The Pharmacokinetics and Pharmacodynamics of Levodopa in the Treatment of Parkinson's Disease

Soo-Peang Khor[a] and Ann Hsu[b,*]

[a]*Clinical Pharmacokinetics and Pharmacodynamics, IMPAX Laboratories, Inc. Hayward, CA, USA;* [b]*Clinical Development, IMPAX Laboratories, Inc. Hayward, CA, USA*

Abstract: Levodopa , a prodrug of dopamine, remains to be one of the main drugs in the treatment of Parkinson's disease. All current levodopa products are formulated with aromatic amino acid decarboxylase inhibitors such as carbidopa or benserazide to prevent the metabolism of levodopa in the gastrointestinal tract and systemic circulation. Levodopa pharmacokinetic profiles remain unchanged after multiple doses, and are similar between healthy volunteers and patients and among patients at different stages of disease. Entacapone inhibits the metabolism of levodopa therefore increases the area under the plasma concentration-time profile of levodopa; however, it may decrease the initial absorption rate of levodopa in some patients probably due to competitive absorption. Food appears to affect the absorption of levodopa, but its effects vary with formulations. The results of positron emission tomography study suggest that a high protein diet may compete with the uptake of levodopa into the brain, therefore, may result in reduced levodopa effects. Since infusion studies demonstrated that it is beneficial to maintain stable plasma concentrations of levodopa, controlled-release formulations have been designed to provide prolonged absorption of levodopa. However, subsequent pharmacokinetic and pharmacodynamic studies demonstrated that a threshold concentration of levodopa appears to be necessary to switch patients "on". Once patients are turned "on", the duration of levodopa effects may be correlated with plasma concentration of levodopa. As such, more recent studies have demonstrated significant clinical benefits such as shorter time to "on" and longer duration of "on" when combining the immediate- and controlled-release levodopa products as compared to controlled-release levodopa products. Given these findings, it is important for physicians to understand the relationship between the pharmacokinetics and pharmacodynamics of levodopa in order to provide dosage regimens that meet patient needs. The pharmacokinetics and pharmacodynamics data of levodopa reported in the literature are reviewed here.

Key Words: Pharmacokinetics, levodopa, carbidopa, Parkinson's disease.

1. INTRODUCTION

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Patients with Parkinson's disease suffer from both motor and non-motor symptoms. The cardinal motor symptoms include resting tremor, rigidity, bradykinesia and postural instability. Examples of non-motor symptoms are diminished sense of smell, depression, and sleep disturbance.

Levodopa (LD), chemically known as (-)-L-∝-amino-β-(3,4-dihydroxybenzene) propanoic acid, was introduced in 1960s for the symptomatic treatment of Parkinson's disease. It remains the gold standard in the management of the motor symptoms of Parkinson's disease today. Nearly all patients with Parkinson's disease eventually receive LD therapy at some stage of the disease. The active metabolite of LD, dopamine, is responsible for the control of symptoms of Parkinson's disease; however, it does not cross the blood brain barrier (BBB). Since LD crosses BBB, it acts as a prodrug of dopamine. However, LD is rapidly decarboxylated to dopamine in extracerebral tissues, especially in the gastrointestinal tract, following oral administrations, and therefore only a small portion of a given LD dose is transported across the BBB to the central nervous system. For this reason, LD is routinely administered with a decarboxylase inhibitor such as carbidopa (CD) or benserazide to prevent the formation of peripheral dopamine.

Currently, LD products are available as standard immediate-release tablet (standard, or IR), controlled-release tablet (CR), orally disintegrated tablet (ODT), and immediate-release CD-LD in combination with a fixed 200 mg dose of entacapone, where entacapone inhibits the metabolism of LD mediated by catechol-O-methyltransferase (COMT). Additionally, a dual release formulation combining immediate- and sustained-release of levodopa and benserazide is available in the Europe [1, 2]. A new product that delivers immediate and sustained release of LD and CD in a single formulation is currently under development[a]. Since the pharmacological effects of LD have been shown to be correlated with plasma concentrations of LD, this article reviews the pharmacokinetics (PK) of LD and CD and the relationships between plasma concentrations of LD and the pharmacodynamic (PD) effects of LD.

2. PHARMACOKINETICS OF LD AND CD

2.1. Absorption

2.1.1. Levodopa

The absorption of LD is *via* the saturable L-neutral amino acid transport system for large amino acids. However, in-

*Address correspondence to this author at the 30831 Huntwood Av., Hayward, CA 94544, USA; Tel: (510) 476-2000; Fax: (510) 476-2093; E-mail: annhsu@impaxlabs.com

[a] Liang E, Wang X, Khor SP, Hsu A. Comparison of pharmacokinetics of levodopa and carbidopa between IPX054 and Sinemet® and Sinemet® CR tablets under fasting conditions. Mov Disord 2006; 21: S125.

1574-8847/07 $50.00+.00

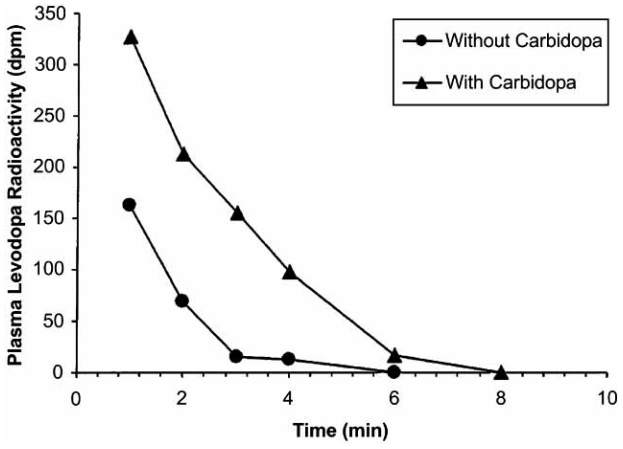

Fig. (1). Concentrations of levodopa in patients with Parkinson's disease treated with oral of L-2-^{14}C-levodopa in the presence and absence of carbidopa.

creasing LD dose resulted in a more than proportional increase of LD plasma concentrations probably because the major metabolism of LD in the GI tract is also by a saturable amino acid decarboxylation pathway [3-5]. Orally administered LD is almost completely absorbed, with only 2% appearing in the feces [5-8]. However, only about 30% of an oral LD dose reached the systemic circulation intact when not administered with CD. The oral bioavailability of LD is increased 2 to 3 times when co-administered with decarboxylase inhibitors [5, 9-11]. Bianchine *et al.* showed that following pretreatment with MK-486 (carbidopa), peak plasma LD concentration increased approximately 3-fold, and plasma radioactivity half-life increased significantly from 3 to 15 hours [8]. Based on the data reported by Bianchine *et al.* [8], it is possible to construct a plasma concentration-time profiles for levodopa in the absence and presence of carbidopa (Fig. (**1**)). In that regard, Nutt *et al.* also showed that the clearance of plasma LD after intravenous infusion of LD in the presence of CD were statistically significantly decreased by about 50% as compared to that determined in the absence of CD [12]. Thus, all current LD products are CD-LD combination formulations.

