopa.
Methods: We retrospectively assessed the disease course, especially the period from the onset of motor symptoms or initiation of levodopa/DCI to the emergence of motor fluctuations, in patients with PD who were initially treated with either levodopa/benserazide (300/75 mg/day) or levodopa/carbidopa (300/30 mg/day).
Results: Of the 186 candidates, 52 patients were enrolled. The mean duration to the emergence of motor fluctuations in the levodopa/carbidopa group was significantly longer than that in the levodopa/benserazide group (5.0 ± 1.4 vs 3.1 ± 1.2 years, $p < 0.01$). The mean duration from onset of motor symptoms to the emergence of motor fluctuations in the levodopa/carbidopa group was also significantly longer than that in the levodopa/benserazide group (6.6 ± 1.6 vs 4.7 ± 1.3 years, $p < 0.01$).
Conclusion: Our study suggests that levodopa/carbidopa therapy with a DCI to levodopa ratio of 1:10 may delay the occurrence of motor fluctuations when compared to levodopa/benserazide therapy with that of 1:4. The difference in the blending ratio of levodopa/DCI may influence the disease progression in PD.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that presents with various motor symptoms resulting from dopaminergic cell loss that leads to the depletion of dopamine in the nigrostriatal system. Levodopa is the gold standard therapy that improves motor symptoms in PD [1]. Since levodopa is largely metabolized by decarboxylase and catechol *O*-methyltransferase (COMT) to dopamine and 3-*O*-methyldopa, respectively, in the serum, only 1% of the oral dose of levodopa is delivered to the dopaminergic neurons in the brain [2,3]. Therefore, levodopa is generally administered with a decarboxylase inhibitor (DCI), such as benserazide or carbidopa as a combination tablet [4]. Concomitant administration of levodopa and DCI increases the levodopa availability by 10-fold in the brain and prolongs the peripheral half-life of levodopa to approximately 90 min [2,5].

Previous studies report that there is no significant difference in the clinical efficacy of 200 mg of levodopa combined with 50 mg of benserazide (levodopa/benserazide 200/50 mg) and 250 mg of levodopa combined with 25 mg of carbidopa (levodopa/carbidopa 250/25 mg) for treating motor symptoms at an early stage after treatment initiation

Abbreviations: CDS, continuous dopaminergic stimulation; Cmax, maximum plasma concentration; COMT, catechol *O*-methyltransferase; DAT, dopamine transporter; DCI, decarboxylase inhibitor; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dosage; MAO-B, monoamine oxidase B; MIBG, 123I-meta-iodobenzylguanidine; PD, Parkinson's disease; SPECT, single-photon emission computed tomography.

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[6]. On the contrary, because the ratios of DCI to levodopa in levodopa/benserazide 200/50 mg and levodopa/carbidopa 250/25 mg were 1:4 and 1:10, respectively, the efficacy of DCI in levodopa/benserazide was stronger than that in levodopa/carbidopa. It has been reported that in healthy young individuals, the maximum plasma concentration (C_{max}) of levodopa after oral administration of levodopa/benserazide 100/25 mg was approximately two-fold higher than that after levodopa/carbidopa 100/10 mg administration [7]. Moreover, in the plasma concentration-time curve of levodopa after levodopa/DCI administration, levodopa/benserazide showed a rapid elevation and reduction, whereas levodopa/carbidopa showed a gradual elevation and reduction [7]. Therefore, levodopa/benserazide may be useful for patients requiring immediate amelioration of motor symptoms, and levodopa/carbidopa may be useful for patients presenting with troublesome dyskinesia resulting from excessive stimulation of dopamine in the striatum [7–9].

