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Comparison of the Pharmacokinetics of an Oral Extended-Release Capsule Formulation of Carbidopa-Levodopa (IPX066) With Immediate-Release Carbidopa-Levodopa (Sinemet®), Sustained-Release Carbidopa-Levodopa (Sinemet® CR), and Carbidopa-Levodopa-Entacapone (Stalevo®)

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Abstract

IPX066 (extended-release carbidopa-levodopa [ER CD-LD]) is an oral extended-release capsule formulation of carbidopa and levodopa. The single-dose pharmacokinetics of ER CD-LD (as 2 capsules; total dose, 97.5 mg-390 mg CD-LD) versus immediate-release (IR) CD-LD (25 mg-100 mg), sustained-release (CR) CD-LD (25 mg-100 mg), and CD-LD-entacapone (25 mg-100 mg-200 mg) was evaluated in healthy subjects. Following IR dosing, LD reached peak concentrations (C_{max}) at 1 hour; LD concentrations then decreased rapidly and were less than 10% of peak by 5 hours. With CR CD-LD and CD-LD-entacapone, LD C_{max} occurred at 1.5 hours, and concentrations were less than 10% of peak by 6.3 and 7.5 hours, respectively. The initial increase in LD concentration was similar between ER CD-LD and IR CD-LD and faster than for CR CD-LD and CD-LD-entacapone. LD concentrations from ER CD-LD were sustained for approximately 5 hours and did not decrease to 10% of peak until 10.1 hours. Dose-normalized LD C_{max} values for ER CD-LD were significantly lower ($P < .05$) than for the other CD-LD products. Bioavailability of LD from ER CD-LD was 83.5%, 78.3%, and 58.8% relative to IR CD-LD, CR CD-LD, and CD-LD-entacapone, respectively.

Keywords

IPX066, levodopa, extended release, pharmacokinetics, Parkinson's disease

Parkinson's disease is an age-related progressive neurodegenerative disease that typically presents with motor symptoms of bradykinesia, rigidity, postural instability, and resting tremor. Levodopa (LD) is the most effective and widely used therapeutic agent in the treatment of Parkinson's disease.[1–4] Levodopa is actively absorbed, mainly in the proximal small intestine and is rapidly metabolized by aromatic L-amino acid decarboxylase (AADC). Therefore, LD products are formulated with an AADC inhibitor, commonly carbidopa (CD), to prevent peripheral metabolism and increase the fraction of levodopa transported to the brain for conversion to dopamine. When combined with CD, immediate-release (IR) LD has a half-life of approximately 1.5 hours. Levodopa in combination with a decarboxylase inhibitor is a mainstay in the treatment of Parkinson's disease.

During the early stages of Parkinson's disease, dosing 3 times a day with IR CD-LD is generally adequate to provide clinical effect. However, because of the short half-life of LD, as disease progresses, the response duration from a single dose of IR CD-LD progressively decreases and the "on" states (ie, period in which the medication is providing benefit in regard to motor function) may last less than 1 hour.[5]

Motor complications, namely, dyskinesia and motor "on/off" fluctuations, develop in about 50% of patients within 5 years of treatment.[6] These deleterious effects have been attributed, at least in part, to fluctuations in

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plasma concentrations of LD.[7–10] Data from intravenous[11,12] and intraduodenal[13,14] LD infusion studies indicate that motor complications may be less likely to develop with more physiologic, continuous dopaminergic stimulation. A goal of Parkinson's disease pharmacotherapy has been the development of an oral formulation with the advantages of continuous infusion, a rapid onset of effect followed by a sustained therapeutic plasma concentration. The only sustained-release product currently approved in the United States is Sinemet CR, which is absorbed over 4 to 6 hours.[15] However, initial LD absorption is delayed, often requiring coadministration of IR CD-LD, particularly for the first morning dose.[16,17] Formulations that add entacapone, a catechol-O-methyl transferase (COMT) inhibitor, to CD-LD increase the exposure to LD by about 33% to 46%,[18–20] and reduce "off" time by about 1 hour[21] compared with IR CD-LD. However, CD-LD products with entacapone have been associated with a shorter time to onset of dyskinesia and increased frequency of dyskinesia compared with CD-LD products.[22]

IPX066 (RYTARY™; carbidopa and levodopa extended-release capsules) is a multiparticulate extended-release (ER) oral capsule formulation of CD-LD for the treatment of Parkinson's disease, postencephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. The ER CD-LD capsule formulation comprises different types of beads including immediate-release and extended-release beads combined in a specific ratio to provide the desired LD plasma profile. The immediate-release component provides the initial rapid increase in LD concentrations with the extended-release beads providing the subsequent delayed and extended-release of LD. Inactive ingredients in the formulation include microcrystalline cellulose, mannitol, tartaric acid, ethylcellulose, hypromellose, sodium starch glycolate, sodium lauryl sulfate, povidone, talc, methacrylic acid copolymers, triethyl citrate, croscarmellose sodium, and magnesium stearate. The CD:LD ratio in ER CD-LD is 1:4, which is similar to marketed formulations of CD-LD. This study was designed to characterize the pharmacokinetics of ER CD-LD in comparison with 3 commonly used CD-LD combination products in healthy volunteers.