In healthy elderly subjects under fasting condition, the absorption of LD from an immediate-release (IR) CD-LD product is rapid (Table **1**), with 60% of the dose absorbed in 30 minutes, and the absorption was complete in 2-3 hours [13]. Interestingly, although the currently available CD-LD-entacapone combination product is an immediate-release

Table 1. Examples of Pharmacokinetic Parameters of LD Following Administration of Various CD-LD Products

Reference	Population	CD-LD Dose (mg)	t_{max} (hr)	C_{max} (μg/mL)	AUC (μg•hr/mL)
Yeh *et al*., 1989	Healthy (n=16)	Sinemet 2 x 25-100	0.8 ± 0.4[a]	1.39 ± 0.34[a]	3.69 ± 0.74[a]
		Sinemet CR 50-200	1.8 ± 1.1[a]	0.47 ± 0.17[a]	1.92 ± 0.82[a]
	Elderly, Healthy (n=16)	Sinemet 2 x 25-100	0.5 ± 0.1[a]	3.26 ± 0.98[a]	5.31 ± 1.71[a]
		Sinemet CR 50-200	2.1 ± 1.4[a]	1.15 ± 0.43[a]	4.01 ± 1.42[a]
Kaakkola *et al*., 1985	Healthy (n=11)	Kardopal 10-100	0.9 ± 0.3[b]	.80 ± .08[b]	1.41 ± 0.11[b]
		Kardopal 25-100	0.9 ± 0.2[b]	1.09 ± .24[b]	1.65 ± 0.12[b]
		Kardopal 25/250	0.6 ± 0.1[b]	1.41 ± .13[b]	3.47 ± 0.27[b]
		Kardopal 62.5/250	0.8 ± 0.2[b]	1.55 ± .11[b]	4.34 ± 0.30[b]
LeWitt *et al.*, 2005[c]	Patients (n=17)	Sinemet CR 50-200	5.4[d]	2.53	10.32
		Stalevo 150	5.1[d]	2.97	10.22
Liang *et al*., 2006	Healthy (n=18)	Sinemet CR 25-100	2	0.77 ± 0.31[a]	2.02 ± 0.60[a]
		Sinemet CR 50-200	2	1.16 ± 0.34[a]	3.78 ± 0.94[a]
		Sinemet 25-100	0.75	1.04 ± 0.26[a]	1.95 ± 0.96[a]
		VADOVA 50-200	1.5	1.47 ± 0.48[a]	4.07 ± 0.70[a]
			0.5[e]	1.17 ± 0.59[e]	

[a] ± S.D.

[b] ± S.E.M.

[c] Geometric mean over an 8-hr dosing period

[d] After Q4H dosing for 8 days, PK parameters of two doses given 4 hours apart were assessed in a crossover manner; t_{max} of LD occurred after the 2nd dose for both regimens.

[e] Since VADOVA (a new product currently under development) is an immediate-release and sustained-release bi-layer formulation, the observed first peak concentration (C_{peak1}) and the time to C_{peak1} (t_{peak1}) were also reported.

formulation, with the addition of entacapone to the formulation, the initial absorption rate for LD appeared to be decreased, and the plasma concentration-time profiles of LD resembled that of the CR formulation [14]. Similar outcomes, i.e. lower C_{max} and prolonged t_{max}, were observed when Sinemet 50-200 was dosed in patients treated with entacapone [15]. These observations are somewhat consistent with the observations that the absorption rate of LD appeared to be affected by entacapone, and the effect appeared to be a function of entacapone dose, probably due to competitive absorption [16-20]. It should be noted that there were also reports showing that the initial absorption rate of levodopa from an IR product was not delayed when co-administered with entacapone following a multiple dose regimen [21]. In general, co-administration of entacapone with CD-LD products tends to increase the total levodopa AUC by increasing the concentrations at the later time points after dosing (Fig. (**2**)).

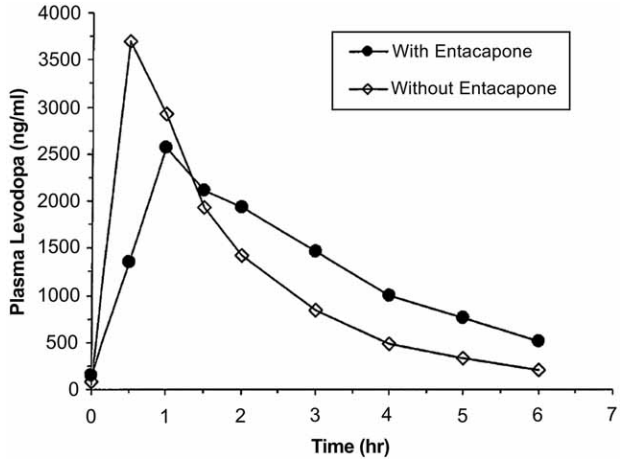

Fig. (2). The concentrations of levodopa after standard immediate release tablet of carbidopa-levodopa with and without entacapone.

Since the transport of LD is through the L-neutral amino acid transport system, studies have been conducted to evaluate the effect of dietary protein on the clinical response to LD [22-29]. The results of these studies showed that the clinical effect of LD was reduced by a daily diet containing protein in excess of 1.6 g/kg or a single protein load of approximately 28 g [23, 25, 29]. A protein-containing diet tends to reduce the oral absorption of LD [26, 27, 30]; however, it should be noted that the decrease in response to LD did not appear to correlate with plasma LD concentrations [23, 29]. A study using positron emission tomography showed the decreased effect appeared to be correlated with a decrease in the uptake of LD into the brain probably due to competition from the increased plasma amino acid concentrations [31].

For a controlled-release (CR) LD product, the absorption was gradual and completed in 4-6 hours under fasting conditions [13, 32]. As shown in Fig. (**3**), the controlled-release

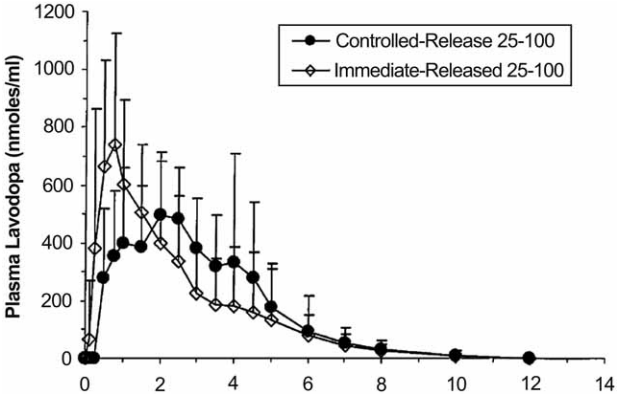

Fig. (3). The concentrations of levodopa in healthy subjects after dosing with immediate-release or controlled-released carbidopa-levodopa tablets in a randomized crossover study.