Levodopa-induced motor complications in the form of motor fluctuations, such as wearing-off phenomena, and dyskinesia caused by pulsatile stimulation of dopamine receptors, lead to molecular and physiological changes in the striatal neurons. This poses a momentous obstacle for performing daily activities in patients with PD. While various other factors such as COMT gene polymorphisms [10], the serotonergic system in the brain [11], glutamatergic transmission in the basal ganglia [12], and gastrointestinal functions [13] are concerned with the emergence of motor complications, continuous dopaminergic stimulation, which involves continuous levodopa delivery to the brain, may reduce the risk of motor complications [14]. In Japan, only two medications of immediate-release levodopa with distinct concentration ratios of DCI, namely levodopa/benserazide 100/25 mg, and levodopa/carbidopa 100/10 mg, are available for the treatment of PD. However, there are no definite guidelines regarding alternatives to levodopa/DCIs. Additionally, while each type of levodopa/DCI shows a different plasma concentration-time curve of levodopa, it remains uncertain whether the distinct ratios of DCI to levodopa in levodopa/benserazide and levodopa/carbidopa longitudinally affect the appearance of motor complications underlying the non-physiological stimulation of dopaminergic neurons in the striatum.

In this retrospective study, we primarily assessed the duration from initiation of levodopa/DCI to the emergence of motor fluctuations in patients with PD who were initially treated with either levodopa/benserazide or levodopa/carbidopa. Our study aimed to elucidate the relationship between the difference in the ratio of DCI to levodopa and the development of motor complications after long-term administration of levodopa.

2. Materials and methods

2.1. Study sample

Showa University Ethics Committee reviewed and approved the study (authorization number: 21–025-B). Informed consent was obtained in the form of opt-out process, with the details on the bulletin board in the hospital. We collected the medical information of the patients with PD who met the following conditions: 1) patients who were in stage 1 or 2 as per the Hoehn & Yahr (H&Y) staging [15] at the first visit to our movement disorder clinic, 2) patients who were administered immediate-release levodopa/benserazide 100/25 mg tablets three times a day as initial therapy, or immediate-release levodopa/carbidopa 100/10 mg tablets three times a day after clinical diagnosis, 3) patients who did not alternate between levodopa and DCIs during the treatment period, 4) patients in whom the medication was adjusted for adequate control of motor symptoms, including an increase in the levodopa/DCI dose or an addition of only one anti-parkinsonian agent, that is, either a dopamine agonist, monoamine oxidase B (MAO-B) inhibitor or a COMT inhibitor after initiation of levodopa/DCI therapy, 5) those who presented with either predictable wearing-off, unpredictable on-off, or sudden off-periods as motor fluctuations resulting from long-term levodopa therapy, and 6) patients in whom at least 2 years had passed since the motor fluctuations emerged. PD was diagnosed based on the Movement Disorders Society clinical diagnostic criteria [16]. At the induction of the levodopa/DCI, there were no specific criteria for the selection of levodopa/DCI. Motor fluctuations were defined according to the practical definition of "off" that was proposed by the Defining "Off" Working Group [17]. For the assessment of drug therapy, motor symptoms and motor complications were evaluated according to the Unified Parkinson's Disease Rating Scale Part III and IV, respectively [18]. Dyskinesias were defined as abnormal involuntary movements, including chorea, dystonia, and ballism, at peak dose or the onset and end of dose (diphasic). All patients were evaluated by the same neurologist (Y.B.) at a movement disorder clinic. Patients who underwent deep brain stimulation or other device-aided therapies were excluded. Patients treated with agents for psychosis and/or dementia, and those experiencing other neurologic and orthopedic disorders that affect daily life activities were also excluded.

2.2. Survey items

Collected historical data included current age, sex, disease duration, age at symptomatic onset, age at diagnosis, age at introduction of levodopa/DCI therapy, the clinical phenotype of PD at the first visit [19], age at adjustment of medication for motor symptoms, details of drug adjustment after initiation of levodopa/DCI, age at the emergence of motor fluctuations, details of initially emerged motor fluctuation, the presence or absence of dyskinesias, and the levodopa equivalent daily dosage (LEDD) at the time of emergence of motor fluctuations [20].

