

A Randomized Controlled Trial of Etilevodopa in Patients With Parkinson Disease Who Have Motor Fluctuations

Parkinson Study Group

Background: Motor fluctuations are a common complication in patients with Parkinson disease (PD) receiving long-term levodopa therapy. Slowed gastric emptying and poor solubility of levodopa in the gastrointestinal tract may delay the onset of drug benefit after dosing. Etilevodopa is an ethyl-ester prodrug of levodopa that has greater gastric solubility, passes quickly into the small intestine, is rapidly hydrolyzed to levodopa, and has a shortened time to maximum levodopa concentration.

Objective: To determine the efficacy, safety, and tolerability of etilevodopa in patients with PD who have motor fluctuations.

Design: A double-blind, randomized, comparative clinical trial.

Setting: Forty-four sites in the United States and Canada.

Patients: Three hundred twenty-seven patients with PD who had a latency of at least 90 minutes total daily time to "on" (TTON) after levodopa dosing.

Intervention: Treatment with either etilevodopa-carbidopa or levodopa-carbidopa for 18 weeks.

Main Outcome Measure: Change from baseline in total daily TTON as measured using home diaries.

Results: The reduction in mean total daily TTON from baseline to treatment was 0.58 hour in the etilevodopa-carbidopa group and 0.79 hour in the levodopa-carbidopa group ($P = .24$). There was no significant difference between the etilevodopa-carbidopa and levodopa-carbidopa groups in the reduction of response failures (-6.82% vs -4.69% ; $P = .20$). Total daily "off" time improved in the etilevodopa-carbidopa (-0.85 hour) and levodopa-carbidopa (-0.87 hour) groups without an increase in on time with troublesome dyskinesias.

Conclusion: Despite the theoretical pharmacokinetic advantage of etilevodopa, there was no improvement in TTON, response failures, or off time compared with levodopa.

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LEVODOPA REMAINS THE MOST effective symptomatic treatment for Parkinson disease (PD), but motor complications arise in many levodopa-treated patients with PD after 3 to 5 years of use.^{1,2} Motor complications can be categorized into dyskinesias and response fluctuations, which include end-of-dose wearing "off," sudden "on"/offs, delayed time to on (TTON), and response failures, where no symptomatic benefit occurs after receiving a levodopa dose.³

Multiple mechanisms, including the poor solubility of levodopa in the gastrointestinal tract and delayed gastric emptying, likely contribute to delayed TTON and response failures.^{4,5} One study⁶ found a gastric emptying time of 56 minutes in healthy individuals, 85 minutes in patients with nonfluctuating early PD, and 221 minutes in patients with advanced PD and motor fluctuations. The options for treating delayed TTON and response failure complications are presently limited but include subcutaneous apomorphine hydrochloride, liquid levodopa suspensions, and duodenal levodopa infusions.^{7,8}

Etilevodopa (TV-1203) is an ethyl-ester prodrug of levodopa that is rapidly hydrolyzed to levodopa and ethanol by nonspecific esterases in the gastrointestinal tract. Compared with standard levodopa, etilevodopa has greater solubility in the stomach, faster passage to the small intestine, and a shortened time to maximum levodopa concentration.⁹ In an early clinical study¹⁰ of etilevodopa, 62 patients with advanced PD were randomized to either continue standard levodopa treatment or replace the first dose of levodopa in the morning and the first dose after lunch with etilevodopa. The mean TTON for the first morning dose decreased by 21% in the etilevodopa group and 9% in the standard levodopa group. The mean latency to on for the first dose after lunch decreased by 17% in the etilevodopa group and 0% in the standard levodopa group. The response failure rate for the dose after lunch decreased from 23% to 19% in the etilevodopa group vs an increase from 17% to 23% in the levodopa group.¹⁰ The objective of the pres-

Group Information: A complete list of the Parkinson Study Group investigators appears in a box on page 215.

ent study is to determine the efficacy, safety, and tolerability of etilevodopa when administered in place of all daily immediate-release levodopa doses in a double-blind manner to patients with advanced PD and motor fluctuations.