CD-LD product has longer t_{max} and lower C_{max} in comparison to the immediate-release product[b]. A CR only product also reaches maximum concentration later that a product with the combination of an immediate and a controlled release properties [1]. Additionally, in healthy elderly volunteers, the LD bioavailability of a CR formulation (Sinemet® CR 50-200 mg) and an IR formulation (Sinemet 2 tablets of 25-100 mg) administered under fasting conditions was reported to be 71% and 99%, respectively, therefore, the bioavailability of a CR formulation has been estimated to be ~70% of an IR formulation under fasting conditions [13]. However, data from a recent randomized crossover study demonstrated that bioavailability of Sinemet 25-100 mg is comparable to that of Sinemet CR 25-100 mg[c], suggesting caution should be exercised when extrapolating the relative bioavailability of LD between different formulations and/or different dose levels. Furthermore, it is important to note that Yeh *et al.* reported that the bioavailability of the CD-LD CR product increased 48% if taking after consuming a meal containing 2 eggs, toast, 8 ounces juice, 8 ounces milk, and decaffeinated coffee, probably due to increased gastric retention which in turn allowed more complete absorption of LD in the upper GI [10]. However, Mearrick *et al.* showed that the absorption of LD from a standard release (IR) CD-LD product was increased during rapid gastric emptying under fasting conditions [33]. Therefore, food effects on LD pharmacokinetics vary with formulations.

The pharmacokinetics of LD does not change after multiple days of dosing. Yeh *et al.* showed that LD plasma levels after every 8 hour dosing for 10 days were essentially

[b] Data were obtained from database within IMPAX Laboratories, Inc., based on studies conducted by IMPAX Laboratories.

[c] Liang E, Wang X, Khor SP, Hsu A. Comparison of pharmacokinetics of levodopa and carbidopa between IPX054 and Sinemet® and Sinemet® CR tablets under fasting conditions. Mov Disord 2006; 21: S125.

Table 2. Estimated Pharmacodynamic Parameters of Levodopa

Patient Group (Hoehn & Yahr Stage)	$t_{1/2eq}$ (min)	EC_{50} (μg/mL)	E_{max}	E_0	N (Hill coefficient)
Tapping Motor Effect					
I	133	0.2	45	144	2
II	78	0.29	35	141	5
III	28	0.6	41	114	7
IV	20	0.94	55	117	18
p	<0.001	<0.001	NS	<0.001	<0.001
Dyskinesic Effect					
I	NA	NA	NA	NA	NA
II	22	0.7	1	0	14
III	19	0.65	3	0	27
IV	17	0.98	3	0	30
p	NS	<0.005	<0.007	--	NS

$t_{1/2eq}$: equilibration half-life between plasma and effect site concentration; EC_{50}: plasma concentration at ½ E_{max}; E_{max}: maximum effect; E_0: baseline effect; NS: Group effect was not statistically significant ($p>0.05$); NA: None in Group I developed dyskinesia. Data were adapted from reference [55].

identical to those obtained after a single dose in healthy elderly volunteers for both Sinemet and a CR formulation [13].

2.1.2. Carbidopa

Approximately 40-70% of an oral dose of CD is absorbed in man [34]. CD is absorbed more slowly than LD, with t_{max} at ~2 hours after oral dosing of an IR formulation containing both CD and LD, and up to 2.8 hours after a CR formulation in healthy elderly subjects [13]. The bioavailability of CD is not affected by the co-administration of LD. [34, 35]. However, the bioavailability of CD in a CR formulation was ~58% of an IR formulation [35]. Unlike LD, the bioavailability of CD in a CR formulation under fed conditions was lower than that under fasting conditions, Yeh *et al.* hypothesized that the systemic inhibitory activity of CD on aromatic amino acid decarboxylase (AAAD) appeared to be similar between the two dosing conditions, because apparent LD renal clearances and the ratio of dopamine-to-dopa remain unaffected by food intake [13].

2.2. Distribution

2.2.1. Levodopa

Levodopa crosses the blood-brain barrier by stereospecific, saturable, facilitated process *via* the large neutral amino acid (LNAA) transport carrier system. Gey and Pletscher showed that 1 hour after a 20 mg/kg ^{14}C-*DL*-dopa subcutaneous dose in rats, only 0.1% of the radioactivity was found in the brain, while most of the radioactivity was found in urine, skin, whole skeletal muscle, intestine, and liver [36]. After an intravenous dose of 50 mg LD alone, the V_{ss} (volume of distribution at steady state) in young healthy volunteers was estimated to be 70% higher than that in elderly volunteers [37]. The V_{ss} of LD was estimated to be approximately 50% higher in young healthy volunteers than that in elderly volunteers when an intravenous LD dose was co-administered with CD. Kaakkola *et al.* reported similar V_{ss}/F for LD after oral dosing of 10-100 to 62.5-250 mg CD-LD in healthy volunteers [38].

Levodopa is not highly bound to plasma proteins [39-41]. The free fraction was found to be 76±8% at a concentration of 500 ng/mL.

2.2.2. Carbidopa

Carbidopa does not cross blood-brain barrier even at high doses [42, 43]. After an intravenous ^{14}C-CD dose in rats, radioactivity was concentrated in the kidneys, lungs, plasma, spleen, liver, small intestine, and adrenals, but was not detected in the brain [34, 44]. One study reported V_d/F of 2.2 ± 0.2 to 4.7± 0.4 L/kg for CD in healthy volunteers after oral dosing of 10-100 to 62.5-250 mg CD-LD tablets [38].

Carbidopa is also not appreciably bound to human plasma proteins [34]. The percent of CD bound to human plasma protein was 36±1.6%.

2.3. Metabolism

2.3.1. Levodopa

Nutt and Fellman conducted a comprehensive review of the metabolism of LD [5]. Levodopa undergoes metabolism *via* four pathways: decarboxylation by AAAD, 3-O-methylation by catechol-O-methyltransferase (COMT), transamination by tyrosine aminotransferase, and oxidation by tyrosinase or other oxidants. AAAD, a nonspecific enzyme, is widely distributed in gut, liver, kidneys, brain, lungs, adre-

nal, spleen, and heart [45]. Human brain capillaries also contain high concentrations of AAAD [46]. The decarboxylation pathway is the major metabolic pathway for LD. More than 95% of orally administered LD was decarboxylated peripherally, and only 1% of the dose entered the brain [10, 47]. The initial product of decarboxylation is dopamine, which may be further metabolized to form 3,4-dihydroxyphenyl acetic acid (DOPAC), homovanillic acid (HVA), and to a lesser extent, norepinephrine and vanillinemandelic acid. After intravenous dosing of LD, about 10% of the dose was accounted for by the 3-O-methylation process [48]. The metabolic product *via* the COMT pathway is 3-O-methyldopa (3-OMD). 3-OMD is further metabolized to vanilpyruvate by transamination and then reduced to vanillactate. COMT is primarily present in peripheral tissues, particularly liver, intestinal tract, and kidneys; comparatively low activity is found in the brain, and no activity is found in dopaminergic nigrostriatal neurons [47]. The transamination pathway is reversible, therefore, 3,4-dihydorxyphenylpyruvate may serve as a precursor for LD. The presence of cysteinyldopa in the urine of parkinsonian patients suggests that oxidation of LD by tyrosinase or other oxidants to dopa quinone intermediate does occur. Dopa quinone can be further metabolized to melanin [5].

