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ORIGINAL ARTICLE

Pharmacokinetics of levodopa/benserazide versus levodopa/carbidopa in healthy subjects and patients with Parkinson's disease

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Abstract

Background: There are two formulations of levodopa in Japan and a few other countries, levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg, which have been generally regarded as interchangeable in Parkinson's disease treatment.

Aim: We investigated the pharmacokinetics of levodopa in the two kinds of levodopa/decarboxylase inhibitor (benserazide or carbidopa) formulations to study their equivalence.

Methods: Population pharmacokinetic analysis was carried out using levodopa data from the healthy subject study and, additionally, for 70 plasma concentration data points from Parkinson's disease patients receiving either levodopa/decarboxylase inhibitor combination in clinical practice.

Results: In healthy subjects, the mean ± standard deviation plasma levodopa maximum observed plasma concentration and area under the plasma concentration time curve from time 0 to 3 h (512 ± 139 *vs* 392 ± 49 μmol•h/L, $P < 0.05$) were significantly higher after levodopa/benserazide compared with levodopa/carbidopa. Levodopa time to maximum observed plasma concentration and plasma elimination half-life were not significantly different when comparing the respective formations. Levodopa pharmacokinetic parameters were the same between the Parkinson's disease patients and healthy subjects, except for levodopa apparent clearance, which was approximately two-thirds lower in Parkinson's disease patients compared with healthy subjects for both levodopa/decarboxylase inhibitor combinations, which might result in higher levodopa area under the curve in patients with Parkinson's disease than in healthy volunteers.

Conclusion: Levodopa pharmacokinetics differ after administration of levodopa/benserazide and levodopa/carbidopa. This information cold be useful for adjustment of medication in Parkinson's disease patients, especially with motor complications.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive loss of dopamine neurons in the substantia nigra and striatum. The shortage of dopaminergic input results in motor symptoms, such as rigidity, akinesia, tremor and postural instability, which is termed PD.

The cardinal treatment for patients with PD is oral administration of levodopa with peripheral decarboxylase inhibitor (DCI).[1] There are two DCI in clinical use: benserazide and carbidopa. In combination with levodopa, they are generally regarded as equally effective.[2,3] The clinical effectiveness was measured, however, in limited clinical settings, and there is little known about their pharmacokinetic differences.

Levodopa treatment is sufficient for patients with early-stage disease, but is associated with motor complications in late-stage disease, when substantial degeneration of nigrostriatal dopaminergic neurons has occurred. As the presynaptic handling and storage of levodopa-derived dopamine is reduced, the strength of dopaminergic stimulation becomes strictly dependent on the plasma levodopa concentration associated with motor complications, such as "wearing off"

and dyskinesia.[4] Drug dose adjustment should be considered carefully to maintain the serum levodopa concentration in the therapeutic window for patients with late-stage PD.

The aim of the present study was to determine whether there is any difference between the two levodopa/DCI combinations in terms of plasma levodopa concentrations. This information will be of clinical utility in achieving more effective treatment for PD.

Methods

Both studies were reviewed and approved by the institutional review board of Ehime University Hospital, and followed the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each participant.

Pharmacokinetic study in healthy volunteers. A single-dose, cross-over study was undertaken in 10 young (age range 23–41 years) male volunteers to determine the pharmacokinetics of levodopa and DCI after the administration of a fixed-dose combination tablet of levodopa/benserazide or levodopa/carbidopa. All participants received a single tablet of levodopa 100 mg plus benserazide 25 mg and, after a 14-day washout period, a single tablet of levodopa 100 mg plus carbidopa 10 mg. The drugs were administered after overnight fasting, and the participants remained fasting throughout blood sampling.