METHODS

PATIENTS

Consenting patients with PD and chronic levodopa-related motor fluctuations (n = 327) were enrolled at 44 participating Parkinson Study Group sites in the United States and Canada. Patients had idiopathic PD, a modified Hoehn and Yahr stage¹¹ of less than 5 in the off state, at least 2.5 hours per day in the off state (confirmed by a 3-day home diary),¹² a TTON of 30 minutes or longer for at least 1 dose of levodopa per day, and an average daily total TTON after all daily levodopa-carbidopa doses of at least 90 minutes (based on a second 3-day home diary completed before baseline). Patients were required to receive a minimum daily dose of 300 mg of immediate-release levodopa divided into at least 4 doses. Sustained-release levodopa-carbidopa was allowed in combination with immediate-release levodopa doses during the day and without immediate-release levodopa-carbidopa only at bedtime and during the night, and the sustained-release levodopa dosage was held constant during the trial. Concomitant treatment with dopamine agonists, amantadine hydrochloride, anticholinergics, selegiline hydrochloride, and entacapone was allowed in cases in which stable dosages were maintained for 4 weeks before baseline and throughout the study. Patients with atypical or secondary parkinsonism, a Mini-Mental State Examination¹³ score of 24 or less, or unstable neurologic, psychiatric, and medical disorders were excluded. Patients were also excluded if they had surgical treatment for PD in the 12 months preceding the baseline visit, had deep brain stimulation programming changes within 1 month of screening, or anticipated having changes in deep brain stimulation programming during the study.

DESIGN AND PROCEDURES

We conducted a randomized, parallel-group, double-blind comparison of etilevodopa and immediate-release levodopa in patients with PD and motor fluctuations receiving optimized levodopa therapy. After a screening visit to ensure that the participants met the enrollment criteria, existing immediate-release levodopa formulations were switched to generic 4:1 immediate-release levodopa-carbidopa (100 mg/25 mg), and patients were optimized on this drug regimen for 2 to 6 weeks before the baseline visit. The optimal dose of levodopa-carbidopa was defined as the dose that provided maximal clinical benefit to the patient. During the screening visit and optimization period, patients underwent standardized diary training to ensure that they could reliably complete the home diaries. Two separate diaries were used, one to quantify the daily TTON and dose failures and one to quantify the total daily off time, on time without dyskinesias or with nontroublesome dyskinesias, on time with troublesome dyskinesias, and sleep¹² (Figure 1). The practice and reliability training consisted of (1) viewing a standardized teaching videotape demonstrating and defining on, off, dyskinesias, and troublesome dyskinesias^{12,14}; (2) reviewing verbal and written instructions for diary completion; and (3) completing practice diaries at home and on-site (concurrently with the investigator or coordinator) during the screening visit. To be eligible for study participation, 75% agreement between the patient and the investigator or coordinator diary ratings was required.

At baseline, patients were randomized in equal numbers to etilevodopa-carbidopa tablets + placebo for levodopa-carbidopa

A
RAPID (TV-1203/111) 22

"TIME TO ON" DIARY (DIA2)
Page of

One Diary is to be completed each day. Leave entries blank if fewer than 12 doses are taken each day. If you are "ON" at the time of taking medication, do not mark any of the boxes in the shaded area.

SUBJECT NO SITE NO VISIT NO

NAME/DOB CODE DATE DIARY

(1st three letters of last name, 1st initial, year of birth) COMPLETED MM DD YEAR

DAILY DOSE	Exact time medication taken	What is your status at the time of taking medication?		If "OFF" at the time of taking medication:	
				Mark the exact time "ON" Began	If No "ON" time before the next dose check box (✓)
9	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/> ON	<input type="checkbox"/> OFF	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/>
10	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/> ON	<input type="checkbox"/> OFF	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/>
11	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/> ON	<input type="checkbox"/> OFF	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/>
12	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/> ON	<input type="checkbox"/> OFF	Hour: <input type="text"/> : <input type="text"/> Minutes: <input type="text"/> AM <input type="checkbox"/> PM <input type="checkbox"/>	<input type="checkbox"/>

B
RAPID (TV-1203/111) 20

24 - HOUR DIARY (DIA1)
Page 1 of 1

One Diary is to be completed each day.