In patients with Parkinson's disease, when 100 mg ^{14}C-LD was administered with a single 100 mg CD dose or after 100 mg CD t.i.d. for 7 days as compared to 100 mg ^{14}C-LD given alone, the majority of LD (~90%) was converted to 3-OMD by COMT in the peripheral tissues, peak plasma LD levels increased from non-detectable to 0.7 and 1.2 μg/mL, 2-hour dopamine levels decreased from 0.3 μg/mL to non-detectable, and peak HVA levels decreased 80% [10, 47, 49]. The corresponding decrease in urinary recovery of dopamine and DOPAC was approximately 3.5-fold and 2-fold, respectively [10]. 3-OMD has a 15-hour plasma half-life, is a poor substrate for AAAD, and appears to compete with LD for transport to the brain *via* the large neutral amino acid transport carrier system. Steady-state plasma 3-OMD concentrations in Parkinsonian patients are correlated with LD dose and do not vary markedly during LD therapy. Although oral challenges with 3-OMD reduce the clinical response to LD, 3-OMD is no more potent than phenylalanine in competing with LD for transport into the brain. Since 3-OMD makes a small contribution to the total concentration of large neutral amino acids competing with LD, Nutt *et al.* has concluded that 3-OMD is not an important determinant of clinical response to LD [50].

2.3.2. Carbidopa

Four metabolites have been detected in the urine of healthy volunteers and Parkinsonian patients after oral administration of 50 mg ^{14}C-CD [51]. Three metabolites, 2-methyl-3-methoxy-4-hydroxy-phenylpropionic acid, 2-methyl-3,4-dihydroxy-phenylpropionic acid, and 3-hydroxy-α-methyl-phenylpropionic acid, each accounted for approximately 10% of the radioactivity excreted in the urine (or ~5% of the dose each). These metabolites are excreted as glucuronides and unconjugated compounds. The fourth metabolite, 3,4-dihydroxy-phenylacetone, accounted for <5% of the radioactivity excreted in the urine. Thus, the loss of the hydrazine functional group represents the major metabolic pathway for CD, probably as molecular nitrogen. There was no published information on the potential pharmacological activities of these metabolites. However, carbidopa is found to undergo N-deamination in rats to form alpha-methyldopa and alpha-methyldopamine. The former metabolite readily crosses the blood-brain-barrier and is hypothesized to mediate some of the central effects of carbidopa [52]. However, it is not clear whether the observed reduction of norepinephrine concentrations in rats treated with carbidopa occurs in humans.

2.4. Excretion

2.4.1. Levodopa

Following oral administration of a 100 mg dose of ^{14}C-LD alone, 90% of the radioactivity (dose) was recovered in the 48-hour urine. The dose recovered in the 48-hour urine was reduced to about 60% when LD was coadministered with a single 100 mg dose of CD or with 100 mg CD t.i.d for 7 days [10], probably because the majority of LD dose is converted to the long half-life 3-OMD during coadministration with CD. The inhibition of AAAD by CD was determined to be pseudo-irreversible.

After an oral dose of 50-200 mg as an IR or a CR formulation, 7.2 ± 2.4% and 3.0 ± 1.4% of the LD dose was excreted in the urine as unchanged drug, respectively, which appeared to be consistent with the relative bioavailability of the respective formulations [13]. The plasma clearance of LD after intravenous administration in the presence of CD was reported to be age dependent, ranging from 781, 697, and 596 mL/min in 23-45, 55-76, and 56-67 year old healthy adults, respectively. Renal clearance accounted for about 10% of the total body clearance. [13]. Robertson *et al.* reported that the apparent plasma clearance (CL/F) of LD averaged 9.3 ± 1.0 mL/min/kg in young healthy volunteers and 5.8 ± 0.9 mL/min/kg in elderly volunteers [37]. The plasma half-life of LD when it is administered alone is about 50 minutes, and increased to ~1.5 hour when coadministered with CD.

2.4.2. Carbidopa

Vickers *et al.* showed that after a single 50 mg oral dose of ^{14}C-CD in Parkinsonian patients, about 64% and 33% of the radioactivity were recovered in the urine and feces, respectively, and the corresponding recoveries in healthy volunteers averaged about 51% and 47%, respectively [34]. Similar amount of the radioactivity (32% and 29%) in the 0-24 hour urine was due to unchanged carbidopa in Parkinsonian patients and healthy subjects, respectively [34]. Yeh *et al.* reported that the apparent renal clearance of CD were relatively similar (124 ± 61 to 177 ± 86 mL/min) in healthy younger and older subjects, after a single 50-200 mg dose of a CR formulation under fasting conditions [13]. The average elimination half-life of CD in plasma is about 2 hours when co-administered with LD [34]. A similar half-life of 2.08 hr was observed when CD was dosed alone [53].

2.5. Pharmacokinetics in Parkinsonian Patients

After multiple dosing, the pharmacokinetics of LD and CD are stable and no unexpected nonlinear accumulation occurs. Nutt *et al.* showed that the LD pharmacokinetic parameters were similar in treatment-naïve, stable, and fluctu-

ating Parkinsonian patients [54]. Consistently, Contin *et al.* showed that the pharmacokinetic parameters of LD and CD were similar among patients at different disease states (n=23, 25, 25, and 13 for Hoehn &Yahr stage I, II, III, and IV patient groups, respectively) [55]. Djaldetti *et al.* showed that the pharmacokinetics of LD were similar in *de novo* patients after the very first dose and after dosing for 1 month [56].

It has been shown that for a fixed total daily CD dose, simultaneous administration of divided doses of LD and CD produced the most favorable (lowest) urinary LD/dopamine ratio as compared to other alternative dosing methods [57]. The optimally effective daily dosage of CD was estimated to be between 75 to 160 mg/day [57]. The recommended minimum daily dose for CD is 70 mg or more [32, 35], and the currently marketed CD-LD products are available with a CD-LD dose ratio of 1:4 or 1:10. However, some studies have demonstrated that across a wide range of LD doses, in patients stabilized with a presumed "effective" 1:10 CD:LD ratio, an increase of CD dose to a 1:4 CD:LD ratio further increased LD bioavailability (C_{max} and AUC) and reduced peripheral adverse effects [38, 58-60].

At clinical doses, CD does not affect the decarboxylation of LD within the central nervous system. The presence of CD does not affect the LD concentration required for producing an optimal clinical response [61]. CD has not been demonstrated to have any overt pharmacodynamic actions at the recommended doses of not more than 200 mg/day [32, 35].

3. PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS OF LEVODOPA

3.1. Long-Duration and Short-Duration Responses

The response to LD during the first month to years of therapy is sustained improvement in motor disability. With disease progression, significant numbers of patients begin to develop motor fluctuations so that the motor disability is variably controlled during the day. Two kinds of pharmacological responses have been identified with LD [3, 50, 62]. The long-duration response (LDR), referring to the improvement in motor disability, is built up over days after initiation of LD therapy and disappears over days after discontinuing LD therapy. The short-duration response (SDR) refers to the transient response between LD doses and usually lasts minutes to hours.