Materials and Methods

An institutional review board (St. Charles Community Institutional Review Board, St. Charles, Missouri) approved the study protocol, and each subject gave written informed consent before any protocol-specified procedures or evaluations were performed. The study was conducted at a single center in the United States in accordance with the ethical principles embodied in the Declaration of Helsinki, Good Clinical Practice guidelines, and the International Conference on Harmonisation guidelines.

Subjects

Healthy male and female subjects (aged 18–45 years, inclusive) with a body mass index (BMI) between 18 and 29.5 kg/m^2 and a supine blood pressure within the range of 90 to 139 mm Hg systolic and 50 to 89 mm Hg diastolic, were eligible to participate in this study. Subjects were excluded if they had any clinically relevant abnormalities as determined by medical history, physical examination, blood chemistry, complete blood count, urinalysis, and electrocardiogram (ECG) or if they had a positive urine drug screen or alcohol breath test. Subjects were also excluded if they had a history of glaucoma or peptic ulcer disease or had used any prescription or over-the-counter medications (excluding contraceptives, acetaminophen, or multivitamins) within 14 days (21 days for monoamine oxidase inhibitors) before study start and throughout the study period. All subjects were required to use a medically accepted method of contraception throughout the study period and for 1 month after study completion. Alcohol and grapefruit consumption were not permitted beginning 72 hours before each dose through 12 hours after dosing.

Study Design

This was a randomized, single-dose, open-label, 4-sequence, 4-treatment crossover study to assess the pharmacokinetics of ER CD-LD versus 3 commercially available formulations of CD-LD.

During each treatment period, subjects received a single oral dose of 1 of 4 treatments (according to the randomization sequence) under fasted conditions: 2 ER CD-LD capsules (48.75 mg CD–195 mg LD; total dose, 97.5 mg CD–390 mg LD), 1 IR CD-LD tablet (Sinemet® 25–100; 25 mg CD–100 mg LD), 1 sustained-release (CR) CD-LD tablet (Sinemet® CR 25–100; 25 mg CD–100 mg LD), or 1 CD-LD-entacapone tablet (Stalevo® 100; 25 mg CD, 100 mg LD, and 200 mg entacapone). There was a washout period of at least 6 days between treatments. The LD dose (100 mg) selected for the commercial products was a clinically relevant dose. The LD dose for ER CD-LD (390 mg) was chosen to approximately match the expected peak LD concentrations for the commercial products.

Plasma Sample Analysis

During each treatment period blood was collected from each subject into tubes containing K_2-EDTA prior to dosing (within 1 hour of dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3,3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours after dosing. Blood samples were centrifuged and plasma samples were transferred to prechilled polypropylene tubes containing hydrazine dihydrochloride and sodium metabisulfite and were stored at −70°C until analysis.

A validated high-performance liquid chromatography (HPLC)/tandem mass spectrometry method using multiple reaction monitoring was developed to measure plasma concentrations of LD and CD. Plasma samples were mixed with internal standard (levodopa-d_3 and carbidopa-d_3) and extracted using solid-phase extraction. Following processing, samples were injected into an HPLC coupled with an API 4000 mass analyzer. Sample response was monitored using peak area ratio. The calibration curves were linear over the range of 10 to 2000 ng/mL for levodopa and 2 to 400 ng/mL for carbidopa ($r \geq 0.99$). Both analytes were stable in plasma through 4 freeze-thaw cycles. The interassay precision, as measured by the percent coefficient of variation (%CV) for quality control samples in the study ranged from 2.3% to 7.3% for LD and 2.0% to 7.1% for CD. The interassay accuracy measured as the percent difference ranged from −2.2% to 1.2% for LD and −1.3% to 0.7% for CD.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic parameters for LD and CD were estimated using noncompartmental pharmacokinetic methods (Phoenix WinNonlin, version 6.2). The maximum plasma concentration (C_{max}), and time to peak concentration (T_{max}) were observed values. The apparent elimination half-life ($t_{1/2}$) was calculated as $-(\ln 2)/k$, where k is the slope of the log-linear regression of the terminal phase of the concentration-versus-time curve. The area under the plasma concentration-versus-time curve from hour 0 to the last quantifiable concentration at time t (AUC_t) was determined by the linear trapezoidal method. The AUC extrapolated to infinity (AUC_{inf}) was calculated as $AUC_{inf} = AUC_t + (C_t)/k$, where C_t is the last measurable concentration. In addition, the duration that LD concentrations were above 50% of C_{max}, time for LD concentrations to decrease to less than 10% of C_{max}, and the ratio of C_{max}/concentration at 6 hours ($C_{6\,h}$) was estimated to characterize the LD profiles of the various formulations. To compare the sustained nature of the LD profile for the various treatments, the time course of C_{max}/C_t and the percent deviation from the mean LD concentration (C_{avg}) were also estimated. In addition, the expected deviation from C_{avg} at steady state was predicted based on superposition of the single-dose pharmacokinetics. In this prediction, ER CD-LD was dosed every 6 hours and the other CD-LD products were dosed every 3 hours.

