Levodopa-Entacapone-Carbidopa Intestinal Gel in Parkinson's Disease: A Randomized Crossover Study

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Abstract

Background: The addition of oral entacapone to levodopa-carbidopa intestinal gel treatment leads to less conversion of levodopa to 3-O-methyldopa, thereby increasing levodopa plasma concentration. The objective of this study was to compare systemic levodopa exposure of the newly developed levodopa-entacapone-carbidopa intestinal gel after a 20% dose reduction with levodopa exposure after the usual levodopa-carbidopa intestinal gel dose in a randomized crossover trial in advanced Parkinson's disease patients.

Methods: In this 48-hour study, 11 patients treated with levodopa-carbidopa intestinal gel were randomized to a treatment sequence. Blood samples were drawn at prespecified times, and patient motor function was assessed according to the treatment response scale.

Results: Systemic exposure of levodopa did not differ significantly between treatments (ratio, 1.10 [95% confidence interval, 0.951-1.17]). Treatment response scale scores did not significantly differ between treatments ($P = 0.84$).

Conclusions: Levodopa-entacapone-carbidopa intestinal gel allowed a lower amount of levodopa administration and was well tolerated. Long-term studies are needed to confirm the results. © 2016 International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; clinical trials; randomized; levodopa infusion; pharmacotherapy

Levodopa-carbidopa intestinal gel (LCIG; Duodopa/Duopa; AbbVie, Chicago, IL) is an effective treatment developed for patients with advanced Parkinson's disease (PD).[1] It provides a stable levodopa plasma concentration compared with oral administration because of continuous infusion into the duodenum/jejunum by a portable pump.

Addition of the cathecol-O-methyltransferase (COMT) inhibitor entacapone, blocking levodopa's second-largest pathway, leads to less levodopa conversion to 3-O-methyldopa (3-OMD), thereby increasing the levodopa plasma concentration.[2,3] Currently, only orally administered entacapone is available.[4]

Levodopa-entacapone-carbidopa intestinal gel (LECIG; LECIGon; LobSor Pharmaceuticals AB, Knivsta, Sweden) is a newly developed formulation for intestinal infusion.

The primary objective of this trial was to compare the systemic levodopa exposure between hours 0-14 ($AUC_{0\text{-}14}$) after continuous infusion of LECIG and conventional LCIG in a crossover study in advanced PD patients.

Methods

Inclusion Criteria

All patients with idiopathic PD currently on a stable LCIG treatment (<125 mL per day) for a minimum of 30 days who were aged 30 years or older with a body mass index (BMI) between 17 and 31 and had not been exposed to entacapone within 3 months of screening were eligible for inclusion. The exclusion criterion was increased fluctuation of PD symptoms within 7 days prior to screening. For additional information, see NCT02448914.

Medication

The study product, LECIG (levodopa [20 mg/mL], entacapone [20 mg/mL], and carbidopa monohydrate [5 mg/mL]; LECIGon; LobSor Pharmaceutical AB, Knivsta, Sweden), was administered via the same gastrojejunostomy tube as used for LCIG infusion.[5,6] LECIG is contained in 50-mL syringes attached to an infusion pump (Cane, Italy), together measuring