3.1.1. Short-Duration Responses

By assessing changes in neurologic disability before and after an oral LD dose after an overnight washout, Muenter *et al.* estimated the duration of SDR to be 5 hours or less after an oral dose of 100 mg LD with concomitant benserazide [3]. Based on the changes in tapping speed before or after a 2-hour intravenous administration of 1 mg/kg/hr LD after the washout, Nutt *et al.* estimated the mean duration of SDR to be 4.0 ± 2.8 hours, and SDR remained stable during the first year of treatment [63]. The duration of SDR is proportional to dose and becomes shorter during chronic LD therapy [64].

3.1.2. Long-Duration Responses

Relatively consistent results have been reported to support the long-duration effects of LD. Muenter *et al.* found that it usually took 3 to 5 days to return to pretherapy disability after discontinuing LD therapy [3], while Barbato *et al.* found that it took 6.8 ± 3.0 days for early-stage patients to return to baseline after withdrawal of CD-LD CR treatment [62]. Ogasahara *et al.* showed that maximal disability was reached 3-4 days after withdrawal of LD in fluctuating patients [65]. Hauser *et al.* [66, 67] estimated that the geometric mean half-life of LDR was 7.9 days (range: 2.2 to 30.4 days) in 20 early-stage Parkinsonian patients. Based on the analysis of longitudinal data from 20 patients treated with LD for 4 years and also from 800 patients treated with LD or placebo or other drugs for over 6 years, Holford *et al.* estimated that LDR peaked at least one year after LD treatment initiation [68], suggesting the potential presence of a third component of LD effects that last longer than days. The magnitude of LDR appeared to be not correlated with baseline disease severity. Based on the dose response to 2-hour infusions on 4 consecutive days (4 different concentrations), Nutt *et al.* concluded that the extended SDR to LD therapy in the stable patients represented instead the LDR [54].

3.2. EC_{50}

Contin *et al.* investigated the relationship between LD concentration and pharmacologic effect measurements based on the data collected from 86 Hoehn & Yahr stage I, II, III, and IV patients (n=23, 25, 25, and 13, respectively) [55]. The four groups were different in mean disease duration (2, 5, 9, 12 years, respectively), LD therapy duration (0.5, 2.0, 6.5, and 9.8 years, respectively), and daily LD dose (200, 200, 400, and 600 mg/day, respectively). The patients received 100 mg LD + 25 mg benserazide after a 12-hour washout of LD and any concomitant antiparkinsonian drugs. The LD pharmacokinetic parameters were similar among the four groups. There were no significant differences in the values of half-life, t_{max}, C_{max} and the area under the 5-hr concentration time curve for levodopa. The median values of the estimated pharmacodynamic parameters ($t_{1/2eq}$, EC_{50}, E_{max}, E_0, and Hill's coefficient) for tapping speed and for dyskinesia for each patient group were estimated (Table **2**). For the tapping motor effect, the $t_{1/2eq}$ decreased, EC_{50} increased, and Hill coefficient increased with severity of disease state, while the E_{max} values were similar among the four disease groups. The duration of the tapping motor effect was >300 min, ~210 min, ~150 min, and ~110 min for Group I, II, III, and IV, respectively [55] (estimated from Fig. (**1**) of Contin *et al.* 2001). For the dyskinesia effect, $t_{1/2eq}$ and Hill coefficient were similar among the four groups, while EC_{50} and E_{max} increased with severity of disease state. For Groups III and IV, the $t_{1/2eq}$ and EC_{50} for "tapping motor effects" and "dyskinesia effects" were similar, which was consistent with clinical observations that the dyskinesia effect was often accompanied by motor effects in moderate or severe Parkinsonian patients. The increase in EC_{50} and Hill coefficient for tapping motor effect with severity of disease state may make doses of LD that would produce some effect in a stable patient become ineffective during long-term LD treatment.

The potential application of the pharmacokinetic-pharmacodynamic (PK-PD) variables in the clinical setting is in helping physician assess patients' clinical needs and optimize levodopa regimen according to disease progression [69]. The practical utility of the PK-PD parameters in the clinical set-

ting has been substantiated by the observed correlation of the PK-PD parameters to a morphological reference using positron emission tomography [70], where Diet *et al.* followed the uptake of 18F-levodopa into striatal dopaminergic neurons using patients treated with levodopa and benserazide. It was observed that $t_{1/2eq}$ and EC_{50} estimated from the pharmacokinetic-pharmacodynamic model correlated with the uptake of tracer ^{18}F-levodopa into the putamen of patients with different stages of Parkinsonism, validating the clinical utility of the PD parameters obtained by PK/PD modeling.

3.3. Effect of CD on LD EC_{50}

Nutt *et al.* showed that the LD concentration required to produce an optimal clinical response in a given patient was not altered by co-administration of CD[d]. The steady state LD concentrations to produce optimal clinical effect were similar with (2.6 μg/mL) and without (2.8 μg/mL) carbidopa in Parkinsonian patients.

3.4. Effect of Long-Term Dosing on PK/PD Parameters

In early-stage Parkinsonian patients, dopaminergic neurons are able to control the storage and release of dopamine after administration of LD, therefore, motor fluctuations rarely occur. In advanced disease stages, small and frequent LD doses are often required because dopaminergic control over dopamine release is significantly impaired, and LD administration elicits only a short burst of central dopaminergic activity due to LD's short $t_{1/2}$.

Following 18 patients for 4 years after the initiation of LD treatment, Nutt *et al.* noticed ~100% increase in the SDR when the subjects stopped LD for 3 days. After stopping LD overnight, the magnitude of SDR remained similar, latency to peak tapping speed was decreased, and the duration of SDR decreased, although the decrease was not statistically significant [71]. In addition, Nutt *et al.* reported that over a 4-year treatment period, the average magnitude of LDR did not change, the rate of decline of LDR after withdrawal of LD was faster, dyskinesia scores were progressively increased [71].

In a longitudinal study over 4 years in 28 mild to moderate (Hoehn and Yahr Stage 1-III) patients, Contin *et al.* demonstrated that by the fourth year, maximum tapping scores remained relatively unchanged, duration decreased (37%), $t_{1/2eq}$ decreased (67%), EC_{50} increased (from 0.37±0.05 to 0.58±0.08 μg/mL), and the Hill coefficient increased (160%); however, pharmacokinetic parameters and E_{max} values remained unchanged [72]. These results are consistent with the findings reported in parallel groups [55].

3.5. Threshold

Based on the results of an LD intravenous infusion study, Nutt *et al.* estimated that in fluctuating patients the threshold concentration was approximately1.6 μg/mL, while a concentration of ~1.2 μg/mL produced no response or brief response (minutes) in this patient population [73]. In this study, the levodopa concentration averaged ~2 μg/mL in patients maintaining sustained response during the infusion of LD. Higher plasma concentrations of LD did not necessarily further increase taping and walking speeds. Mouradian *et al.* later demonstrated that clinically observed threshold doses are similar in untreated, stable, and fluctuating-response patients [74].