Statistical analyses were conducted to evaluate the C_{max} and AUC of LD absorption from ER CD-LD relative to the 3 reference formulations. A mixed-effect analysis of variance model, which included treatment, period, and sequence as fixed factors and subject-within-sequence as a random effect, was used for the analysis of log-transformed (dose-normalized) AUC and C_{max}. The least-squares estimate of the mean for the ratio and a 90% confidence interval (CI) are presented. Statistical analyses were conducted using SAS, version 9.1.3 (Cary, North Carolina). Subjects who completed all treatments were included in the statistical analyses.

Assuming a ratio of unity for the mean AUC values for a test and reference formulation and a standard deviation of 0.4 (SD in logarithmic scale), a sample size of 20 subjects would assure with 90% confidence that the ratio of the AUC means is between 0.81 and 1.23. Twenty-four subjects were enrolled to account for any dropouts.

Safety Assessments

Adverse events were monitored throughout the study. Vital signs (heart rate, blood pressure, and respiratory rate) were measured periodically following administration of study drugs after the subject had been resting supine for 5 minutes and again after the subject had been standing for 2 minutes. Safety assessments performed prestudy and poststudy included physical examinations, electrocardiograms (12-lead), and clinical laboratory tests (chemistry, hematology, and urinalysis).

Results

A total of 24 healthy subjects (13 men and 11 women) were enrolled and treated; 22 subjects completed the study. Two subjects did not receive all treatments: 1 subject withdrew consent, and 1 subject was withdrawn for a protocol violation of a positive drug screen. Of the 24 subjects enrolled, 9 were white and 15 were African American, and the mean age was 24.6 years (range, 18–42 years). The mean body weight was 68.6 kg (range, 51.0–95.7 kg), and mean BMI was 23.6 kg/m^2 (range, 19.0–28.8 kg/m^2).

Pharmacokinetics of Levodopa and Carbidopa

The mean plasma concentration–time profiles of levodopa and carbidopa following a single dose of ER CD-LD, IR CD-LD, CR CD-LD, and CD-LD-entacapone are displayed in Figure 1. The estimated LD and CD pharmacokinetic parameters for the 4 treatments are summarized in Table 1. With IR CD-LD, LD was rapidly absorbed with median time to peak plasma concentrations at 1 hour. Levodopa plasma concentrations then decreased rapidly and were less than 10% of peak by 5 hours. With both CR CD-LD and CD-LD-entacapone, median time to peak LD plasma concentrations was 1.5 hours, and concentrations were less than 10% of peak by 6.3 and 7.5 hours, respectively. With ER CD-LD, LD plasma concentrations increased rapidly, reaching an initial plateau at approximately 1 hour, with median T_{max} noted at approximately 4.5 hours. Plasma concentrations were less than 10% of peak at 10.1 hours.

The mean peak LD plasma concentration after a single dose of 2 ER CD-LD capsules (total LD dose, 390 mg)