Venous blood samples (5-mL aliquots into ethylenediaminetetraacetic acid-2Na tubes) were taken immediately before drug administration and every 30 min until 3 h. Blood samples were centrifuged for 10 min at 1000 *g*, and plasma was collected and stored at –80°C until measurement. Plasma concentrations of levodopa were measured using high-performance liquid chromatography (HPLC) with electrochemical detection. Plasma aliquots (100 μL) were mixed with 500 μL of ice-cold 0.2 mol/L perchloric acid containing 0.1 mmol/L ethylenediaminetetraacetic acid and 5 μL of 15 pg/mL 3,4-dihydroxybenzamine. Samples were centrifuged at 20 000 *g* for 15 min at 4°C (Himac CF 16RX; Hitachi, Tokyo, Japan). The supernatant was filtered through a 0.45-μm membrane filter (Chromatodisc 4A; GL Science, Tokyo, Japan), and a 10-μL aliquot of filtered solution was injected into the HPLC system with an electrochemical detector. The HPLC system included a delivery pump, a degasser and an electrochemical detector (HTEC-500; Eicom, Kyoto, Japan) with a Gilson 234 autoinjector (Eicom). Analytical separation was carried out on a reverse-phase column (C18 phase; 150 × 2.1 mm; EICOMPAK SSC-5-ODS, Eicom) at 30°C. The mobile phase consisted of 12% (v/v) methanol containing 0.1 mol/L phosphate buffer (pH 2.7) and 232 mg/L sodium octyl sulfate. The flow rate was maintained at 0.25 mL/min. Plasma concentrations of benserazide and carbidopa were measured with the same preparation with the mobile phase consisting of 12% of (v/v) methanol containing 0.1 mol/L phosphate buffer (pH 2.7) and 100 mg/L sodium octyl sulfate.

Pharmacokinetic parameters such as maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}) and plasma elimination half-life ($t_{1/2}$), and area under the plasma concentration-time curve from time 0 to 3 h ($AUC_{0–3\ h}$) were determined for levodopa and benserazide or carbidopa in each participant (Phoenix WinNonLin version 6.1, Certara, L.P., St. Louis, MO, USA). C_{max} and T_{max} were obtained directly from experimental data, and $t_{1/2}$ was calculated from the slope of the plasma concentration–time curve during the elimination phase. AUC was calculated using the linear trapezoidal rule. Data are presented as mean values ± SD. Paired data were compared using the Wilcoxon signed-rank test, and *P*-values <0.05 were considered significant.

Population pharmacokinetic study. A population pharmacokinetic study of levodopa was carried out among PD patients after the administration of a levodopa/DCI for comparison with results in healthy participants. The study population included PD patients attending our outpatient clinic who had been taking the previously described formulations of levodopa/benserazide or levodopa/carbidopa at therapeutic doses. Any patient receiving a catechol-O-methyl transferase inhibitor (COMT-I) was excluded, as such drugs potentially affect the metabolism of levodopa. A total of 47 blood samples were collected from 32 patients (14 men and 18 women; age 69 ± 12 years) taking levodopa/benserazide, and 23 blood samples were collected from 16 patients (8 men and 8 women; age 64 ± 10 years) taking levodopa/carbidopa. All blood samples were taken in the morning in a non-fasted state, and the duration between drug administration and taking of blood samples was recorded, as well as the drug dose they were receiving. Blood sampling, plasma collection and storage, and determination of levodopa concentrations were as described previously for healthy subjects.

Non-linear, mixed-effect modeling was used for pharmacokinetics analysis using NONMEM software (version 7.2.2; ICON Development Solutions, Ellicott City, MD, USA). Different structural models were tested and pharmacokinetic parameters, such as the absorption rate constant (K_a), apparent total body clearance (CL/F) and apparent volume of distribution (Vd/F), were estimated for each combination (levodopa/benserazide and levodopa/carbidopa) in each group (healthy subjects and patients) using first-order conditional estimation method with interaction (FOCE-INTER).