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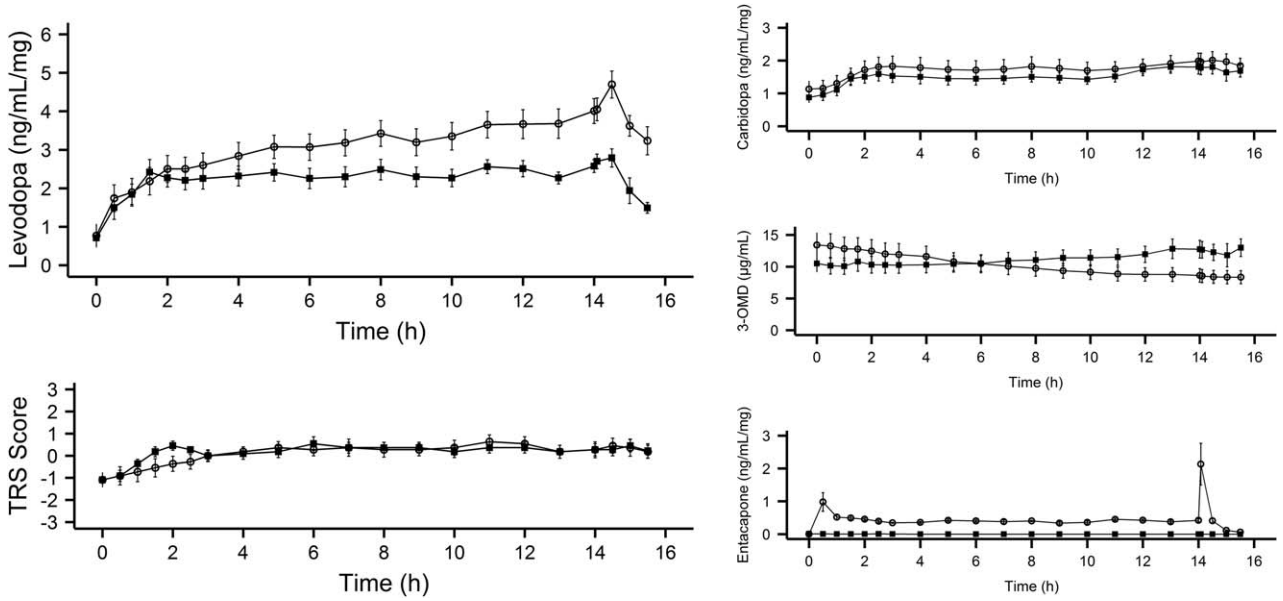

FIG. 1. Pharmacokinetic mean (±SE) dose-adjusted plasma concentrations (0-15.5 h) of levodopa (n = 11), carbidopa (n = 11), 3-O-methyldopa (n = 11) and entacapone (n = 6), and mean TRS score. Filled squares = levodopa/carbidopa infusion (LCIG), open circles = levodopa/entacapone/carbidopa infusion (LECIG); TRS: treatment response scale.

55 × 150 mm (Fig. 1). The weight of the LECIG pump is 139 g, and a full syringe weighs 88 g, resulting in a total weight of 227 g.

The reference product was LCIG (levodopa [20 mg/mL] and carbidopa monohydrate [5 mg/mL]; Duodopa; AbbVie Ltd, Chicago, IL). The LCIG pump and cassette (100 mL) measured 100 × 197 mm, and the weight of the LCIG pump system with a full cassette is approximately 550 g.

Study Design and Intervention

This randomized, open-label, 2-day crossover clinical trial was conducted at the Clinical Trial Consultants AB (CTC) center at Uppsala University Hospital between May and July 2015. The local Uppsala Ethical Review Board in Sweden approved the study, and all patients provided written informed consent.

Prior to the study start, a set of closed randomization envelopes were sent to CTC. The allocation ratio was 1:1.

Patients were randomized to receive 1 of 2 treatment sequences, LECIG/LCIG or LCIG/LECIG, over 2 consecutive days. Patients received LECIG morning doses corresponding to 80% (n = 5) or 90% (n = 6) of their individual morning dose of LCIG, 80% of the LCIG maintenance dose, and 80% of extra doses. The LECIG dose reduction was based on a previous study.[3] The duration of the infusions was 14 hours, and after the infusion stopped, the tube was flushed with water, as is needed with both treatments. Study nurses changed the syringe/cassette during the study and weighed them before and after the infusion. Oral levodopa-carbidopa immediate-release tablets were allowed after the infusion stopped and until 3 hours before the infusion started. Standardized low-protein meals were served at predefined times.

Pharmacokinetic Sampling and Motor Function Assessment

Blood samples on days 1 and 2 were drawn immediately prior to dosing, half-hourly between 0 and 3 hours, and hourly between 3 and 14 hours. A blood sample was collected within 5 minutes after flushing and then half-hourly between 14.5 and 17 hours.

During the interim analysis it was found that the entacapone was degraded by the stabilizer (sodium metabisulfite) used in the blood collection tubes; subsequently the blood samples were collected in 2 separate tubes, one with and one without stabilizer.

Trained study nurses assessed patient motor function according to the treatment response scale (TRS) at the same times as the pharmacokinetic sampling. The TRS is a 7-point scale ranging from -3 (severe parkinsonism) to 0 ("on" state without dyskinesia) to + 3 ("on" state with severe choreatic dyskinesia).[7]

Outcomes

The primary outcome was to compare the systemic exposure ($AUC_{0\text{-}14\,h}$) of levodopa after continuous infusion of LECIG and LCIG. Additional outcomes included TRS scores and safety and pharmacokinetics of levodopa, carbidopa, 3-OMD, and entacapone.