SUBJECT NO SITE NO VISIT NO

NAME/DOB CODE DATE DIARY

(1st three letters of last name, 1st initial, year of birth) COMPLETED MM DD YEAR

Midnight				Noon			
Time	ON1 NO dyskinesia OR WITHOUT Troublesome dyskinesia	ON2 WITH Troublesome dyskinesia	OFF3 A sympt L P4	Time	ON1 NO dyskinesia OR WITHOUT Troublesome dyskinesia	ON2 WITH Troublesome dyskinesia	OFF3 A sympt L P4
1. 12:00am - 12:30am				25. 12:00pm - 12:30pm			
2. 12:30am - 1:00am				26. 12:30pm - 1:00pm			
3. 1:00am - 1:30am				27. 1:00pm - 1:30pm			
4. 1:30am - 2:00am				28. 1:30pm - 2:00pm			
5. 2:00am - 2:30am				29. 2:00pm - 2:30pm			
6. 2:30am - 3:00am				30. 2:30pm - 3:00pm			
7. 3:00am - 3:30am				31. 3:00pm - 3:30pm			
8. 3:30am - 4:00am				32. 3:30pm - 4:00pm			
9. 4:00am - 4:30am				33. 4:00pm - 4:30pm			
10. 4:30am - 5:00am				34. 4:30pm - 5:00pm			
11. 5:00am - 5:30am				35. 5:00pm - 5:30pm			

Figure 1. Time to "on" (A) and 24-hour (B) diary forms.

or placebo for etilevodopa + immediate-release levodopa-carbidopa tablets. The computer-generated randomization plan, created by Parkinson Study Group biostatisticians, provided for stratification by medical center and blocking to ensure approximate balance among the treatment groups within each center. The levodopa/etilevodopa dosage could be adjusted during the first 8 weeks of the study at the discretion of the investigator, but it was held constant for the last 10 weeks. Patients had visits 4, 8, 13, and 18 weeks after baseline for safety and efficacy monitoring. Home diaries were completed at baseline and before the week 8, 13, and 18 visits. Urinalysis, complete blood cell counts, and serum chemistry profiles were performed at screening, at baseline, and after 18 weeks of treatment at a central facility (Covance Inc, Princeton, NJ). Physical and neurologic examinations and electrocardiograms were performed at screening and at week 18, and vital signs were assessed at every visit.

OUTCOME MEASURES

The prespecified primary measure of efficacy was the change from baseline in mean total daily TTON, as measured using home diaries, averaged across the treatment period (weeks 8, 13, and 18 combined). Secondary measures of efficacy included the change from baseline in mean total daily off time, in percentage of dose

STATISTICAL ANALYSES

The primary analysis of efficacy used an analysis of covariance model that included the change from baseline in mean total daily TTON as the dependent variable, adjusted for the baseline mean total daily TTON, and treatment group as the independent variable of interest. The analysis of covariance model also included the following effects in the analysis: medical center and baseline mean number of levodopa-carbidopa doses. The treatment \times center interaction was to be included if it was significant at $P < .10$. For each participant, the TTON was calculated for each day by summing the TTONs for each dose. The TTON for reported dose failures was calculated as the time from dosing until the time of the next dose. The TTON for doses taken in the on state was assigned a value of zero, which was more conservative than omitting these data points. The mean total daily TTON was then calculated for each patient by averaging the total daily TTONs across all days for which that patient had data. The primary statistical analyses were performed according to the intention-to-treat principle using data from all patients with post-randomization diary data ($n = 301$). For the analyses of the non-diary efficacy measures, if a patient was missing a response, the last available observation for that patient was carried forward and imputed for that visit. To determine the impact of patient withdrawals on the primary analyses for efficacy, the analyses were repeated including only patients who completed the study ($n = 285$) and patients who completed all the procedures according to the protocol ($n = 258$). The results of these analyses did not differ from those of the primary analyses and hence are not reported. An overall significance level of 5% was set for these analyses. All methods of analysis were prespecified before patient treatment assignments were revealed.