2.3. Statistical analysis

Demographic and clinical data were compared between patients with PD treated with levodopa/benserazide and those treated with levodopa/carbidopa. Our study determined the duration from the initiation of levodopa/DCI therapy to the emergence of motor fluctuations as a primary evaluation item. The chi-square test was used for categorical data, and the Mann–Whitney test was used for interval data. Statistical analyses were performed using JMP Pro 16 (JMP Inc., Cary, NC, USA), and the significance level was set at $p < 0.05$.

3. Results

Of the 186 candidate patients with PD, 52 met the selection criteria and were enrolled in this study. The clinical characteristics of the 52 patients are presented in Table 1. Twenty patients were initially treated with levodopa/benserazide 300/75 mg/day and 32 with levodopa/carbidopa 300/30 mg/day. All patients had undergone cardiac 123I-metaiodobenzylguanidine (MIBG) single-photon emission computed tomography (SPECT) and dopamine transporter (DAT) using N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[123I]iodophenyl) nortropane SPECT as additional imaging before drug therapy. The patients were eventually diagnosed with PD [21,22]. For all patients, levodopa/DCI therapy was initiated immediately after the diagnosis. None of the characteristics, including the mean current age, sex distribution, mean age at clinical onset, mean age at diagnosis and initiation of levodopa/DI therapy, or mean disease duration, were significantly different between the treatment groups. The H&Y staging and clinical phenotypes of PD were also similar between the levodopa/DCI groups.

The treatment interventions after levodopa/DCI therapy in 52 patients are shown in Table 2. The initial levodopa/DCI therapy was adjusted for several years after drug therapy according to the changes or mild deterioration of the motor symptoms in all patients at the physician's discretion. The mean duration from the initiation of levodopa/DCI therapy to the drug adjustment was significantly longer in the levodopa/carbidopa group than that in the levodopa/benserazide group

Table 1
Clinical characteristics of patients with PD.

	Treatment groups by initial levodopa/DCI therapy		*P*-value
	Levodopa/benserazide ($N = 20$)	Levodopa/carbidopa ($N = 32$)	
Age, years	75.0 (7.5)	77.6 (6.9)	ns
Female, n (%)	16 (80.0)	17 (53.1)	ns
Age at clinical onset, years	67.7 (8.5)	68.8 (7.1)	ns
Age at diagnosis and levodopa/DCI therapy, years	69.3 (8.3)	70.5 (7.3)	ns
H&Y staging at the first visit, n (%)			ns
1	14 (70.0)	25 (78.1)	
2	6 (30.0)	7 (21.9)	
Clinical phenotype of PD, n (%)			ns
Tremor dominant	4 (20.0)	7 (21.9)	
Mixed type	15 (75.0)	20 (62.5)	
PIGD	1 (5.0)	5 (15.6)	
Disease duration, years	7.3 (3.9)	8.7 (3.6)	ns

H&Y staging, Hoehn & Yahr staging; PD, Parkinson's disease; PIGD, postural instability, and gait difficulties; DCI, decarboxylase inhibitor; ns, not significant.
All data except the patients' sex and clinical phenotype of PD are in the form of the mean (standard deviation).

Table 2
Treatment intervention after levodopa/DCI therapy in PD patients.

	Treatment groups by initial levodopa/DCI therapy		P-value
	Levodopa/benserazide (100/25 mg) (N = 20)	Levodopa/carbidopa (100/10 mg) (N = 32)	
Duration from initiation of levodopa/DCI to drug adjustment, years	2.0 (1.0)	3.0 (1.4)	<0.01
Details of drug adjustment, n (%)			
Increase of levodopa/DCI dose	3 (15.0)	8 (25.0)	ns
Combined use adjunct to levodopa/DCI			ns
Dopamine agonist	9 (45.0)	13 (40.6)	
MAO-B inhibitor	8 (40.0)	9 (28.1)	
COMT inhibitor	0	2 (6.3)	
LEDD at emergence of wearing- off, mg/day	418.9 (66.6)	548.3 (131.7)	<0.01

COMT, catechol *O*-methyltransferase; DCI, decarboxylase inhibitor; LEDD, levodopa equivalent daily dosage; MAO, monoamine oxidase B; PD, Parkinson's disease; ns, not significant.
All data except for the details of drug adjustment are presented as mean (standard deviation).