Since the duration during which the plasma concentrations are above the EC_{50} is often significantly shorter than the duration of motor effect (tapping effect), and since E_0+E_{max} is relatively similar among the four disease groups, Contin *et al.* has hypothesized that once LD concentration is above a threshold value, the duration of LD effect may be correlated with plasma concentration [55]. Nutt *et al.* suggested that the duration of clinical response to LD appears to be correlated with magnitude of the difference between the peak concentration and the minimum effective concentration LD. The observation that a threshold concentration needs to be reached for response appears to be consistent with reports that some subjects do not have a motor response when taking Sinemet CR, and hence, need a concomitant dosing of one or ½ of a Sinemet (immediate-release) tablet.

Although it has been reported that the threshold concentration for dyskinesias is higher than that required for anti-parkinsonian effects in stable patients [75], in the study conducted to assess the dose response to 2-hour infusions on 4 consecutive days (4 different concentrations) in three groups of patients (untreated, stable, and fluctuating), Nutt *et al.* showed that the dyskinesias began before clinical improvement in all 3 stable patients who developed dyskinesias. Therefore, the apparent threshold for inducing dyskinesias does not necessarily greater than the threshold for improvement in Parkinsonsonism symptoms in stable patients [63].

Mouradian *et al.* showed that after continuous LD infusion for 7 to 12 days in 12 advanced Parkinson patients, the therapeutic window of LD, defined as the difference between threshold dose for dyskinesia and for parkinsonism reduction, widened by about 50% and motor fluctuations decreased by more than 40% [76]. The results of this study are consistent with other observations that chronic intermittent oral LD treatment probably partly contributed to motor complications, and support the benefit of stable plasma concentration of LD [77, 78].

Due to very rapid metabolism of levodopa, the initial goal of levodopa therapy has focused on maintaining stable levodopa concentration. Although the controlled-release formulation provided prolonged absorption of levodopa, it appears that the initial absorption rate of levodopa from the controlled-release products may be too slow to provide needed threshold concentration for some patients. As such, studies have been conducted to demonstrate clinical benefits of combining immediate-release and controlled-release formulations of levodopa in motor fluctuating Parkinsonian patients. The results of these studies demonstrated that these combination formulations provided faster onset, sustained duration of response, improved efficacy scores, and reduced adverse events rates such as dyskinesias and end of dose wearing off as compared to IR or CR products [1, 2, 79]. These results suggest that formulations with immediate- and extended-release features may provide additional treatment options to Parkinsonianpatients.

[d] Nutt JG, Woodward WR, Anderson JL, Hammerstad JP. What is the function of carbidopa in the treatment of Parkinsonism? Ann Neurol 1983; 14: 133-34.

CONCLUSIONS

Levodopa has been the mainstay of therapeutic agent in treating the symptoms of Parkinson's disease. The results of pharmacokinetic and pharmacodynamic studies demonstrated that the effectiveness of levodopa is greatly influenced by its pharmacokinetic characteristics. It appears that once patients are turned "on", the duration of levodopa effects may be correlated with plasma concentration of levodopa. Although maintaining stable plasma concentrations of levodopa is beneficial for controlling motor fluctuations, a threshold concentration of levodopa appears to be necessary to turn patient "on". Given these findings, it is important for physicians to consider the pharmacokinetics of levodopa when prescribing levodopa products in order to maximize the therapeutic effects of levodopa.

ABBREVIATIONS

3-OMD	=	3-O-methyldopa
AAAD	=	Aromatic amino acid decarboxylase
AUC	=	Area under the concentration time curve
BBB	=	Blood brain barrier
CD	=	Carbidopa
CL/F	=	Apparent plasma clearance
C_{max}	=	Maximum concentration
COMT	=	Catechol-O-methyltransferanse
CR	=	Controlled release
DOPAC	=	3,4-dihydroxyphenyl acetic acid
E0	=	Baseline effect
EC_{50}	=	Concentration associated with 50% of maximum effect
Emax	=	Concentration associated with maximum effect
HVA	=	homovanillic acid
IR	=	Immediate release
LD	=	Levodopa
LDR	=	Long duration response
LNAA	=	Large neutral amino acid
ODT	=	Orally disintegrated tablet
PD	=	Pharmacodynamic
PK	=	Pharmacokinetic
SDR	=	Short duration response
$t_{1/2eq}$	=	Equilibration half-life between plasma and effect site concentration
t_{max}	=	Time to maximum concentration
Vd	=	Volume of distribution associated with terminal phase
Vss	=	Volume of distribution at steady state

REFERENCES

[1] Descombes S, Bonnet A, Gasser U*, et al.* Dual-release formulation, a novel principle in L-dopa treatment of Parkinson's disease. Neurology 2001; 56: 1239-1242.

[2] Ghika J, Gachoud J, Gasser U, Study Group L-DD-R. Clinical efficacy and tolerability of a new levodopa/benserazide dual-release formulation in parkinsonian patients. L-Dopa Dual-Release Study Group. Clin Neuropharmacol 1997; 20: 130-139.

[3] Muenter MD, Tyce GM. L-dopa therapy of Parkinson's disease: plasma L-dopa concentration, therapeutic response, and side effects. Mayo Clin Proc 1971; 46: 231-9.

[4] Sasahara K, Nitanai T, Habara T, Morioka T, Nakajima E. Dosage form design for improvement of bioavailability of levodopa III: Influence of dose on pharmacokinetic behavior of levodopa in dogs and Parkinsonian patients. J Pharm Sci 1980; 69: 1374-8.

[5] Nutt JG, Fellman JH. Pharmacokinetics of levodopa. Clin Neuropharmacol 1984; 7: 35-49.

[6] Peaston MJ, Bianchine JR. Metabolic studies and clinical observations during L-dopa treatment of Parkinson's disease. Br Med J 1970; 1: 400-3.

[7] Morgan JP, Bianchine JR, Spiegel HE, Rivera-Calimlim L, Hersey RM. Metabolism of levodopa in patients with Parkinson's disease. Radioactive and fluorometric assays. Arch Neurol 1971; 25: 39-44.

[8] Sasahara K, Nitanai T, Habara T, Morioka T, Nakajima E. Dosage form design for improvement of bioavailability of levodopa II: bioavailability of marketed levodopa preparations in dogs and parkinsonian patients. J Pharm Sci 1980; 69: 261-5.

[9] Tissot R, Gaillard JM, Guggisberg M, Gauthier G, De Ajuriaguerra J. Therapy of Parkinson's syndrome with L-dopa per os combined with a decarboxylase inhibitor (Ro 46.02). Neurol Neurocir Psiquiatr 1969; 10: 1-25.