Analyses of secondary and exploratory end points were performed in a manner similar to that described previously herein. Adverse experiences were tabulated by treatment group. Laboratory and vital sign data were analyzed by calculating descriptive statistics, including means and standard deviations at baseline and the last observed value, and the change between visits.

RESULTS

PATIENT DISPOSITION AND CHARACTERISTICS

Of 473 screened patients, 327 fulfilled the entry criteria and consented to be randomized to receive either etilevodopa-carbidopa or levodopa-carbidopa (**Figure 2**). The 2 treatment groups had no significant baseline differences in demographic and clinical characteristics, except the mental subscale score of the Unified Parkinson Disease Rating Scale was slightly worse in the levodopa-carbidopa group (**Table 1**). The baseline mean total daily TTON was 3.9 hours in both groups, and the mean total daily off time was approximately 6.5 hours in both groups. Therefore, in this PD cohort, the mean total daily TTON represented almost 60% of daily off time. Response failures occurred in approximately 67% of enrolled patients at baseline, and these failures involved more than 20% of all daily levodopa doses taken at off. Mean \pm SD total daily levodopa dosage was similar in the 2 groups at baseline (**Table 1**) but showed a trend toward higher dosages in the etilevodopa-carbidopa group during the maintenance phase of the study (etilevodopa: 833 ± 464 mg/d; levodopa: 745 ± 332 mg/d; $P = .06$).

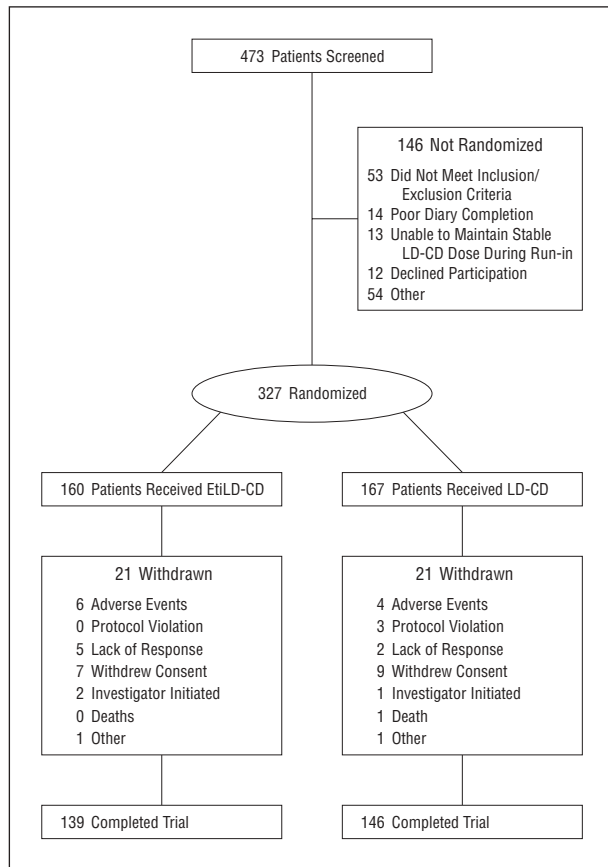


Figure 2. Flow diagram illustrating patient flow through screening, randomization, and 18 weeks of double-blind treatment. CD indicates carbidopa; EtiLD, etilevodopa; and LD, levodopa.

failures (defined as no on state by 90 minutes after dosing) of doses taken in the off state, and in total daily on time without dyskinesias or with nontroublesome dyskinesias. A prespecified responder analysis dichotomized the change from baseline in the mean total daily TTON as either improved (a reduction of ≥ 45 minutes) or not improved (a reduction of < 45 minutes or an increase). Exploratory analyses included the change from baseline in mean TTON for each individual visit; the change from baseline in total, motor, and activities of daily living Unified Parkinson Disease Rating Scale scores¹⁵ and Schwab and England activities of daily living scores¹⁶; and the change from baseline in the number of daily doses and total milligrams of levodopa or etilevodopa per day. Change from baseline during treatment of the standard deviation of the TTON was explored as a measure of dose predictability. Investigators also rated their global impression of change from baseline to week 18 on a 7-point global impression scale. Measures of safety included the frequency and severity of reported adverse experiences, changes in vital signs, laboratory test results, and electrocardiographic findings.