(3.0 ± 1.4 vs 2.0 ± 1.0 years, $p < 0.01$). The drug adjustment either entailed an increase in the levodopa/DCI dose or the combined use of a dopamine agonist, MAO-B inhibitor, or COMT inhibitor as an adjunct to levodopa/DCI. There was no significant difference in levels of drug adjustment between the levodopa/DCI groups. The mean LEDD at the emergence of motor fluctuations was significantly higher in the levodopa/carbidopa group than that in the levodopa/benserazide group (548.3 ± 131.7 vs 418.9 ± 66.6 mg, $p < 0.01$).

The clinical course from the onset of motor symptoms to the emergence of motor complications in both the levodopa/DCI groups is shown in Fig. 1. There was no significant difference in the mean duration from the onset of motor symptoms to the diagnosis of PD and initiation of levodopa therapy between the levodopa/benserazide and levodopa/carbidopa groups (1.6 ± 1.1 vs 1.6 ± 1.0 years). However, the mean duration from the initiation of levodopa/DCI therapy to the emergence of motor fluctuations in the levodopa/carbidopa group was significantly longer compared with that in the levodopa/benserazide group (5.0 ± 1.4 vs 3.1 ± 1.2 years, $p < 0.01$). Consequently, the mean duration from the onset of motor symptoms to the emergence of motor fluctuations in the levodopa/carbidopa group was also significantly longer compared with that in the levodopa/benserazide group (6.6 ± 1.6 vs 4.7 ± 1.3 years, $p < 0.01$). The subtypes of motor fluctuations in the levodopa/benserazide group included wearing off in 17 (85.0%) and on-off fluctuations in three (15.0%) patients and those in the levodopa/carbidopa group included wearing off in 27 (84.4%), on-off fluctuations in four (12.5%), and sudden off period in one patient (4.1%). All patients were in stage 3 in the H&Y staging when the motor fluctuations emerged. After the emergence of motor fluctuations, the mean time with levodopa/DCI treatment in the levodopa/benserazide and levodopa/carbidopa groups were 4.2 ± 1.7 and 3.7 ± 1.2 years, respectively (p = ns). Subsequent dyskinesias after the emergence of wearing off were observed in 10 patients (50%, 8 females) in the levodopa/benserazide group and 16 patients (50%, 9 females) in the levodopa/carbidopa group. For these 26 patients, the H&Y stage on the emergence of dyskinesias was still 3. Dyskinesias in patients in both the levodopa/DCI groups were revealed at the peak dose. The mean duration from initiation of levodopa/DCI to the emergence of dyskinesias in the levodopa/carbidopa group was also significantly longer compared with that of the levodopa/benserazide group (5.7 ± 1.1 vs 4.6 ± 1.4 years, $p < 0.05$). However, no significant difference was seen in the mean duration from the onset of motor symptoms to the emergence of dyskinesias for the levodopa/benserazide and levodopa/carbidopa groups (6.2 ± 1.7 vs 7.3 ± 2.0 years). Moreover, the period from motor fluctuations to dyskinesias in levodopa/carbidopa therapy tended to be shorter than that in the levodopa/benserazide therapy (1.4 ± 0.8 vs 0.8 ± 0.5 years), although it was not statically significant. The mean LEDD at the emergence of dyskinesias was significantly higher in the levodopa/carbidopa group than in the levodopa/benserazide group (573.1 ± 133.7 vs 415.0 ± 62.8 mg, $p < 0.01$).