Results

Pharmacokinetic study in healthy volunteers. Plasma levodopa concentration versus time curves after administration of levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg are shown in Figure 1a. Mean levodopa C_{max} was significantly higher after the administration of levodopa/benserazide 100/25 mg than after levodopa/carbidopa 100/10 mg (8.37 ± 3.19 *vs* 4.95 ± 1.65 μmol/L, $P < 0.001$). Mean T_{max} (33.0 ± 9.5 *vs* 51.0 ± 31.8 min) and $t_{1/2}$ (72.0 ± 15.3 *vs* 82.7 ± 24.0 min) for levodopa were not significantly different when comparing levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg, respectively. Mean levodopa $AUC_{0–3\ h}$ was significantly higher after the administration of levodopa/benserazide 100/25 mg than after levodopa/carbidopa 100/

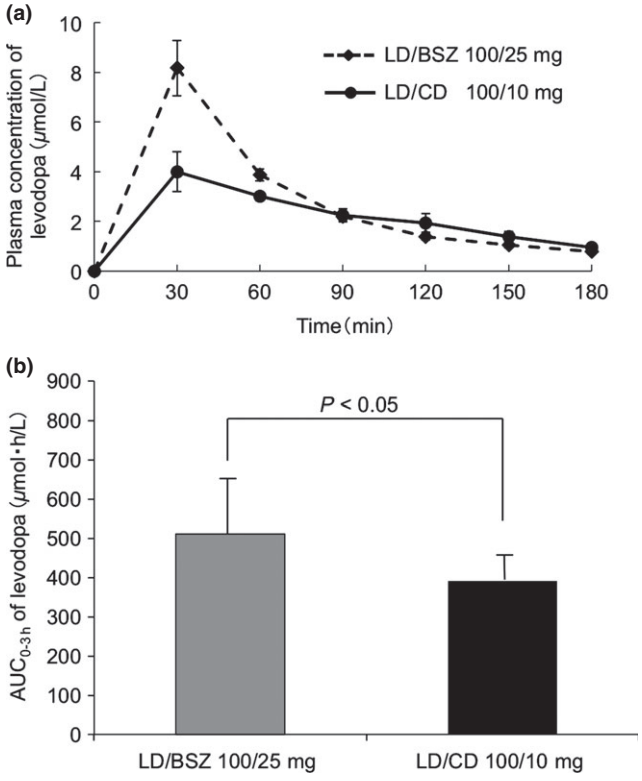

Figure 1 Levodopa pharmacokinetics in healthy subjects after administration of levodopa/benserazide 100/25 mg (LD/BSZ) or levodopa/carbidopa 100/10 mg (LD/CD). (a) Plasma concentration versus time curve. (b) Area under the plasma concentration–time curve from time 0 to 3 h ($AUC_{0-3\ h}$). Values are mean ± SD.