[10] Bianchine JR, Messiha FS, Hsu TH. Peripheral aromatic L-amino acids decarboxylase inhibitor in parkinsonism. II. Effect on metabolism of L-2- 14 C-dopa. Clin Pharmacol Ther 1972; 13: 584-94.

[11] Kuruma I, Bartholini G, Tissot R, Fletscher A. Comparative investigation of inhibitors of extracerebral dopa decarboxylase in man and rats. J Pharm Pharmacol 1972; 24: 289-94.

[12] Nutt JG, Woodward WR, Anderson JL. The effect of carbidopa on the pharmacokinetics of intravenously administered levodopa: the mechanism of action in the treatment of parkinsonism. Ann Neurol 1985; 18: 537-543.

[13] Yeh KC, August TF, Bush DF*, et al.* Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies. Neurology 1989; 39: 25-38.

[14] LeWitt P, Jennings D, Lyons KE*, et al.* Pharmacokinetic and pharmacodynamic comparison of sinemet CR 50/200 and Stalevo 150 in Parkinson's disease: A 2 x 2 crossover study. Neurology 2005; 64 (Suppl 1): A106-107.

[15] Piccini P, Brooks DJ, Korpela K*, et al.* The catechol-O-methyltransferase (COMT) inhibitor entacapone enhances the pharmacokinetic and clinical response to Sinemet CR in Parkinson's disease. J Neurol Neurosurg Psychiatry 2000; 68: 589-94.

[16] Keranen T, Gordin A, Harjola VP*, et al.* The effect of catechol-O-methyl transferase inhibition by entacapone on the pharmacokinetics and metabolism of levodopa in healthy volunteers. Clin Neuropharmacol 1993; 16: 145-56.

[17] Myllyla VV, Sotaniemi KA, Illi A, Suominen K, Keranen T. Effect of entacapone, a COMT inhibitor, on the pharmacokinetics of levodopa and on cardiovascular responses in patients with Parkinson's disease. Eur J Clin Pharmacol 1993; 45: 419-23.

[18] Heikkinen H, Nutt JG, LeWitt PA, Koller WC, Gordin A. The effects of different repeated doses of entacapone on the pharmacokinetics of L-Dopa and on the clinical response to L-Dopa in Parkinson's disease. Clin Neuropharmacol 2001; 24: 150-7.

[19] Heikkinen H, Varhe A, Laine T*, et al.* Entacapone improves the availability of L-dopa in plasma by decreasing its peripheral metabolism independent of L-dopa/carbidopa dose. Br J Clin Pharmacol 2002; 54: 363-71.

[20] Nutt JG. Effect of COMT inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 2000; 55: S33-7; discussion S38-41.

[21] Nutt JG, Woodward WR, Beckner R*, et al.* Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics

and pharmacodynamics of levodopa in parkinsonian patients. Neurology 1994; 44: 913-919.

[22] Karstaedt PJ, Pincus JH, Coughlin SS. Standard and controlled-release levodopa/carbidopa in patients with fluctuating Parkinson's disease on a protein redistribution diet. A preliminary report. Arch Neurol 1991; 48: 402-5.

[23] Carter JH, Nutt JG, Woodward WR, Hatcher LF, Trotman TL. Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease. Neurology 1989; 39: 552-6.

[24] Frankel JP, Kempster PA, Bovingdon M*, et al.* The effects of oral protein on the absorption of intraduodenal levodopa and motor performance. J Neurol Neurosurg Psychiatry 1989; 52: 1063-7.

[25] Mena I, Cotzias GC. Protein intake and treatment of Parkinson's disease with levodopa. N Engl J Med 1975; 292: 181-4.

[26] Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The "on-off" phenomenon in Parkinson's disease: Relation to levodopa absorption and transport. N Engl J Med 1984; 310: 483-488.

[27] Robertson DR, Higginson I, Macklin BS*, et al.* The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. Br J Clin Pharmacol 1991; 31: 413-7.

[28] Simon N, Gantcheva R, Bruguerolle B, Viallet F. The effects of a normal protein diet on levodopa plasma kinetics in advanced Parkinson's disease. Parkinsonism Relat Disord 2004; 10: 137-42.

[29] Tsui JK, Ross S, Poulin K*, et al.* The effect of dietary protein on the efficacy of L-dopa: a double-blind study. Neurology 1989; 39: 549-52.

[30] Baruzzi A, Contin M, Riva R*, et al.* Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. Clin Neuropharmacol 1987; 10: 527-537.

[31] Leenders KL, Poewe WH, Palmer AJ, Brenton DP, Frackowiak RS. Inhibition of L-[18F]fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography. Ann Neurol 1986; 20: 258-62.

[32] SINEMET® CR [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2002.

[33] Mearrick PT, Wade DN, Birkett DJ, Morris J. Metoclopramide, gastric emptying and L-dopa absorption. Aust N Z J Med 1974; 4: 144-8.

[34] Vickers S, Stuart EK, Bianchine JR*, et al.* Metabolism of carbidopa (1-(-)-alpha-hydrazino-3,4-dihydroxy-alpha-methylhydrocinnamic acid monohydrate), an aromatic amino acid decarboxylase inhibitor, in the rat, rhesus monkey, and man. Drug Metab Dispos 1974; 2: 9-22.

[35] LODOSYN® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2002.

[36] Gey KF, Pletscher A. Distribution and metabolism of DL-3,4-dihydroxy[2-14C]-phenylalanine in rat tissues. Biochem J 1964; 92: 300-8.

[37] Robertson DR, Wood ND, Everest H*, et al.* The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa. Br J Clin Pharmacol 1989; 28: 61-9.

[38] Kaakkola S, Mannisto PT, Nissinen E, Vuorela A, Mantyla R. The effect of an increased ratio of carbidopa to levodopa on the pharmacokinetics of levodopa. Acta Neurol Scand 1985; 72: 385-91.

[39] Stalevo® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corp; 2003

[40] Rizzo V, Memmi M, Moratti R, Melzi d'Eril G, Perucca E. Concentrations of L-dopa in plasma and plasma ultrafiltrates. J Pharm Biomed Anal 1996; 14: 1043-6.

[41] Hinterberger H, Andrews CJ. Catecholamine metabolism during oral administration of levodopa. Arch Neurol 1972; 26: 245-52.

[42] Lotti VJ, Porter CC. Potentiation and inhbition of some central actions of L(-)-dopa by decarboxylase inhibitors. J Pharmacol Exp Ther 1970; 172: 406-15.

[43] Porter CC. Inhibitors of Aromatic Amino Acid Decarboxylase - Their Biochemistry, Advances in Neurology, Raven Press, New York, 1973; Vol. 2, pp. 37-58.

[44] Porter CC, Watson LS, Titus DC, Totaro JA, Byer SS. Inhibition of DOPA decarboxylase by the hydrazino analog of alpha-methylDOPA. Biochem Pharmacol 1962; 11: 1067-77.

[45] Porter BA, Rosenfield RL, Lawrence AM. The levodopa test of growth hormone reserve in children. Am J Dis Child 1973; 126: 589-92.