4. Discussion

This study assessed the duration from the initiation of levodopa/DCI to the emergence of motor fluctuations in patients with PD. It was found that a levodopa/carbidopa therapy with a DCI to levodopa ratio of 1:10 that shows a unique plasma concentration-time curve of levodopa, which delays the occurrence of subsequent motor fluctuations throughout the course of illness. Recent studies have indicated that the initial dose of levodopa therapy is an important risk factor for motor fluctuations and dyskinesias after treatment intervention [23]. As a regimen of optimum levodopa therapy to avoid early motor complications, a daily dose of 400 mg or less has been recommended as an initial treatment [24]. Even though the drug treatment was initiated by the advocated optimal levodopa therapy, motor fluctuation or dyskinesia developed in 25%–75% of individuals after 3–4 years of treatment [24]. Additionally, several studies have reported that, regardless of the induction time of levodopa, motor fluctuations were provoked during a mean of 5–6 years from the onset of motor symptoms [25,26]. These observations are based on the interventions using levodopa/DCI, with a DCI to levodopa ratio of 1:4. In our study, levodopa/benserazide therapy with a DCI to levodopa ratio of 1:4 caused motor fluctuations at approximately 3 years after the initiation of levodopa, and at 5 years after the onset of motor symptoms. However, the duration from the initiation of levodopa to the emergence of motor fluctuations and the onset of motor symptoms to the emergence of motor fluctuations in levodopa/carbidopa therapy with the DCI to levodopa ratio of 1:10 were approximately 5 and 7 years, respectively. The durations were significantly longer than those in the levodopa/benserazide group. Pharmacokinetic factors based on intermittent stimulation of dopamine receptors by short-acting levodopa play an important role in the development of motor fluctuations leading to wearing off [27].

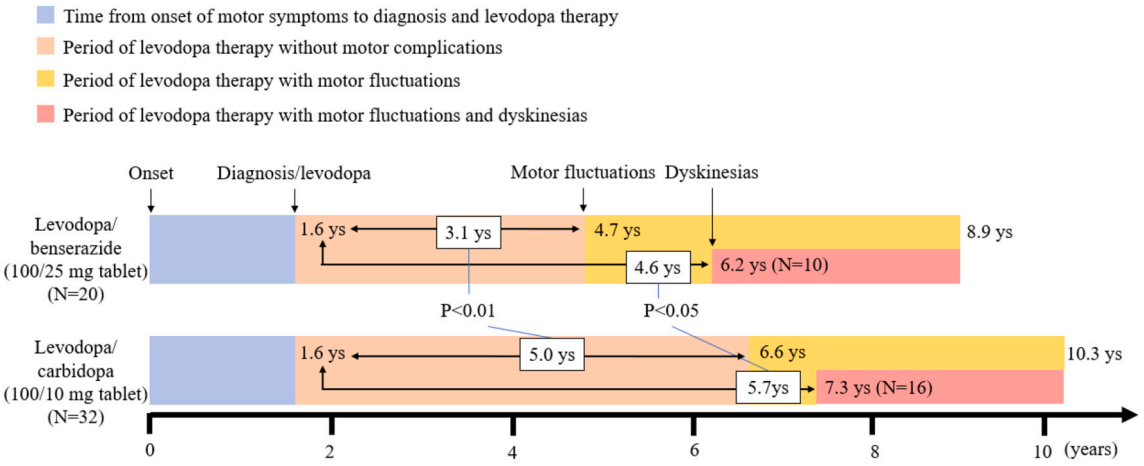

Fig. 1. The clinical course from the onset of motor symptoms to the emergence of motor complications in each of the levodopa/benserazide and levodopa/carbidopa therapy groups. The mean duration of the emergence of motor fluctuations in the levodopa/carbidopa group was significantly longer compared to that in the levodopa/benserazide group (5.0 ± 1.4 vs 3.1 ± 1.2 years, $p < 0.01$). The mean duration from the initiation of levodopa/DCI to the emergence of dyskinesias in the levodopa/carbidopa group was also significantly longer compared to that in the levodopa/benserazide group (5.7 ± 1.1 vs 4.6 ± 1.4 years, $p < 0.05$). DCI: decarboxylase inhibitor.