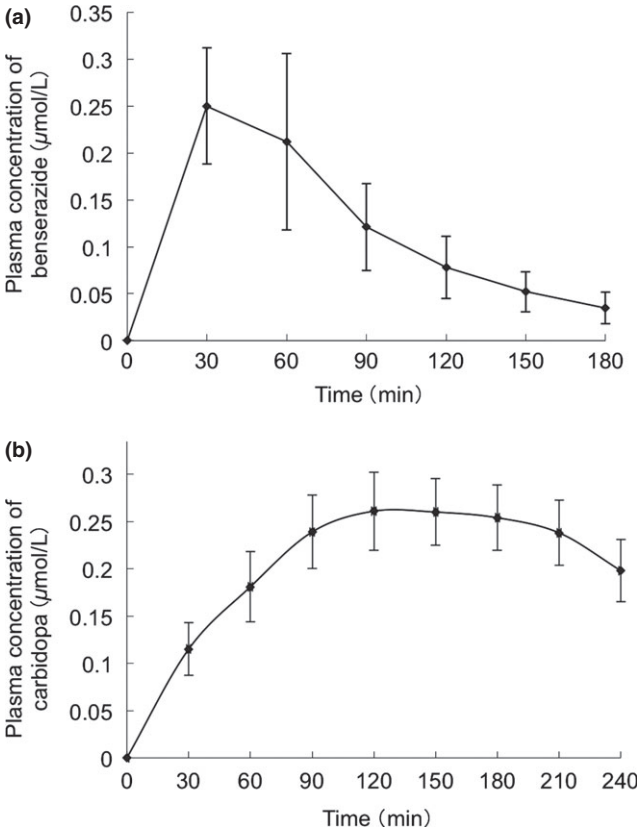

Figure 2 Plasma concentrations of (a) benserazide and (b) carbidopa in healthy subjects after administration of levodopa/benserazide 100/25 mg or levodopa/carbidopa 100/10 mg, respectively. Values are mean ± SD.

10 mg (511 ± 139 *vs* 391 ± 49 μmol•h/L, $P < 0.05$; Fig. 1b).

Plasma concentration versus time curves for benserazide and carbidopa after administration of levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg are shown in Figure 2a,b, respectively. The following pharmacokinetic parameters were found for benserazide after the administration of levodopa/benserazide 100/25 mg: mean C_{max} 0.287 ± 0.174 μmol/L, T_{max} 36.0 ± 12.6 min and $t_{1/2}$ 48.6 ± 12.1 min. The following pharmacokinetic parameters were found for carbidopa after the administration of levodopa/carbidopa 100/10 mg: mean C_{max} 0.292 ± 0.078 μmol/L and T_{max} 147 ± 39 min. The $t_{1/2}$ was not determined, because four of the 10 participants did not reach the elimination phase within the observation period (up to 4 h after the administration).

Population pharmacokinetics. Figure 3a,b shows the plasma levodopa concentration for individual patients at various time-points after administration of levodopa in combination with benserazide or carbidopa, respectively. Concentrations of levodopa were generally higher after administration of levodopa/benserazide compared with levodopa/carbidopa. Population pharmacokinetics of levodopa were best described by a one-compartment model.

Estimated pharmacokinetic parameters are summarized in Table 1. As all the blood samples were taken at least 1 h after medication, it was not possible to estimate the absorption rate constant (K_a). K_a was therefore fixed at 10/min. Levodopa CL/F was lower after the administration of levodopa/benserazide as compared with levodopa/carbidopa in both healthy participants (0.734 *vs* 0.889 L/min) and patients (0.493 *vs* 0.555 L/min), although the differences were small. CL/F was consistently lower in patients as compared with healthy participants. Levodopa Vd/F was smaller after the administration of levodopa/benserazide as compared with levodopa/carbidopa in both healthy participants (44.7 *vs* 80.0 L) and patients (55.0 *vs* 81.4 L).

Discussion

Our cross-over study in healthy subjects showed that the pharmacokinetics of levodopa were different after oral administration of levodopa/benserazide 100/25 mg and levodopa/carbidopa 100/10 mg, even though these formulations are generally regarded as providing identical levodopa exposure in practice in Japan and a few other countries. In the non-compartmental analysis among the healthy subjects, mean C_{max} of levodopa was 1.7-fold higher and

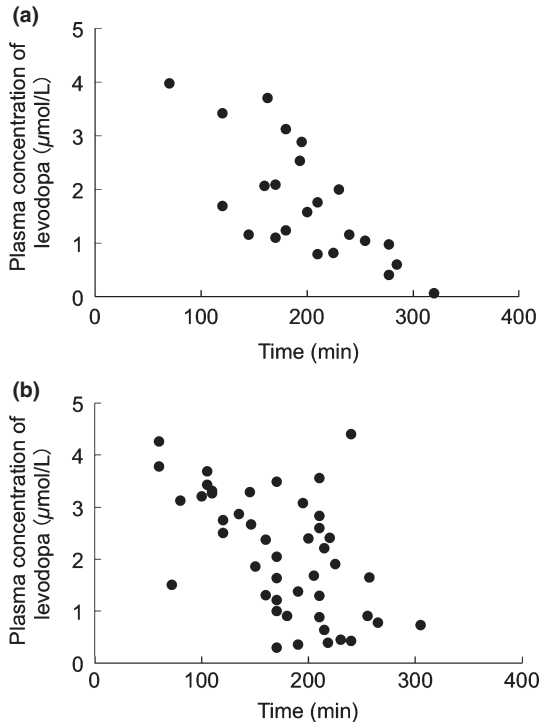

Figure 3 Plasma levodopa concentrations for individual patients with Parkinson's disease after administration of (a) levodopa/benserazide or (b) levodopa/carbidopa. Plasma levodopa concentration equivalent to a 100 mg dose plotted versus the time from dosing to sampling.