Safety Assessment

The patients were monitored for adverse events throughout the study.

TABLE 1. Pharmacokinetic parameters of LCIG and LECIG during 0 to 14 hours; mean (SD) values (n = 11)

	Treatment			
	LCIG	LECIG	*P*	Ratio LECIG/LCIG (95% CI)
Levodopa				
$AUC_{0\text{-}14}$[a] (ng·h/mL)	35,479.1 (14,693.0)	39,016.1 (17,327.6)	0.27	1.10 (0.95-1.17)
$AUC_{0\text{-}14/dose}$ (ng·h/mL)/mg	31.9 (9.4)	42.7 (14.1)	0.00013	1.34 (1.19-1.45)
C_{max}[a] (ng/mL)	3269.0 (1140.4)	3668.0 (1481.1)	0.089	1.12 (0.98-1.19)
Carbidopa				
$AUC_{0\text{-}14}$[a] (ng·h/mL)	5950.1 (3236.3)	5582.4 (3605.3)	0.03	0. 938 (0.815-0.990)
$AUC_{0\text{-}14/dose}$ (ng·h/mL)/mg	20.9 (7.7)	24.1 (11.3)	0.03	1.15 (1.02-1.22)
C_{max}[a] (ng/mL)	559.3 (292.4)	498.1 (297.8)	0.02	0.89 (0.79-0.98)
3-OMD				
$AUC_{0\text{-}14}$[a] (ng·h/mL)	154,714.1(56,931.0)	145,745.7 (61182.8)	0.21	0.94 (0.79-1.01)
$AUC_{0\text{-}14/dose}$ (ng·h/mL)/mg	—	—		
C_{max}[a] (ng/mL)	13,281.8 (4861.0)	13,518.2 (6116.2)	0.74	1.02 (0.82-1.15)
Entacapone				
$AUC_{0\text{-}14}$[a] (ng·h/mL)	—	5205.9 (1073.7)		
$AUC_{0\text{-}14/dose}$ (ng·h/mL)/mg	—	5.6 (1.1)		
C_{max}[a] (ng/mL)	0.03[b]	935.3 (550.9)		

[a]Results are presented as mean values (SD) for C_{max}, $AUC_{0\text{-}14}$, and CV.
[b]Geometric mean,

Statistical Analysis

A sample size of 15 patients was initially calculated for the study. A blinded interim analysis for sample size recalculation was done by estimating the coefficient of variation for $AUC_{0\text{-}14/dose}$ on the paired patient data. Based on this, a sample size of 11 patients was calculated.

All pharmacokinetic and statistical analyses were performed in R 3.2.2.[8] The following pharmacokinetic parameters for the analytes were estimated with the ncappc-package[9]: maximum concentration in plasma (C_{max}) and area under the plasma concentration-time curve between the hours 0 and 14 ($AUC_{0\text{-}14}$), using the trapezoid rule. For levodopa, carbidopa, and entacapone, the dose-adjusted $AUC_{0\text{-}14}$ ($AUC_{0\text{-}14/dose}$) was calculated by dividing $AUC_{0\text{-}14}$ with the total administered dose between the hours 0 and 14. Statistical comparison of $AUC_{0\text{-}14}$ and C_{max} for levodopa, carbidopa, and 3-OMD and $AUC_{0\text{-}14/dose}$ for levodopa and carbidopa was conducted with the paired, 2-tailed Student *t* test on the logarithmic values, with back-transformation to nominal values of point estimates and the 95% confidence interval (CI). The statistical comparison of the ordinal mean TRS scores was done with Wilcoxon's signed rank test.

Bioanalytical Assay

The blood sample analyses were conducted by OnTarget Chemistry, Uppsala, Sweden (at SVA laboratories), using the ultra-performance liquid chromatography/mass spectrometry method, validated in accordance with the Guideline on Bioanalytical Method Validation.[10]

Results

Patient Characteristics

Enrollment was conducted by the investigator. Of 12 screened patients 1 did not meet the inclusion criteria because of a too-high BMI. The 11 patients included had a mean age ± SD of 71.2 ± 4.1 years with 14 ± 5.1 years since diagnosis and a BMI of 23.8 ± 1.9 (Supplemental Table e-1). All 11 patients completed the study.