[46] Hardebo JE, Emson PC, Falck B, Owman C, Rosengren E. Enzymes related to monoamine transmitter metabolism in brain microvessels. J Neurochem 1980; 35: 1388-93.

[47] Dingemanse J. Issues important for rational COMT inhibition. Neurology 2000; 55: S24-7; discussion S28-32.

[48] Goodall M, Alton H. Metabolism of 3,4-dihydroxyphenylalanine (L-dopa) in human subjects. Biochem Pharmacol 1972; 21: 2401-8.

[49] Bartholini G, Pletscher A. Decarboxylase inhibitors. Pharmacol Ther 1975; 1: 407-21.

[50] Nutt JG, Carter JH, Lea ES, Woodward WR. Motor fluctuations during continuous levodopa infusions in patients with Parkinson's disease. Mov Disord 1997; 12: 285-92.

[51] Vickers S, Stuart EK, Hucker HB. Further studies on the metabolism of carbidopa, (minus)-L-alpha-hydrazino-3,4-dihydroxy-alpha-methylbenzenepropanoic acid monohydrate, in the human, Rhesus monkey, dog, and rat. J Med Chem 1975; 18: 134-8.

[52] Shelton RC, Karoum F, Chuang LW, Wyatt RJ. Metabolism of carbidopa to alpha-methyldopamine and alpha-methylnorepinephrine in rats. Biochem Pharmacol 1985; 34: 3623-6.

[53] Vickers S, Stuart EK, Bianchine JR*, et al.* Metabolism of carbidopa (1-(-)-alpha-hydrazino-3,4-dihydroxy-alpha-methylhydrocinnamic acid monohydrate), an aromatic amino acid decarboxylase inhibitor, in the rat, rhesus monkey, and man. Drug Metab Dispos 1974; 2: 9-22.

[54] Nutt JG, Woodward WR, Carter JH, Gancher ST. Effect of long-term therapy on the pharmacodynamics of levodopa. Relation to on-off phenomenon. Arch Neurol 1992; 49: 1123-30.

[55] Contin M, Riva R, Martinelli P*, et al.* Levodopa therapy monitoring in patients with Parkinson disease: a kinetic-dynamic approach. Ther Drug Monit 2001; 23: 621-9.

[56] Djaldetti R, Rosmarin V, Ziv I, Melamed E. The pharmacokinetic profile of the "first ever" oral dose of levodopa in *de novo* patients with Parkinson's disease. Clin Neuropharmacol 2001; 24: 95-8.

[57] Jaffe ME. Clinical studies of carbidopa and L-DOPA in the treatment of parkinson's disease, Advances in Neurology, Raven Press, New York, 1973; Vol. 2, pp. 161-172.

[58] Hoehn MM. Increased dosage of carbidopa in patients with Parkinson's disease receiving low doses of levodopa. A pilot study. Arch Neurol 1980; 37: 146-9.

[59] Bermejo Pareja F, Martinez-Martin P, Muradas V, de Yebenes JG. Carbidopa dosage modifies L-dopa induced side effects and blood levels of L-dopa and other amino acids in advanced parkinsonism. Acta Neurol Scand 1985; 72: 506-11.

[60] Cedarbaum JM, Kutt H, Dhar AK, Watkins S, McDowell FH. Effect of supplemental carbidopa on bioavailability of L-dopa. Clin Neuropharmacol 1986; 9: 153-9.

[61] Nutt JG, Woodward WR, Anderson JL. The effect of carbidopa on the pharmacokinetics of intravenously administered levodopa: the mechanism of action in the treatment of parkinsonism. Ann Neurol 1985; 18: 537-43.

[62] Barbato L, Stocchi F, Monge A*, et al.* The long-duration action of levodopa may be due to a postsynaptic effect. Clin Neuropharmacol 1997; 20: 394-401.

[63] Nutt JG, Carter JH, Van Houten L, Woodward WR. Short- and long-duration responses to levodopa during the first year of levodopa therapy. Ann Neurol 1997; 42: 349-355.

[64] Nutt JG, Holford NH. The response to levodopa in Parkinson's disease: imposing pharmacological law and order. Ann Neurol 1996; 39: 561-573.

[65] Ogasahara S, Nishikawa Y, Takahashi M*, et al.* Dopamine metabolism in the central nervous system after discontinuation of L-dopa therapy in patients with Parkinson disease. J Neurol Sci 1984; 66: 151-163.

[66] Hauser RA, Holford NH. Quantitative description of loss of clinical benefit following withdrawal of levodopa-carbidopa and bromocriptine in early Parkinson's disease. Mov Disord 2002; 17: 961-968.

[67] Hauser RA, Koller WC, Hubble JP*, et al.* Time course of loss of clinical benefit following withdrawal of levodopa/carbidopa and bromocriptine in early Parkinson's disease. Mov Disord 2000; 15: 485-489.

[68] Holford NH, Chan P, Lee Y-Y, Nutt JG. Disease progression and increased L-dopa efficacy with time in Parkinson's disease, 7th International Congress of Parkinson's Disease and Movement Disorders, Miami, FL, 2002, pp. S112.

[69] Contin M, Riva R, Martinelli P*, et al.* Levodopa therapy monitoring in patients with Parkinson disease: A kinetic-dynamic approach. Ther Drug Monit 2001; 23: 621-629.

[70] Dietz MA, Harder S, Graff J*, et al.* Levodopa pharmacokinetic-pharmacodynamic modeling and 6-[^{18}F]levodopa positron emission tomography in patients with Parkinson's disease. Clin Pharmacol Ther 2001; 70: 33-41.

[71] Nutt JG, Carter JH, Lea ES, Sexton GJ. Evolution of the response to levodopa during the first 4 years of therapy. Ann Neurol 2002; 51: 686-693.

[72] Contin M, Riva R, Martinelli P*, et al.* Longitudinal monitoring of the levodopa concentration-effect relationship in Parkinson's disease. Neurology 1994; 44: 1287-1292.

[73] Nutt JG, Woodward WR. Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients. Neurology 1986; 36: 739-744.

[74] Mouradian MM, Juncos JL, Fabbrini G*, et al.* Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II. Ann Neurol 1988; 24: 372-378.

[75] Mouradian MM, Juncos JL, Fabbrini G*, et al.* Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II. Ann Neurol 1988; 24: 372-8.

[76] Mouradian MM, Heuser IJ, Baronti F, Chase TN. Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. Ann Neurol 1990; 27: 18-23.

[77] Chase TN. Levodopa therapy: consequences of the nonphysiologic replacement of dopamine. Neurology 1998; 50: S17-25.

[78] Agid Y, Ahlskog E, Albanese A*, et al.* Levodopa in the treatment of Parkinson's disease: a consensus meeting. Mov Disord 1999; 14: 911-3.

[79] Stocchi F, Quinn NP, Barbato L*, et al.* Comparison between a fast and a slow release preparation of levodopa and a combination of the two: a clinical and pharmacokinetic study. Clin Neuropharmacol 1994; 17: 38-44.

Received: 19 October, 2006 Revised: 04 December, 2006 Accepted: 20 April, 2007