Moreover, a higher levodopa dose is associated with more severe motor fluctuations [24]. Although in both therapies, the induction dose of levodopa was the same as 300 mg/day; the emergence of motor fluctuations in the levodopa/carbidopa therapy group was seen later than in the levodopa/benserazide group. These observations may indicate that the different pharmacokinetics of levodopa in levodopa/DCIs affects the duration from initiation of levodopa/DCI to the emergence of motor fluctuations. Nishikawa et al. [28] reported that the C_{max} of levodopa after an administration of levodopa/benserazide 100/25 mg was approximately 1.1 times higher than that of levodopa/carbidopa 100/10 mg, but no significant difference was observed. Additionally, both levodopa/DCI groups showed a similar plasma concentration-time curve of levodopa. In this study, approximately 60% of the participants had a disease duration of 6 to 30 years, and the mean disease duration of the participants at evaluation was 7.7 years, whereas, in the present study, the mean disease duration at the emergence of motor fluctuations in levodopa/benserazide and levodopa/carbidopa therapy groups was 4.7 and 6.6 years, respectively. Contrarily, Rinne et al. [6] reported that the C_{max} after an administration of levodopa/benserazide 200/50 mg was approximately 1.5 to 1.8 times higher than that of levodopa/carbidopa 200/20 mg in patients with de novo Parkinson's disease. Additionally, as with the pharmacokinetics of levodopa in healthy individuals, the plasma concentration-time curves of levodopa after administrations of levodopa/carbidopa showed a relatively gradual elevation and reduction. These observations suggest that the C_{max} and the plasma concentration-time curve of levodopa may differ between levodopa/benserazide and levodopa/carbidopa in disease duration or duration of levodopa therapy. Previous studies have shown that the area under the curve (AUC) of levodopa in an administration of levodopa/benserazide 100/25 or 200/50 mg was consistently higher than that of levodopa/benserazide 100/10 or 200/20 mg regardless of disease duration [6,7,28]. Therefore, compared with levodopa/carbidopa, levodopa/benserazide has higher bioavailability of levodopa and contributes to higher delivery of levodopa to the brain. In the present study, however, the mean duration from the initiation of levodopa/DCI therapy to a drug adjustment for adequate control of motor symptoms was significantly shorter in the levodopa/benserazide group than the levodopa/carbidopa group, suggesting that the therapy using levodopa/carbidopa 300/30 mg/day showed rather more prolonged and stable courses of disease in the early stage compared with that using levodopa/benserazide 300/75 mg/day. Thus, compared with levodopa/carbidopa, the increased C_{max} and AUC of levodopa in levodopa/benserazide may provide pulsatile and excessive dopaminergic stimulations and may cause a subsequent unsteadiness of motor control in the early period after levodopa/DCI therapy [24.27]. The difference in the pharmacokinetics of levodopa has not been reported so far between levodopa/benserazide and levodopa/carbidopa in the early stage of PD. However, we believe that each of the pharmacokinetic factors, such as the C_{max} and the plasma concentration-time curve, of levodopa in levodopa/benserazide and levodopa/carbidopa may differ by disease duration or duration of levodopa therapy, and increased C_{max} and AUC of levodopa in levodopa/benserazide may also affect the course of illness in the early stage of the disease.

A large, open-label, pragmatic randomized trial study found that dyskinesia developed in approximately 25% of the individuals after 5 years of treatment [29]. Additionally, it has been reported that dyskinesia was induced during a mean of 6 to 7 years after the onset of motor symptoms [25,26]. These observations are also considered to be the result of levodopa/DCI therapy in which the ratio of DCI to levodopa is 1:4. Consistent with this data, regardless of the ratio of levodopa to DCI, dyskinesia developed in 50% of individuals in both levodopa/DCI therapy groups 6 to 7 years after the onset of motor symptoms. However, the duration from initiation of levodopa to the emergence of dyskinesia was significantly longer in levodopa/carbidopa therapy group than in levodopa/benserazide therapy group. Additionally, the duration from the onset of motor symptoms to the emergence of dyskinesia was similar between the levodopa/DCI therapy groups. Moreover, the period from motor fluctuations to dyskinesias in levodopa/carbidopa therapy tended to be shorter than that in the levodopa/benserazide therapy, although it was not statistically significant between the two groups. Levodopa-induced dyskinesia develops in a dose-dependent manner, and the pharmacodynamics of levodopa as well as excessive stimulation of dopamine receptors plays a role in the occurrence of dyskinesia [8,24]. Moreover, disease duration and severity are also important factors in the development of dyskinesia [24,25]. For the levodopa/DCI therapy groups, the disease duration was the same, and the H&Y stage on the emergence of dyskinesia was 3 in all patients. However, the LEDD was significantly higher in the levodopa/carbidopa than in the levodopa/benserazide therapy groups, whereas dyskinesia was observed at a later period after the initiation of levodopa in the levodopa/carbidopa therapy group. One possible explanation is the relatively long-acting pharmacokinetics of levodopa/carbidopa with a DCI to levodopa ratio of 1:10, which may delay the emergence of motor fluctuation, and consequently lead to late dyskinesia. However, the denervation of striatal neurons resulting from excessive stimulation of dopamine receptors