Pharmacokinetics and Motor Function

Systemic exposure ($AUC_{0\text{-}14}$) for levodopa did not significantly differ between treatments, but the dose-adjusted levodopa exposure ($AUC_{0\text{-}14/dose}$) was found to be significantly higher during LECIG administration compared with LCIG (Fig. 1, Table 1). Six patients had a 40% or higher increase in levodopa systemic exposure, whereas 3 patients had the expected 20% increase, and 2 patients did not reach the target systemic exposure. An incline in the levodopa LECIG plasma concentration profile during the day was observed. When increasing the morning dose of LECIG from 80% (n = 5) to 90% (n = 6), the initial levodopa plasma concentration-time profile mimicked the LCIG profile more closely (Supplemental e-Figure).

As expected, the mean $AUC_{0\text{-}14}$ for carbidopa was significantly lower with LECIG; however, $AUC_{0\text{-}14/dose}$ for carbidopa was found to be significantly higher. The 3-OMD concentration decreased during LECIG

administration. Three of 4 patients randomized to receive LCIG on day 2 had low but detectible plasma concentrations of entacapone left during the first hours of LCIG administration; maximum measured concentration was 0.03 μg/mL.

Mean TRS scores did not differ significantly between treatments ($P = 0.84$).

Adverse Events/Safety and Tolerability

Six adverse events (AEs) were reported by 2 patients (18%) after LCIG administration, and 10 adverse events were reported by 6 patients (55%) after LECIG administration. Headache was reported by 1 patient after administration of LCIG and 3 patients after LECIG administration. Five unique adverse events in 3 patients were assessed as related to study drug: nausea (1 event after each treatment), diarrhea (after LCIG administration), and dizziness and headache (both occurring after LECIG administration). All AEs were mild.

No serious or severe AEs were reported, and no AEs led to discontinuation or change in therapy. No clinically significant changes in vital signs, electrocardiograms, or physical examinations occurred.

Discussion

This is the first clinical trial performed with the levodopa-entacapone-carbidopa intestinal gel (LECIG). The results suggest that the required levodopa dose can be successfully reduced with LECIG without lowering levodopa exposure. Possible differences in COMT activity between individuals, seen as a higher-than-expected increase in $AUC_{0\text{-}14/dose}$, may have contributed to the higher variability in levodopa exposure after LECIG treatment.[11] The undesired levodopa plasma concentration increase during the day suggests that the dose for some patients could be decreased more than 20%, for example, by decreasing the flow rate of the maintenance dose in the afternoon. Mean TRS scores propose that LECIG can provide therapeutically effective plasma concentrations despite the dose reduction. The peak concentration observed after flushing the tube may be a challenge for patients who are susceptible to developing dyskinesia with small changes in dose.[12] It was observed to be most pronounced for entacapone because of its small central volume of distribution (0.08 ± 0.03 L/kg).[13]

Carbidopa has previously been reported to be a COMT substrate in vitro,[14] which may partly explain the observed higher dose-adjusted carbidopa AUC.

Entacapone displayed its coveted effect while decreasing 3-OMD plasma concentration during the LECIG treatment. The formation of 3-OMD requires methyl groups, which is hypothesized to be a part of a cascade of events that may lead to the development of neuropathy.[15] Speculatively, COMT inhibition may thus reduce the risk of this side effect.[16,17]

The reported AEs in this trial are common with both LCIG and oral administration of levodopa products and entacapone; however, this trial was short and with a small number of patients, which limited the possibility to detect rare and long-term side effects. However, entacapone is a well-established drug with known side effects and has been on the market for more than a decade, ensuring a thorough safety profile.

The main positive outcome from this treatment is the reduction in levodopa dose and 3-OMD concentration without the addition of oral entacapone several times daily. The patient population with the most to gain from this treatment is patients who have previously obtained good treatment effect and tolerability from oral entacapone.

A possibly similar effect may be achieved with opicapone, a newly developed COMT inhibitor with the advantage of once-daily administration, which has been found to be noninferior to entacapone.[18] The combination LCIG and opicapone could be a possible alternative to LECIG, but this needs to be investigated further.

Because of the short treatment time, conclusions have to be drawn with caution, and long-term comparative efficacy studies are needed to confirm the results and investigate the possible long-term side effects with the addition of entacapone. However, the present clinical trial indicates that LECIG may offer adequate therapeutic levodopa exposure at a lower dose, using a smaller pump, compared with LCIG. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.