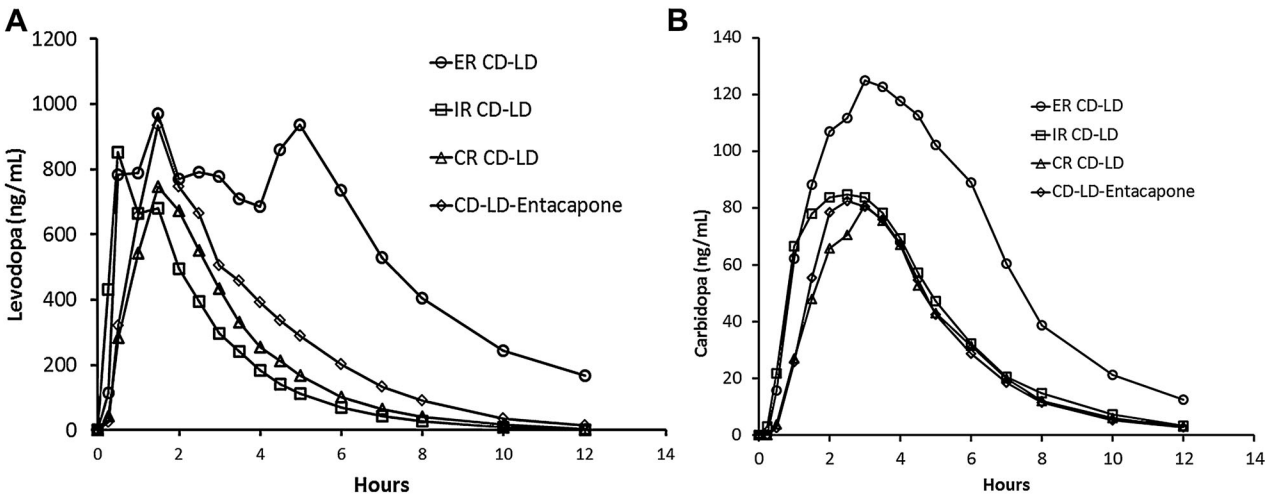

Figure 1. Mean levodopa (A) and carbidopa (B) plasma concentration–time profiles following a single dose of 2 capsules of ER CD-LD (total dose, 97.5 mg CD-390 mg LD), IR CD-LD (25 mg-100 mg), CR CD-LD (25 mg-100 mg), and CD-LD-entacapone (25 mg-100 mg-200 mg) under fasting conditions. ER, extended release, CR, sustained release; IR, immediate release; CD, carbidopa; LD, levodopa.

was approximately 21%, 55%, and 29% higher than the mean C_{max} value for 25-100 mg IR CD-LD, 25-100 mg CR CD-LD, and 25-100-200 mg CD-LD-entacapone, respectively. The mean terminal half-life of LD was comparable for the 4 treatments (1.6–1.9 hours). ER CD-LD provided sustained LD concentrations as noted by the lower $C_{max}/C_{6\,h}$ ratio. This ratio, which reflects the fold decrease in LD concentration from the peak to 6 hours, provides an estimate of how

Table 1. Single-Dose Plasma Pharmacokinetic Parameters for Levodopa and Carbidopa, Fasting Conditions (n = 22)

	Treatment			
Pharmacokinetic Parameter[a]	ER CD-LD (97.5 mg-390 mg)	IR CD-LD (25 mg-100 mg)	CR CD-LD (25 mg-100 mg)	CD-LD-Entacapone (25 mg-100 mg-200 mg)
Levodopa				
C_{max} (ng/mL)	1326 ± 268	1094 ± 401	855 ± 299	1027 ± 284
C_{max}/D (ng/[mL · mg])	3.4 ± 0.7	10.9 ± 4.0	8.55 ± 3.0	10.3 ± 2.8
T_{max} (h)	4.5 (0.5–8.0)	1.0 (0.5–2.0)	1.5 (1.0–2.0)	1.5 (1.0–2.0)
$t_{1/2}$ (h)	1.9 ± 0.7	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2
AUC_{inf} (ng · h/mL)	7244 ± 2553	2251 ± 664	2403 ± 680	3291 ± 1149
AUC_{inf}/D (ng · h/[mL · mg])	18.6 ± 6.5	22.5 ± 6.6	24.0 ± 6.8	32.9 ± 11
Relative bioavailability (%)	—	83.5 ± 21	78.3 ± 20	58.8 ± 18
$C_{max}/C_{6\,h}$	2.4 ± 1.5	19.0 ± 13	9.4 ± 4.0	6.0 ± 2.4
%CV in concentration (%)	64.9 ± 12	121.4 ± 25	101.7 ± 12	92.4 ± 12
Duration LD $C_{max}/C_t \leq 2$	4.0 ± 2.5	1.5 ± 0.7	2.1 ± 0.7	2.1 ± 1.0
Duration LD concentrations above 50% C_{max} (h)	4.9 ± 2.4	1.5 ± 0.7	2.1 ± 1.0	2.1 ± 1.0
Time LD concentrations decrease below 10% C_{max} (h)	10.1 ± 1.7	5.0 ± 1.1	6.3 ± 1.0	7.5 ± 1.1
Carbidopa				
C_{max} (ng/mL)	148 ± 49	106 ± 43	86 ± 32	92 ± 29
C_{max}/D (ng/[mL · mg])	1.5 ± 0.5	4.2 ± 1.7	3.4 ± 1.3	3.7 ± 1.2
T_{max} (h)	3.5 (1.5–6.0)	2.5 (1.5–5.0)	3.0 (2.0–4.5)	2.5 (2.0–4.0)
$t_{1/2}$ (h)	2.5 ± 1.0	1.8 ± 0.2	2.0 ± 0.4	1.8 ± 0.3
AUC_{inf} (ng · h/mL)	822 ± 276	448 ± 157	373 ± 117	381 ± 112
AUC_{inf}/D (ng · h/[mL · mg])	8.4 ± 2.8	17.6 ± 6.3	14.9 ± 4.7	15.2 ± 4.5
Relative bioavailability (%)	—	49.5 ± 14	58.9 ± 18	59.8 ± 29
AUC_{LD}/AUC_{CD}	9.58 ± 4.18	5.59 ± 2.33	6.93 ± 2.23	9.07 ± 3.13

