Conversion From Sustained Release Carbidopa/Levodopa to Carbidopa/Levodopa/Entacapone (Stalevo) in Parkinson Disease Patients

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Objectives: This study was performed to determine if conversion from sustained release carbidopa/levodopa (SR-CL) with or without entacapone to carbidopa/levodopa/entacapone (CLE; Stalevo) improves motor functioning and quality of life in Parkinson disease (PD) patients and to assess patient tolerance and drug preference.

Methods: PD patients reporting suboptimal symptom control with SR-CL were converted to CLE. The basic conversion was 1 SR-CL 25/100 to 1 25/100/200 CLE and 1 SR-CL 50/200 to 1 37.5/150/200 CLE with additional changes as necessary.

Results: There were 62 patients with an average age of 68 years and an average disease duration of 11 years. CLE was preferred by 42 patients and SR-CL was preferred by 20 patients. In those that preferred CLE, Unified Parkinson Disease Rating Scale (UPDRS) mentation and motor subscores, Parkinson Disease Questionnaire-39 (PDQ-39) quality-of-life activities of daily living (ADL) and bodily discomfort subscores, and Epworth Sleepiness Scale (ESS) scores were significantly improved. There were no significant changes in any measures in the group that preferred SR-CL. Common adverse effects in the group that preferred CLE included nausea, vomiting, increased dyskinesia or off time, dizziness, and somnolence. The most common adverse events in the group preferring SR-CL were increased off time or dyskinesia, nausea, and vomiting.

Conclusions: A majority of patients suboptimally controlled on SR-CL can be successfully converted to CLE with improvements in motor function, quality of life, and sleepiness. Older patients, with longer disease duration not previously exposed to entacapone, may better tolerate CLE after the addition of entacapone.

Key Words: Parkinson disease, sustained release carbidopa/levodopa, carbidopa/levodopa/entacapone, Stalevo

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Levodopa was shown to be efficacious for the treatment of Parkinson disease (PD) in the 1960s. It is still the most efficacious medication for PD and is the gold standard for the management of the disease. Levodopa is routinely combined with carbidopa to reduce the peripheral metabolism of levodopa to dopamine. Long-term use of levodopa is associated with motor fluctuations and dyskinesia.[1,2] There are multiple adjunctive medications available for the treatment of motor fluctuations. Entacapone is a peripherally acting, reversible inhibitor of catechol-*O*-methyltransferase (COMT) that reduces the metabolism of levodopa.[3] Multiple studies have reported the efficacy of entacapone for increasing on time and reducing off time in PD patients with motor fluctuations.[3–5] Recently, a triple combination preparation of levodopa, namely, carbidopa/levodopa/entacapone (CLE, Stalevo), was approved by the U.S. Food and Drug Administration (FDA) for the treatment of motor fluctuations in PD. CLE combines carbidopa, levodopa, and entacapone in 1 tablet. CLE is currently approved for patients who are taking carbidopa/levodopa and entacapone as a direct switch and also for patients who are taking carbidopa/levodopa less than or equal to 600 mg/d and having end of dose wearing off but not having any dyskinesia. An open label study reported improvement of off time in PD patients on standard carbidopa/levodopa converted to CLE.[6] Although there are guidelines for converting patients on standard carbidopa/levodopa to CLE, there are no guidelines for converting patients on sustained release carbidopa/levodopa (SR-CL) to the triple levodopa combination. The main aim of the study was to determine if the conversion from SR-CL, with or without entacapone, to CLE improves motor functioning and quality of life in PD patients and to examine patient preference between the 2 treatments.

METHODS

This was an open label study in which patients who were currently on SR-CL or SR-CL plus entacapone or a combination of SR-CL and standard carbidopa/levodopa with or without entacapone were converted to CLE. The patients were recruited from the PD clinic at the University of Kansas Medical Center. Inclusion criteria included the diagnosis of PD (2 of the 3 cardinal motor signs: rigidity, bradykinesia, resting tremor) and patients currently on SR-CL therapy with suboptimal control of PD symptoms. Exclusion criteria included patients with previous exposure to CLE, significant adverse effects or allergic reaction to entacapone, atypical PD, presence of unstable medical conditions, concurrent monoamine oxidase inhibitors except for selegiline (less than 10 mg/d), and females of childbearing potential who were not using an effective method of contraception. All patients signed a consent form approved by the University of Kansas Medical Center's Institutional Review Board before participation in the study.