SAMPLE SIZE

A blinded analysis of the aggregate data after approximately 100 individuals completed the study demonstrated that 300 patients would give 90% power to detect a difference of 41 minutes between groups in the adjusted change from baseline in the mean total daily TTON. This sample size also gave 90% power to detect noninferiority of etilevodopa treatment compared with levodopa treatment in the change from baseline in total daily off time, with a noninferiority threshold set at 45 minutes.

Table 1. Patient Characteristics at Baseline

Characteristic	EtiLD-CD Group (n = 160)	LD-CD Group (n = 167)	P Value
Age, mean (SD), y	62.4 (9.5)	63.5 (10.0)	.30
Male sex, No. (%)	103 (64.4)	108 (64.7)	.96
Parkinson disease duration, mean (SD), y	10.0 (5.2)	10.1 (5.6)	.98
Duration of LD use, mean (SD), y	9.0 (5.3)	9.3 (5.4)	.75
Daily LD dose, mean (SD), mg	753 (415)	735 (397)	.91
Concomitant medication use, No. (%)			
Dopamine agonists	125 (78)	136 (81)	.46
Entacapone	71 (44)	64 (38)	.27
Amantadine	45 (28)	46 (28)	.91
Daily "off" time, mean (SD), h	6.5 (2.3)	6.5 (2.2)	.91
Total daily TTON, mean (SD), h	3.9 (1.8)	3.9 (2.1)	.63
"On" without troublesome dyskinesias, mean (SD), h	9.2 (2.6)	9.1 (2.5)	.79
On with troublesome dyskinesias, mean (SD), h	1.0 (1.8)	1.0 (1.9)	.95
UPDRS score, mean (SD)			
Total (on)	30.4 (14.9)	32.6 (16.4)	.32
Motor (on)	22.6 (11.7)	24.0 (12.9)	.41
ADL (on)	6.2 (4.8)	6.5 (5.5)	.84
ADL (off)	17.7 (6.8)	17.9 (7.2)	.82
Mental	1.7 (1.5)	2.1 (1.6)	.03
Daily LD doses, mean (SD), No.	5.7 (1.7)	5.6 (1.7)	.62
Doses taken at off, mean (SD), %	68.5 (22.5)	66.4 (22.9)	.34
Daily dose failures (of doses taken at off), mean (SD), %	21.3 (23.2)	22.4 (23.5)	.64
Patients with dose failures, No. (%)	105 (65.6)	115 (68.9)	.53

Abbreviations: ADL, activities of daily living; CD, carbidopa; EtiLD, etilevodopa; LD, levodopa; TTON, time to "on"; UPDRS, Unified Parkinson Disease Rating Scale.

SAFETY AND TOLERABILITY

Two-hundred eighty-five patients (87% of those enrolled) completed 18 weeks of treatment. The number of patients withdrawing from the study because of an adverse event or for any reason was not different between treatment groups (Figure 2). Adverse events led to study withdrawal in 6 patients in the etilevodopa-carbidopa group (increased off time or dyskinesias in 3, painful dystonia in 2, and angina pectoris in 1) and in 4 in the levodopa-carbidopa group (confusion, anxiety, and hyperkinesia in 1; pain in 1; encephalopathy in 1; and overdose in 1).

Adverse events of any severity were reported in 71% of patients receiving etilevodopa-carbidopa and in 77% receiving levodopa-carbidopa, but this difference did not reach significance ($P = .25$). Adverse events that occurred in 5% or more of the patients are summarized in **Table 2**. Only peripheral edema was reported significantly more frequently in the etilevodopa-carbidopa group compared with the levodopa-carbidopa group ($P = .003$); however, when mild events were excluded, this difference was no longer significant.