ER, extended release; IR, immediate release; CR, sustained release; CD, carbidopa; LD, levodopa; C_{max}, maximum observed plasma concentration; C_{max}/D, dose-normalized C_{max}; T_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; AUC_{inf}, area under the concentration–time curve from time zero extrapolated to infinity; AUC_{inf}/D, dose-normalized AUC; $C_{6\,h}$, observed plasma concentration at hour 6; CV, coefficient of variation.

[a]Pharmacokinetic parameter values are expressed as mean ± SD except for T_{max}, which is expressed as median (range).

sustained the levodopa concentrations are following the peak. The bioavailability of LD from ER CD-LD relative to IR CD-LD, CR CD-LD and CD-LD-entacapone was 83.5%, 78.3%, and 58.8%, respectively. As expected, the dose-normalized levodopa C_{max} (C_{max}/D) following ER CD-LD was lower compared with the other CD-LD products (30%–40% of C_{max} compared with the other products; Table 1, Table 2).

Figure 2 presents the time course of C_{max}/C_t (Figure 2A) and percent deviation from C_{avg}(Figure 2B) for LD for the CD-LD treatments. The mean C_{max}/C_t and percent deviation from C_{ave} for LD were generally lower for ER CD-LD compared with the other CD-LD products. The mean LD C_{max}/C_t ratio–time profile for ER CD-LD was below 2 for up to 4 hours, whereas for IR CD-LD, CR CD-LD, and CD-LD-entacapone the durations averaged 1.5, 2.1, and 2.1 hours, respectively (Table 1). The steady-state LD plasma concentration profile for ER CD-LD dosed every 6 hours and the other CD-LD products dosed very 3 hours was predicted based on superposition of the observed data following the single-dose administrations. The predicted maximum absolute deviation from C_{ave} at steady state (Figure 2C) was 32% for ER CD-LD dosed every 6 hours compared with 72% to 87% for the other CD-LD products dosed every 3 hours.

Similar to observations made for LD, peak plasma concentrations of CD occurred later with ER CD-LD than with IR CD-LD, CR CD-LD, and CD-LD-entacapone. The terminal half-life was approximately 2 hours and was comparable for all 4 treatments. The bioavailability of CD from ER CD-LD was 49.5%, 58.9%, and 59.8% relative to IR CD-LD, CR CD-LD, and CD-LD-entacapone, respectively (Table 1).

Clinical Observations

Following ER CD-LD treatment, 6 of 24 subjects (25%) had at least 1 adverse event (AE). Following the IR CD-LD, CR CD-LD, and CD-LD-entacapone treatments, 4 (17%), 2 (9%), and 2 (9%) subjects, respectively, had at least 1 AE. All AEs were characterized as mild with the exception of an ankle fracture, which was characterized as severe and unrelated to study treatment. No serious AEs were reported. Common AEs (experienced by $\geq$2 subjects) were nausea, vomiting, and headache (Table 3). The incidence of nausea and vomiting appeared higher during the ER CD-LD treatment period than during the other treatment periods in this healthy volunteer population. No notable patterns in hematology, chemistry, urinalysis, ECGs, or vital signs were noted for any subject.