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TABLE 1. Baseline Characteristics

Characteristics	*N* = 62
Gender	45 (72.6%) Male; 17 (27.4%) Female
Age, years (mean ± SD)	67.6 ± 9.2
Disease duration, years (mean ± SD)	11.1 ± 6.2
Daily levodopa dose, mg/d (mean ± SD)	669 ± 271
No. patients with off time	49 (79%)
No. patients with dyskinesia	29 (47%)
UPDRS mentation	2.0 ± 1.4
UPDRS ADL	14.3 ± 5.3
UPDRS motor	24.6 ± 9.1
PDQ-39 total	30.7 ± 17.1
ESS	10.7 ± 4.7
MMSE	28.1 ± 2.0
Global examiner ratings	32 mild; 28 moderate; 2 marked
Global patient ratings	28 mild; 25 moderate; 6 marked; 3 severe

Before conversion, the following data were collected: demographics, current medications, Unified Parkinson Disease Rating Scale (UPDRS), global rating scales, Parkinson Disease Questionnaire-39 (PDQ-39) quality-of-life assessment, Epworth Sleepiness Scale (ESS), and the Mini-Mental State Examination (MMSE). The primary outcome measure was change in PDQ-39 scores at 1 month compared with baseline. Patients were converted from SR-CL to CLE overnight. In general, each SR-CL 50/200 was converted to 1 CLE 37.5/150/200 and each SR-CL 25/100 was converted to 1 CLE 25/100/200. Additional adjustments of CLE were clinically made, as necessary. The cost of CLE was covered by the study in the form of vouchers provided to each subject before conversion. Other antiparkinsonian medications were not adjusted during the 1-month study period. One month after conversion, the scales were repeated and drug preference, reasons for preference, and adverse effects were recorded. Statistical analysis was performed using Wilcoxon signed rank comparisons for nonparametric data and *t* tests for parametric data. A *P* value of 0.05 was considered significant.

RESULTS

Sixty-two patients with a mean age of 68 years (range, 46–92 years) and a mean disease duration of 11 years (range, 2.5–27.4 years) participated in the study. The mean levodopa dose (100 mg of standard levodopa dose = 125 mg of SR-CL) at baseline was 669 mg/d. Baseline demographics are shown in Table 1.

Forty-nine patients completed the study, and at the end of the 1-month follow-up there were significant improvements in UPDRS motor scores, PDQ-39 total scores, and PDQ-39 activities of daily living (ADL) and bodily discomfort subscale scores. Of the 49 subjects that completed the study, 21 were taking entacapone at baseline and 28 had not been previously exposed to entacapone. There were no significant differences between these 2 groups at baseline. In the entacapone group, there were significant improvements at the 1-month follow-up only in UPDRS motor scores and 20 preferred CLE (95.2%) compared with SR-CL. In contrast, in those not previously exposed to entacapone, there were significant improvements in UPDRS motor scores, ESS scores, PDQ-39 total scores, and PDQ-39 mobility, ADL,

TABLE 2. Baseline and 1-Month Follow-Up Data for All Subjects Completing the Study as an Entire Cohort and Split by Baseline Entacapone Use (Means ± SD)

	Study Completers		Baseline Entacapone		No Baseline Entacapone	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
n		49	21	21	28	28
Age (years)	66.1 (8.7)		64.3 (7.6)		67.5 (9.3)	
Disease duration (years)	10.7 (6.5)		10.8 (7.0)		10.6 (6.2)	
Sex (M/F)	35/14		17/4		18/10	
Levodopa (mg)	670 (264)	656 (208)	688 (178)	699 (183)	657 (316)	624 (223)
UPDRS mentation	1.9 (1.5)	1.6 (1.7)	1.8 (1.8)	1.5 (2.0)	2.0 (1.2)	1.7 (1.4)
UPDRS ADL	14.0 (4.8)	13.7 (5.7)	13.0 (3.9)	12.0 (4.7)	14.8 (5.3)	14.9 (6.2)
UPDRS motor	24.5 (8.2)	19.6 (9.0)*	25.2 (9.2)	18.3 (8.5)*	24.0 (7.4)	20.5 (9.4)*
PDQ-39 Total	28.8 (15.7)	26.3 (14.2)*	25.7 (14.5)	25.2 (14.6)	31.0 (16.4)	27.2 (14.0)*
PDQ mobility	36.0 (24.4)	32.9 (22.8)	29.8 (20.7)	30.0 (17.7)	40.6 (26.3)	35.0 (26.1)*
PDQ ADL	33.2 (18.7)	28.3 (18.2)*	28.4 (16.9)	25.6 (15.8)	36.8 (19.4)	30.4 (19.8)*
PDQ emotional	24.3 (15.6)	22.4 (17.0)	20.6 (15.7)	20.4 (20.2)	27.1 (15.2)	24.0 (14.4)*
PDQ stigma	21.8 (21.3)	18.8 (19.6)	20.8 (23.7)	19.9 (22.7)	22.5 (19.7)	17.9 (17.2)
PDQ Social support	13.6 (16.0)	12.1 (14.6)	8.3 (12.4)	8.7 (12.5)	17.6 (17.6)	14.6 (15.8)
PDQ Cognition	25.6 (18.0)	25.3 (18.6)	21.7 (17.4)	26.8 (22.3)	28.6 (18.1)	24.1 (15.6)*
PDQ communication	27.4 (20.8)	25.7 (20.9)	27.4 (23.6)	26.6 (24.0)	27.4 (19.0)	25.0 (18.7)
PDQ bodily discomfort	43.9 (21.3)	34.7 (20.3)*	44.4 (22.1)	37.7 (19.3)	43.5 (21.1)	32.4 (21.1)*
ESS	10.9 (4.9)	10.1 (4.1)	10.8 (4.7)	10.7 (4.3)	11.0 (5.1)	9.7 (4.0)*
MMSE	28.0 (2.0)	28.3 (2.6)	27.8 (2.6)	27.8 (3.4)	28.2 (1.5)	28.6 (1.8)