$AUC_{0-3\ h}$ was 1.3-fold larger with levodopa/benserazide as compared with levodopa/carbidopa. As levodopa dosing was the same (100 mg) for both formulations, it is assumed that benserazide 25 mg has a more significant inhibitory effect towards AADC than carbidopa 10 mg. Levodopa $t_{1/2}$ in the levodopa/benserazide group was shorter, but not significantly, compared with the levodopa/carbidopa group. It is interesting to note the different pharmacokinetics of the two DCI; that is, benserazide showed a rapid increase and rapid decrease in its plasma concentration, whereas carbidopa showed a slow increase and slow decrease in its plasma concentration. One possible explanation for the similarity of levodopa $t_{1/2}$ with both levodopa/DCI combinations might be that the DCI pivotally provided their inhibitory effects of AADC in the gut where extensive presystemic levodopa metabolism takes place, and systemic DCI only have limited efficacy for maintaining plasma levodopa levels.[5] Another levodopa metabolizer, COMT, could play an important role in this phenomenon. COMT is regarded as a predominant metabolizer when the AADC pathway is blocked.[6] Thus, it might compensate for the effect of systemic DCI against levodopa metabolism. We did not examine downstream products of levodopa metabolism in the present study, and this needs to be further investigated to clarify the mechanistic differences between levodopa $t_{1/2}$ and DCI pharmacokinetics. Additionally, we cannot exclude the possibility of ordering effect because of the non-randomized cross-over design of the study; however, we consider the effect to be negligible for the following three reasons. First, the 14-day washout period was long enough to eliminate the possibility of any carry-over effect. Second, the washout period was not so long that the conditions of the study participants and the surrounding co-factors were likely to have changed significantly during the period. Finally, drug concentration is an objective marker, so it was not affected by participants' subjective reactions.

The present population pharmacokinetic study showed that levodopa CL/F and Vd/F were lower after administration of levodopa/benserazide compared with levodopa/carbidopa in both healthy subjects and patients. The difference in levodopa CL/F and Vd/F after administration of levodopa/benserazide and levodopa/carbidopa might reflect the higher bioavailability (F) of levodopa with the levodopa/benserazide combination, which was shown in the previous analysis. Intergroup difference of levodopa Vd/F was relatively small between healthy subjects and patients. In contrast, levodopa CL/F was approximately two-thirds lower among the patients than in healthy subjects with both levodopa/DCI formulations. There are many factors that have been reported to affect levodopa pharmacokinetics in PD patients, such as sex, duration of the disease, meal content, time between medication and meal, renal function, and gastric pH.[7–9] Age also seems to have a considerable impact on levodopa pharmacokinetics, because it globally affects organs and functions associated with levodopa absorption, distribution, metabolism and clearance, although reports measuring the impact of age are sparse. In the present study,

Table 1 Levodopa population pharmacokinetics following administration of levodopa/benserazide or levodopa/carbidopa in healthy subjects or patients with Parkinson's disease

	Healthy subjects		Parkinson's disease patients	
	Levodopa/benserazide	Levodopa/carbidopa	Levodopa/benserazide	Levodopa/carbidopa
Population mean				
K_a (1/min)	10 (fixed)	10 (fixed)	10 (fixed)	10 (fixed)
CL/F (L/min)	0.734	0.889	0.493	0.555
Vd/F (L)	44.7	80.0	55.0	81.4
CL/F inter-individual variability (CV%)	12.2	22.4	NE	48.2
CL/F residual variability (CV%)	27.6	32.7	45.8	18.9