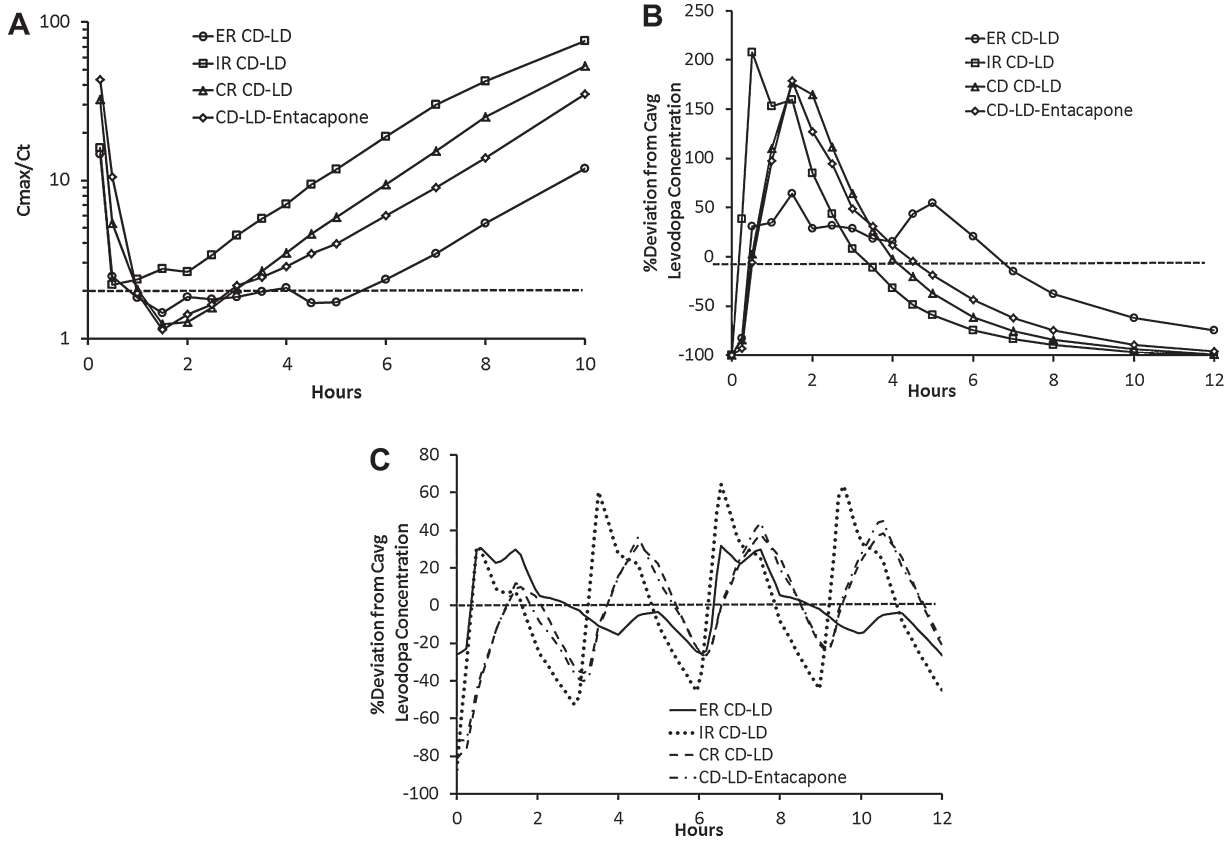

Figure 2. (A) Mean ratio of levodopa C_{max}/C_t. (B) Mean percent deviation from LD C_{avg} following a single dose. (C) Predicted mean percent deviation from LD C_{avg} at steady state. C_{max}, maximum concentration, C_{avg}, average concentration.

Table 2. Comparison of Dose-Normalized Pharmacokinetic Parameters for Levodopa and Carbidopa Following Single Doses of ER CD-LD, IR CD-LD, CR CD-LD, and CD-LD-Entacapone (n = 22)

		Ratio of Geometric Least-Squares Mean (90% Confidence Interval)		
Test	Reference	C_{max}	AUC_t	AUC_{inf}
Levodopa				
ER CD-LD	IR CD-LD	32.04 (28.51–36.02)	77.23 (71.54–83.36)	80.35 (74.30–86.89)
ER CD-LD	CR CD-LD	40.83 (36.33–45.89)	71.85 (66.56–77.56)	75.11 (69.45–81.22)
ER CD-LD	CD-LD-entacapone	33.54 (29.84–37.70)	53.60 (49.65–57.86)	56.12 (51.90–60.69)
CR CD-LD	IR CD-LD	78.48 (69.82–88.21)	107.49 (99.57–116.03)	106.98 (98.93–115.69)
CD-LD-entacapone	IR CD-LD	95.53 (84.99–107.37)	114.08 (133.48–155.53)	143.17 (132.39–154.83)
Carbidopa				
ER CD-LD	IR CD-LD	36.63 (32.31–41.53)	45.75 (40.50–51.69)	47.53 (42.25–53.46)
ER CD-LD	CR CD-LD	45.32 (39.97–51.38)	55.20 (48.86–62.36)	57.03 (50.69–64.15)
ER CD-LD	CD-LD-entacapone	40.92 (36.10–46.40)	52.82 (46.76–59.68)	54.95 (48.85–61.82)
CR CD-LD	IR CD-LD	80.83 (71.36–93.63)	82.88 (73.36–93.63)	83.34 (74.08–93.75)
CD-LD-entacapone	IR CD-LD	89.50 (78.94–101.47)	86.61 (76.66–97.85)	86.49 (76.88–97.29)

ER, extended release; IR, immediate release; CR, sustained release; CD, carbidopa; LD, levodopa.