*$P < 0.05$ (follow-up compared with baseline).

TABLE 3. Baseline and One-Month Follow-Up by Drug Preference (Means and SD)

	Preferred CLE		Preferred SR-CL		Dropped	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
n		42		7		13
Age (years)	65.7 (8.9)		68.6 (7.0)		73.0 (9.4)	
Disease Duration (years)	10.0 (6.3)		11.7 (8.1)		12.6 (4.6)	
Sex (M/F)	31/11		4/3		10/3	
Levodopa (mg)	660 (272)	642 (210)	731 (220)	764 (244)	666 (306)	664 (316)
UPDRS Mentation	1.9 (1.5)	1.5 (1.7)*	2.1 (1.7)	2.6 (1.0)	2.2 (1.1)	—
UPDRS ADL	13.4 (4.6)	12.6 (4.9)	17.4 (4.9)	19.9 (6.8)	15.6 (7.1)	—
UPDRS Motor	24.5 (8.4)	18.0 (7.7)*	24.9 (7.3)	29.1 (10.7)	24.8 (12.5)	—
PDQ-39 Total	27.4 (14.2)	25.1 (13.8)	40.8 (17.7)	33.8 (14.9)	38.2 (20.5)	—
PDQ Mobility	33.5 (22.2)	30.8 (20.9)	50.7 (33.2)	45.0 (31.6)	50.4 (29.0)	—
PDQ ADL	31.4 (18.7)	26.6 (17.8)*	43.5 (15.7)	38.7 (18.0)	41.0 (27.2)	—
PDQ Emotional	22.8 (15.0)	21.4 (17.8)	33.3 (16.8)	28.6 (9.8)	28.2 (18.7)	—
PDQ Stigma	20.1 (21.4)	18.9 (20.0)	32.1 (18.9)	17.9 (18.2)	37.0 (30.9)	—
PDQ Social Support	11.1 (13.5)	9.7 (13.0)	28.6 (22.5)	26.2 (17.0)	21.8 (22.2)	—
PDQ Cognition	25.0 (18.5)	25.0 (19.7)	29.5 (14.8)	26.8 (9.4)	29.3 (19.0)	—
PDQ Communication	27.4 (20.5)	26.1 (21.5)	31.0 (22.9)	22.6 (17.8)	38.5 (25.8)	—
PDQ Bodily Discomfort	40.3 (19.8)	32.7 (17.6)*	65.5 (17.6)	46.4 (31.5)	41.0 (26.0)	—
ESS	11.2 (4.9)	10.2 (4.2)*	9.4 (4.8)	9.6 (3.2)	9.6 (3.8)	—
Mini Mental State Exam	28.2 (2.1)	28.4 (2.6)	26.9 (1.1)	27.4 (2.4)	28.1 (1.8)	

*$P < 0.05$ (follow-up compared with baseline).

CLE indicates carbidopa/levodopa/entacapone; SR-CL, sustained release carbidopa/levodopa; UPDRS, Unified Parkinson Disease Rating Scale; PDQ-39, Parkinson Disease Questionnaire-39.

emotional well-being, cognition, and bodily discomfort subscale scores. In this group, 22 (78.6%) preferred CLE to SR-CL. Table 2 contains baseline and 1-month follow-up data for the 49 patients that completed the study as an entire cohort and split by baseline entacapone use. Thirteen patients withdrew from the study before 1 month due to adverse effects from CLE, primarily nausea, vomiting, increased off time, and increased dyskinesia. None of these patients had been previously exposed to entacapone; 7 patients were taking only SR-CL and 6 patients were taking SR-CL + standard carbidopa/levodopa.