caused by levodopa can induce dyskinesia through the direct influence of pharmacodynamic factors but not pharmacokinetic factors, with cumulative exposure to levodopa and other dopaminergic agents [14,27,30].

In this cohort, both levodopa/DCI therapy groups had similar baseline characteristics with simultaneous initiation of levodopa treatment and the same daily dosages after the diagnosis of PD. Since the present study involved a survey, a possibility that the treatment bias of each physician affected the assessment of progression of individual motor symptoms leading to the difference in the period to the emergence of motor fluctuations cannot be ruled out. Moreover, there exists a possibility that because of the interviewed-based survey, the period of the emergence of motor fluctuation exhibiting varied phenotypes from mild to severe was not correctly obtained. Therefore, more detailed evaluations for motor fluctuations using appropriate scales and diaries of motor symptoms are required in future study. The duration from initiation of levodopa/DCI to drug adjustment also differed in both the groups; however, this reflects the difference in the transition of motor symptoms based on the pharmacokinetic properties of levodopa/benserazide and levodopa/carbidopa. Additionally, while the levels of drug adjustment were similar between the two groups, the effect of each dopaminergic drug on disease progression was not evaluated because of the small sample size. It has been reported that being female was a factor that affects the pharmacokinetics of levodopa because of lower body weight [28] and was associated with an increased risk of dyskinesia [24]. In the present study, the data on body weight was not available. Moreover, due to the small sample size, analyses for association between sex and motor complications in each therapy group have not been thereby performed. Further considerations regarding the effects of body weight and sex on the emergence of motor complications in each type of DCI will be needed. Consistent with our results, a community-based study reported that approximately half of the patients developed dyskinesia during a disease duration of 10 or more years [25]. However, a study analyzed from cumulative literature has estimated that approximately 90% of patients develop dyskinesia during their illness [31]. In the present study, the patients without dyskinesia with a disease duration of 9 to 10 years may cause concern regarding the clinical misdiagnosis of PD. We believe that the results of MIBG SPECT and DAT SPECT for all patients support the clinical diagnosis of PD [21,22]. Furthermore, since levodopa therapy using levodopa and DCI in which the ratio of DCI to levodopa is 1:4 is globally accepted, regardless of the use of benserazide or carbidopa, detailed pharmacokinetics of its repeated and long-term administration remains unclear. The generalizability results in the present study on Japanese patients with PD needs to be verified. Various factors other than the difference in the ratio of DCI to levodopa and the difference in the type of levodopa/DCI also affect the course of illness in PD. Nonetheless, we believe that our results will be useful for better clinical managing of PD.

In conclusion, to the best of our knowledge, the long-term effects of different DCI to levodopa ratios on motor complications have not yet been reported. The results of our study suggest that a levodopa/carbidopa therapy with a DCI to levodopa ratio of 1:10 may delay the occurrence of subsequent motor fluctuations throughout the course of illness. Further large-scale studies are needed to elucidate the relationship between the blending ratio of levodopa/DCI and disease progression in PD.

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Declaration of Competing Interest

None.

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