Table 3. Common Adverse Events in Healthy Subjects Under Fasting Conditions

	Number of Subjects With AEs (%)			
	ER CD-LD (97.5 mg-390 mg)	IR CD-LD (25 mg-100 mg)	CR CD-LD (25 mg-100 mg)	CD-LD-Entacapone (25 mg-100 mg-200 mg)
n[a]	24	23	22	22
At least 1 AE	6 (25.0)	4 (17.4)	2 (9.1)	2 (9.1)
Nausea	5 (20.8)	2 (8.7)	1 (4.5)	1 (4.5)
Vomiting	2 (8.3)	1 (4.3)	0	0
Headache	2 (8.3)	1 (4.3)	0	0

Common AEs, any AE experienced by 2 or more subjects; ER, extended release; IR, immediate release; CR, sustained release; CD, carbidopa; LD, levodopa; AE, adverse event.
[a]Number of subjects.

Discussion

The need to develop an improved oral extended-release LD product that can rapidly achieve and sustain constant LD plasma concentrations has been recognized as an unmet need in the treatment of Parkinson's disease.[23] Various approaches including adding enzyme inhibitors (such as COMT inhibitors), gastric-retention formulations, duodenal infusion delivery systems, and prodrug approaches have been explored to extend the duration of effect. Gastric retention formulations generally require concomitant administration of food to retain the dosage form in the stomach after swelling. This constantly fed state may not be feasible for Parkinson's disease patients. Drawbacks of intraduodenal infusion systems include the invasive surgical procedure, risk of infections, the inconvenience of carrying and refilling the pump, and issues related to device malfunction. For this reason, this surgical option is typically reserved for the most severe patients. At this time, LD prodrugs have not shown an advantage over immediate-release formulations.[24,25]

The present study was conducted in healthy adults and focused on comparing LD and CD pharmacokinetics of ER CD-LD with those of currently marketed CD-LD products. This single-dose study showed that ER CD-LD provides an initial increase in LD concentration comparable to that with IR CD-LD and sustains the concentration (defined as >50% of C_{max}) for 1.9 to 2.5 hours longer than the other CD-LD products. These results are consistent with the pharmacokinetic and efficacy results reported by Hauser et al (2011) in an open-label phase 2 study in patients with advanced Parkinson's disease. In that study, ER CD-LD resulted in a rapid onset and longer duration of motor control compared with IR CD-LD.[26]

The CR matrix formulations of CD-LD have reduced drug availability, and because of the slower absorption, peak plasma concentrations are delayed compared with the IR CD-LD formulation. As a result, time to an "on"

state is delayed with the CR product, particularly for the first morning dose[5,27–29] and supplemental doses of IR CD-LD may be required for onset of effect.[30] ER CD-LD would not require supplementation with an IR dose because the ER CD-LD capsule formulation includes an immediate-release portion designed to provide the initial rapid increase in LD concentration, followed by delayed and extended release to provide the sustained LD concentrations. Although the LD dose with ER CD-LD was 3.9-fold higher compared with IR and CR CD-LD, it should be noted that the LD peak concentration with ER CD-LD is only 20%–30% higher and the dose-normalized C_{max} is considerably lower (Table 1, Table 2). Thus, the rapid initial increase in LD concentration with ER CD-LD is a result of the immediate-release portion of the formulation and not due to the higher LD dose.