CL/F, apparent clearance; CV%, percent coefficient of variation; K_a, absorption rate constant; Vd/F, apparent volume of distribution.

the PD group was older, included women and might have had poorer kidney function compared with the healthy subject group. All those factors would contribute to the lower CL/F in the patient group. Finally, the interindividual variability and residual variability were larger in the PD group, presumably because the study conditions for the patient group were not as rigorously controlled compared with the study in healthy subjects. Nevertheless, the parameters derived from the patient data were similar to those from the healthy subject data.

In clinical settings, both levodopa/DCI combinations have been used for PD patients for decades, and have been generally considered as similarly reliable, although some studies in smaller populations have emphasized differences between DCI. For example, Admani *et al.*[10] reported that levodopa/benserazide showed more improvement in all parkinsonian signs and symptoms compared with levodopa/carbidopa in a double-blind study in 60 PD patients, although the differences did not reach statistically significance. Rinne and Mölsä concluded that levodopa/benserazide 200/50 mg had the same clinically efficacy as levodopa/carbidopa 250/25 mg in a randomized, double-blind, cross-over trial in 49 PD patients, although levodopa/carbidopa induced significantly more nausea and vomiting.[2] Diamond *et al.*[11] carried out a double-blind comparison of levodopa/benserazide and levodopa/carbidopa in 20 PD patients, and reported that the majority of patients fared distinctly better on either levodopa/benserazide or levodopa/carbidopa. In a cross-over study in 19 PD patients, Greenacre *et al.*[12] also found that most patients preferred either levodopa/benserazide or levodopa/carbidopa. These reported differences between levodopa/benserazide and levodopa/carbidopa might be partly explained by our current findings. Levodopa/benserazide would possibly be a better candidate for patients requiring immediate treatment because of its higher C_{max} and stronger DCI efficacy. In contrast, levodopa/carbidopa might be useful for patients with motor complications, such as troublesome dyskinesia, because its levodopa pharmacokinetics is relatively stable.[13–15]

Regarding the dosage of combined carbidopa, not only a tablet of levodopa/carbidopa 100/10 mg, but also a 100/25-mg tablet is available outside Japan. We only used 100/10-mg tablets, so the results of the present study should be carefully translated. A larger proportion of carbidopa is reportedly associated with better therapeutic outcomes and fewer adverse events in some reports, whereas the Japanese approval document concluded that the significant increase of levodopa was not observed with higher carbidopa combinations.[16,17] Although detailed pharmacokinetic features remain unknown, one study showed an approximately 20% increase of levodopa AUC when 450 mg/day carbidopa was orally administered with levodopa infusion, compared with 75 mg/day.[18] The higher carbidopa proportion is possibly associated with a higher C_{max} and AUC, but the impact might be limited. Another limitation of the study is that all the study participants were ethnically identical; that is, they were all Asians. Most previous reports were from the USA and Europe, but there have not been any ethnic factors associated with levodopa pharmacokinetics reported, and the present results are in accord with other reports.

In conclusion, administration of levodopa/benserazide 100/25 mg provided higher levodopa C_{max} and larger $AUC_{0-3\ h}$ as compared with levodopa/carbidopa 100/10 mg. Benserazide had a stronger AADC inhibitory effect, although differences in the pharmacokinetics of systemic benserazide and carbidopa did not seem to contribute to the elimination of levodopa. The population study showed that the pharmacokinetics of levodopa after the administration of levodopa/benserazide and levodopa/carbidopa were similar in PD patients and healthy subjects apart from the lower levodopa CL/F in patients, which could result in the higher AUC of levodopa in patients with Parkinson's disease than healthy volunteers. Levodopa/benserazide might be a better choice for patients with more severe adverse effects or inadequate levodopa efficacy, and levodopa/carbidopa might be more useful for patients with motor complications.

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