There were 25 serious adverse events: 14 in the etilevodopa-carbidopa group and 11 in the levodopa-

Table 2. Adverse Events Occurring in 5% or More of Patients in Either Group

Adverse Event	Patients, No. (%)	
	EtiLD-CD Group (n = 160)	LD-CD Group (n = 167)
Extrapyramidal syndrome	19 (11.9)	10 (6.0)
Infection	14 (8.8)	13 (7.8)
Dyskinesias	13 (8.1)	9 (5.4)
Peripheral edema*	13 (8.1)	1 (0.6)
Headache	12 (7.5)	9 (5.4)
Dizziness	11 (6.9)	9 (5.4)
Sleep disorder	11 (6.9)	7 (4.2)
Nausea	10 (6.3)	14 (8.4)
Accidental injury	10 (6.3)	16 (9.6)
Pain	8 (5.0)	9 (5.4)
Diarrhea	4 (2.5)	9 (5.4)

Abbreviations: CD, carbidopa; EtiLD, etilevodopa; LD, levodopa.

* $P = .003$.

carbidopa group. One serious adverse event in the etilevodopa group was classified as probably drug related (severe off dystonia and pain), and 2 were classified as possibly related (severe dyskinesias and off time combined and angina pectoris). All the other serious adverse events were classified as either unrelated or unlikely to be related to study drug. There were no significant group differences in vital signs, laboratory test values, or electrocardiographic findings during treatment.

EFFICACY

The primary end point, the unadjusted change from baseline in mean total daily TTON, decreased by a mean \pm SD of 0.55 ± 1.85 hours in the etilevodopa-carbidopa group and 0.76 ± 1.71 hours in the levodopa-carbidopa group (**Table 3**). The effect size for the primary end point, adjusted for baseline TTON, baseline number of levodopa doses, and medical center, was not significant (-0.21 hour; 95% confidence interval, -0.57 to 0.14 hour; $P = .24$). When the treatment groups were subdivided post hoc into the lower, middle, and upper thirds for baseline TTON, there were no significant differences in the unadjusted means.

There was no significant improvement in the response failure rate in the etilevodopa-carbidopa group vs the levodopa-carbidopa group (-6.82% vs -4.69% ; $P = .20$). The total daily off time improved in both groups without an increase in on time with troublesome dyskinesias (Table 3). There was no significant difference in the improved off time for patients with or without a dose increase. There were also no significant differences between the treatment groups in the other secondary and exploratory end points (data not shown).

COMMENT

Etilevodopa-carbidopa treatment was well tolerated but did not demonstrate better efficacy compared with standard levodopa-carbidopa treatment. Despite the pharmacokinetic advantage demonstrated in earlier studies of etilevodopa,⁹ etilevodopa-carbidopa showed no clini-

Table 3. Efficacy End Points

	EtiLD-CD Group (n = 149)	LD-CD Group (n = 151)	P Value
Change from baseline in mean total daily TTON, adjusted mean (SE), h	-0.58 (0.13)	-0.79 (0.13)	.24
Subgroups, mean (SD), h			
Baseline TTON <2.6 h	0.20 (1.3) (n = 48)	0.01 (1.2) (n = 50)	.45
Baseline TTON 2.6-4.2 h	-0.46 (1.4) (n = 47)	-0.63 (1.4) (n = 55)	.52
Baseline TTON >4.2 h	-1.31 (2.3) (n = 54)	-1.75 (2.0) (n = 46)	.32
Change from baseline in dose-response failures, adjusted mean (SE), %	-6.82 (1.2)	-4.69 (1.2)	.20
Change from baseline in total daily "off" time, adjusted mean (SE), h	-0.85 (0.17)	-0.87 (0.17)	.93
Change in mean total daily "on" time without troublesome dyskinesias, adjusted mean (SE), h*	0.81 (0.18)	0.66 (0.18)	.56
Change in mean total daily on time with troublesome dyskinesias, adjusted mean (SE), h*	0.02 (0.11)	0.03 (0.11)	.96
Change from baseline in total daily off time (patients without a dose increase), adjusted mean (SE), h	-1.11 (0.21)	-0.87 (0.19)	.39

Abbreviations: CD, carbidopa; EtiLD, etilevodopa; LD, levodopa; TTON, time to "on."
*Interaction term included in model.

cal superiority over levodopa-carbidopa in reducing daily TTON in patients with advanced PD who were optimized on their PD drug regimen before randomization.