Although the present study was conducted in healthy volunteers and thus did not include assessment of efficacy, published reports indicate a good concentration–effect relationship for LD.[31–33] The similar initial increase in LD plasma concentrations for ER CD-LD and IR CD-LD in healthy subjects correlates with the onset of effect in patients with advanced Parkinson disease (PD). The time to onset of effect (defined as an increase of more than 15% from baseline in the rate of finger tapping) for IR CD-LD and ER CD-LD in advanced PD patients was 0.39 and 0.36 hours, respectively.[34]

The pharmacokinetics of the reference drugs in the present study are comparable to published reports (Table 4). With IR CD-LD (100 mg LD), peak levodopa plasma concentrations were approximately 1 μg/mL and were noted 1 hour after dosing in the present study (Table 1). Previous investigators have reported peak levodopa concentrations between 0.85 and 2.0 μg/mL (Table 4).[19,20,35–37] There is a paucity of pharamacokinetic data with CR CD-LD, but LD peak concentrations noted in the present study compare favorably with published data (Table 4). Levodopa C_{max} and AUC from CD-LD-entacapone noted in the present study were comparable to those reported by Keränen et al (1993)[19] and higher than those noted by Rouru et al (1999)[38] and Heikkinen et al (2002).[36] Importantly, all studies, including the present study, show that the time to maximum LD concentration for CD-LD-entacapone is later than with IR CD-LD.

The smoothness of the LD concentration–time curve is an important consideration in the treatment of patients with advanced Parkinson's disease. Continuous levodopa administration is associated with reduced motor complications compared with pulsatile delivery.[27] The CR CD-LD formulation has a slower initial absorption, with a mean time to peak concentration of approximately 1.5–2 hours compared with 1 hour for the IR formulation. This often requires supplementation of a CR dose with an IR tablet, particularly for the first morning dose. The ER CD-LD capsule formulation includes both an IR and ER components and would not require supplementation with an IR tablet. If CD-LD can be delivered orally in a manner that is similar to the plasma profile of an infusion, it may result in reduced motor complications. The variability in

Table 4. Summary of Single-Dose Levodopa Pharmacokinetic Parameters for Sinemet, Sinemet CR, and Stalevo (100-mg Dose) From Published Reports

Study	n	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng · h/mL)	AUC_L/AUC_C[a]
Sinemet (IR CD-LD)					
Kaakkola 1985	11	1091.8 ± 242.4	0.9 ± 0.2	1648 ± 124	2.20
Heikkinen 2002	14–16	850 ± 310	0.58 ± 0.25	1430 ± 340[b]	4.27
Keränen 1993	12	1210 ± 579	0.94 ± 0.49	2340 ± 438	1.19
Myllylä 1993[e]	8	2080	0.78	3620	6.44
Liang 2006	18	1040 ± 260	0.75	1950 ± 960	—
Sinemet CR (CR CD-LD)[c]					
Hammerstad 1994[e]	9	887 ± 355	1.3 ± 0.6	—	—
Liang 2006	18	770 ± 310	2	2020 ± 600	—
Stalevo (CD-LD-Entacapone)					
Rouro 1999	12	701 ± 243	0.8 ± 0.4	1704 ± 319[d]	10.3
Heikkinen 2002	14–16	720 ± 250	1.16 ± 0.59	1930 ± 350[b]	6.17
Keränen 1993	12	1040 ± 141	1.27 ± 0.66	3330 ± 580	1.71
Myllylä 1993[e]	8	1490	1.17	5280	11.4

C_{max}, maximum concentration; T_{max}, time to C_{max}; AUC_{inf}, area under the curve to infinity; IR, immediate release; CR, sustained release; CD, carbidopa; LD, levodopa.

[a]Ratio of $AUC_{levodopa}$ to $AUC_{carbidopa}$. Calculated based on a ratio of the reported means for individual drugs.

[b]AUC_{0-12} is reported.

[c]Data are scaled proportionally to allow comparison to a LD dose of 100 mg.

[d]AUC_{0-24} is reported.

[e]Data reported in patients.

LD plasma concentration as measured by the %CV was lower with ER CD-LD (64.9%) than with IR CD-LD (121.4%), CR CD-LD (101.7%), and CD-LD-entacapone (92.4%). Similarly, the decline in LD plasma concentration from the peak to 6 hours, calculated as the ratio of $C_{max}/C_{6\,h}$, was 2.36 for ER CD-LD. The reference drugs all had much steeper declines: $C_{max}/C_{6\,h}$ ratios ranged from about 6 to 19. Notably, ER CD-LD also had a smaller deviation from average LD concentration ($\sim$32%) compared with the other CD-LD products (72% to 87%).

ER CD-LD was well tolerated in this single-dose pharmacokinetic study in healthy subjects. The incidence of nausea following ER CD-LD dosing was higher compared with the other CD-LD products, which may be attributed to the higher LD dose or longer LD exposure in a population (healthy subjects) that is typically not accustomed to dopaminergic effects.

In summary, the sustained LD concentrations with reduced peak-trough fluctuations achieved with ER CD-LD may result in consolidation of "on" periods without an increase in the incidence of dyskinesia compared with the frequent cycles of "on" and "off" periods with current IR and CR CD-LD therapy.

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