At the end of the study, 42 patients (68%) continued CLE and 20 patients chose to restart SR-CL. Of those that completed the study, 86% preferred CLE over SR-CL. CLE was preferred due to better control of symptoms (30 patients), convenience (8 patients), lower cost (3 patients), and faster action (1 patient). The patients who preferred CLE were taking the following levodopa combinations at baseline: 16 on SR-CL + entacapone, 16 on only SR-CL, 6 on standard carbidopa/levodopa + SR-CL, and 4 on standard carbidopa/levodopa + SR-CL + entacapone. The remaining 14% preferred SR-CL (5 better control, 1 fewer adverse events, 1 faster action). At baseline, the patients who preferred SR-CL were on the following levodopa combinations: 2 on only SR-CL, 4 on standard carbidopa/levodopa + SR-CL + entacapone, and 1 on SR-CL + entacapone.

The mean age of patients who preferred CLE was 66 years with a mean disease duration of 10 years (Table 3). There were 31 men and 11 women. The mean levodopa dose at baseline was 660 mg/d and at the end of the study was 642 mg/d. UPDRS mentation and motor subscores were significantly improved, as well as PDQ-39 ADL and bodily discomfort subscores and ESS scores (Table 2). There was no significant improvement in MMSE or UPDRS ADL scores. Eight patients had a reduction in dyskinesia, 28 patients were unchanged, and 6 patients were worsened. Off time was reduced in 12 patients, unchanged in 25 patients, and worsened in 5 patients. Adverse effects were mild in this group and resolved with medication adjustments (Table 4).

The mean age of patients who preferred SR-CL was slightly older at 69 years with a mean disease duration of 12 years (Table 3). There were 4 men and 3 women. The mean levodopa dose at baseline was 731 mg/d and at the end

TABLE 4. Adverse Effects With CLE Seen in Greater Than 5% of Patients

Adverse Event	Preferred CLE	Preferred SR-CL	Dropped
n	42	7	13
Nausea/GI symptoms	8 (19.0%)	3 (42.9%)	7 (53.8%)
Increased dyskinesia	5 (11.9%)	2 (28.6%)	3 (23.1%)
Urine discoloration	5 (11.9%)	1 (14.3%)	1 (7.7%)
Dizziness	5 (11.9%)	0	3 (23.1%)
Increased off time	4 (9.5%)	4 (57.1%)	5 (38.5%)
Somnolence	4 (9.5%)	1 (14.3%)	1 (7.7%)
Insomnia	1 (2.4%)	2 (28.6%)	3 (23.1%)
Confusion	0	2 (28.6%)	0
Falling	0	1 (14.3%)	0
Freezing	0	1 (14.3%)	0

GI indicates gastrointestinal.

of the study was 764 mg/d. There was no significant change in the MMSE, ESS, UPDRS, or PDQ-39 scores (Table 3). One patient had a reduction in dyskinesia and 6 patients were unchanged. Off time was reduced in 2 patients, unchanged in 2 patients, and worsened in 3 patients. Adverse effects for this group and those who discontinued the study are shown in Table 4.

DISCUSSION

This study evaluated the safety, tolerability, and efficacy after the conversion of patients from SR-CL to CLE. Most patients suboptimally controlled on SR-CL were converted to CLE resulting in improved motor control and quality of life and less sleepiness. Although the study duration was only 1 month, most of the previous entacapone studies have reported that most patient dropouts occurred in the first few weeks of treatment initiation.[3–5]. Koller et al[6] reported the conversion of patients on standard carbidopa/levodopa experiencing end of dose motor fluctuations to CLE. They reported fewer dropouts (8%) compared with the current study (21%); however, their patient population had a shorter disease duration (5 years) and lower levodopa dose at baseline compared with patients in this study. In the current study, patients who preferred CLE were younger, had a shorter disease duration, and were on lower levodopa doses compared with patients who preferred SR-CL. When those that dropped out of the study were compared with those that preferred CLE, they were significantly older (73 vs 66 years) and had a significantly longer disease duration (12.6 vs 10.0 years). Also of note, as mentioned previously, 100% of the patients who dropped from the study had not been previously exposed to entacapone. This suggests that in older patients with more advanced disease who have not been previously exposed to entacapone, one may consider a slower titration schedule on conversion or first add entacapone to SR-CL and then convert patients to CLE.

Adverse effects seen in the current study was similar to those reported in the other study with CLE.[6] Common adverse events included nausea, dizziness, increased dyskinesia, somnolence, and insomnia. These are most likely related to excessive dopaminergic stimulation. Increased off time was reported by 11 patients, and 5 of these patients discontinued the study.

In conclusion, most patients on SR-CL can be successfully converted to CLE; however, older patients not previously exposed to entacapone may have fewer side effects if entacapone is added before an attempt to convert to CLE.

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