The trial outcome could be explained by either a true lack of superiority of etilevodopa or limitations inherent in the trial design. Pharmacokinetic data documenting the levodopa time to occurrence of maximum concentration (T_{max}) and maximum concentration (C_{max}) in each individual patient were not acquired as a part of this study. Therefore, it is not known whether the shortened T_{max} of etilevodopa compared with levodopa seen in a previous single-dose substitution was consistently reproduced when multiple doses of this drug were given during the day. Furthermore, pharmacokinetic studies of standard levodopa have shown dramatic variability in plasma levodopa levels despite the maintenance of constant oral doses, and pharmacodynamic studies have demonstrated an imperfect correlation of blood levodopa levels to clinical responses.^{17,18} Patients were instructed to keep the timing of meals in relation to levodopa dosing constant before and after randomization. However, the impact of protein on the absorption of etilevodopa and levodopa cannot be ignored. Data regarding the exact timing and content of meals were not collected in sufficient detail to determine whether this variable had an effect on the study outcome. One other explanation is that perhaps delayed gastric emptying is not an important mechanism for delayed TTON in most patients.^{18,19}

The sensitivity of patient diaries as an assessment tool to measure change in TTON and response failures has not been previously validated; however, both treatment groups showed an improvement in these measures from baseline. It is possible that as the trial progressed, study participants in both treatment groups became more astute at detecting their TTON, and this "practice effect" biased the outcome measure in both groups. In addition, a "placebo" effect cannot be excluded as a potential cause for improvement in both groups due to more frequent visits and increased attention associated with participation in a controlled study. Furthermore, it could be argued that the patient population selected was so advanced that any change from baseline in TTON and response failures represented a regression to the mean that could likewise diminish any measurable difference between treatment groups. Also, the

percentage of doses taken while in the on state increased from baseline by 8.5% in the levodopa group and 5.8% in the etilevodopa group. Because doses taken while on were assigned a TTON of zero, this factor could have incidentally lowered the TTON in the levodopa group as well.

Patients in both groups had a reduction in off time corresponding with an improvement in on time without an increase in troublesome dyskinesias, despite being optimized on their PD drug regimen before randomization. Even when initially optimized, then, it seems that additional fine-tuning of the levodopa regimen can lead to symptomatic improvement. Although patients in the etilevodopa-carbidopa group were receiving a somewhat greater dosage of medicine during the maintenance phase of the study, they still showed no added benefit.

This trial shows that the delayed TTON accounted for a majority of the daily off time in these patients with advanced PD and motor fluctuations and that response failures occurred relatively frequently in many of these patients. It is unclear if these observations would also apply to a less selective group of patients with fluctuating PD.

This study illustrates that there remains an unmet need to reduce delayed TTON in patients with PD and motor fluctuations. If delayed gastric emptying causes delayed TTON, then alternative means of delivering dopaminergic compounds could benefit these patients. Because a rapidly dissolving formulation of levodopa did not resolve this problem, it may be necessary to use agents that bypass the gastrointestinal tract, such as subcutaneous or transdermal compounds. In contrast, investigations²⁰⁻²³ of oral liquid levodopa-carbidopa and duodenal levodopa-carbidopa infusions have demonstrated either improvement in motor function or reduction in motor fluctuations. Our end points of total daily TTON and dose-response failures were not tested in these earlier studies, however. Alternatively, shortening the interval between doses of standard levodopa-carbidopa to account for the latency of on might also be of benefit. Finally, another consideration could include adjunctive therapy with a drug that would hasten gastric emptying.

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