HIGH LIGHT CME VIDEO

Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease

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Abstract—*Objectives:* To compare daytime intraduodenal levodopa/carbidopa infusion as monotherapy with individually optimized conventional combination therapies in patients with advanced Parkinson disease (PD) for motor fluctuations and quality of life (QoL). *Methods:* Twenty-four patients with motor fluctuations and dyskinesia were studied in a randomized crossover design to compare individualized conventional treatment and intraduodenal infusion of a levodopa/carbidopa gel for 3 + 3 weeks. Video scoring of motor function was assessed by blinded assessors on a global Treatment Response Scale from −3 to 0 to +3 (from severe "off" to "on" to "on" with severe dyskinesia). Patient self-assessment of motor performance and QoL was done using an electronic diary. *Results:* Median percentage of ratings in a functional "on" interval (−1 to +1) was increased from 81 to 100% by infusion therapy ($p < 0.01$). This improvement was accompanied by a decrease in "off" state ($p < 0.01$) and no increase in dyskinesia. Median Unified Parkinson's Disease Rating Scale score decreased from 53 to 35 in favor of infusion ($p < 0.05$). QoL was improved, using the two instruments: Parkinson's Disease Questionnaire-39 and 15D Quality of Life Instrument ($p < 0.01$). Adverse events were similar for both treatment strategies. *Conclusions:* Continuous intraduodenal infusion of the levodopa/carbidopa enteral gel as monotherapy is safe and clinically superior to a number of individually optimized combinations of conventional oral and subcutaneous medications in patients with motor fluctuations. Intraduodenal infusion of levodopa offers an important alternative in treating patients with advanced Parkinson disease.

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Continuous dopaminergic stimulation is the predominant treatment strategy for patients with Parkinson disease (PD) with motor fluctuations.[1] Levodopa combined with long-acting dopamine agonists and enzyme inhibitors is often prescribed.[2] The role of pharmacokinetics seems crucial for a stable motor response of antiparkinsonian drugs. Levodopa has a short half-life; thus, fluctuations in plasma concentrations are accompanied by fluctuations in motor performance.[3] Keeping levodopa concentrations as constant as possible is the target for oral drug development. New treatment strategies are needed for many patients because combinations of individually optimized conventional medications do not provide adequate control of motor performance. Deep brain stimulation (DBS) of the subthalamic nucleus or the internal globus pallidus[4] is currently the most widely investigated of the "last-line" therapies. Infusions of apomorphine,[5] lisuride,[6] and levodopa[7] are other options. DBS can produce remarkable improvement of advanced motor fluctuations, but severe complications may occur.[8] Earlier studies of IV and enteral infusions of water solutions of levodopa have shown a milder and more predictable pattern of side effects.[9,10] Several independent infusion studies have shown reduced fluctuations both in plasma levodopa

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levels and in clinical response,[11-13] but the delivery systems were impractical and the acceptance therefore was hampered. Thus, a new formulation of levodopa/carbidopa, intended for long-term enteral infusion therapy, has been developed (see Medication).[14] This formulation, allowing high concentrations of levodopa/carbidopa (20/5 mg/mL), has simplified infusion via a portable pump and an intestinal tube into a feasible treatment alternative.[7] The pharmacokinetics of this constant-rate infusion of levodopa/carbidopa has shown to be significantly smoother vs oral sustained-release tablets of levodopa/carbidopa in a crossover study.[15] In our experience, the levodopa/carbidopa gel infusion can successfully be used as monotherapy.[7] Therefore, infusion as monotherapy was compared with conventional medication in a randomized, controlled, crossover study. Nasoduodenal infusion of the levodopa/carbidopa gel was used in one treatment arm and any individually optimized combination of pharmacotherapy in the other arm. The study involved a new method for assessment of functional "on" time with and without dyskinesia and "off" time, namely, video scoring done by two blinded, independent raters.

Methods. *Patients.* Twenty-five patients (6 women and 19 men) with advanced, clinically diagnosed idiopathic PD, experiencing motor fluctuations and dyskinesia in spite of individually optimized treatment, were enrolled in the study from September 2002 to March 2003 (table 1). Exclusion criteria included atypical parkinsonism, dementia, severe psychiatric disorder, other substantial medical problems, or laboratory abnormalities. Patients were recruited by neurologists (four sites) or geriatricians (one site) in the reception areas of five hospitals in Sweden. All patients gave written informed consent. The protocol was approved by the ethics committees of each participating center. Assumption of sample size was based on data from two earlier studies of levodopa infusion using similar efficacy variables.[15,16] Based on 80% power to detect a significant difference, 6 to 19 patients were required. To compensate for nonevaluable patients, 25 patients were enrolled.

Study design. The study, called DIREQT (Duodopa Infusion: Randomized Efficacy and Quality of Life Trial), was a randomized, controlled, multicenter trial involving five centers in Sweden. At baseline, patients were examined according to figure 1. Patients were randomized (1:1) into Group 1 (n = 12), starting with conventional oral and, in some cases, combined with subcutaneous pharmacotherapy (Conventional), crossing over to daytime continuous intraduodenal levodopa/carbidopa gel infusion (Infusion) as monotherapy; or Group 2 (n = 12), with the treatments in the opposite order. When a patient was included in the study, treatment allocation was determined by calling Statisticon AB (Uppsala, Sweden); thus, allocation concealment was used. The randomization list, generated from a computer program at Statisticon AB, was stratified by site. There were no differences between the two groups for demographics or disease severity. The first week of each treatment arm was intended for dose adjustments so that both treatments would be optimized. One video recording day during each of weeks 2 and 3 of each treatment period was carried out with the patients hospitalized. Standard hospital meals were served. During these 4 days, patients were video recorded for 1 to 2 minutes every 30 minutes from 9 AM to 5 PM, that is, 17 recordings/day. The video sequences were subsequently assessed by two blinded, independent neurologists for the primary efficacy variable (see Video Scoring). On video recording days during the Conventional arm of the study, the patients were equipped with a dummy tube inserted into one nostril so that the actual treatment arm could not be judged from the video sequences, thus ensuring a blinded assessment. Only the assessors were blinded, whereas allocation was open to patients and investigators for practical reasons regarding dose adjustments. Patient self-assessments of motor performance and quality of life (QoL) using an electronic diary were performed on the remaining 12 days of weeks 2 and 3 of each treatment period. On these days, patients were in their home environment. The Unified Parkinson's Disease Rating Scale (UPDRS) was used at baseline and at the end of each treatment arm as a secondary efficacy variable, and modified Hoehn and Yahr staging was used at baseline and at the end of the study.[17] A retrospective and a prospective period, both of 6 months, were also included in the trial, intended for assessment of QoL and health economy (to be reported separately).

Medication. In the Conventional arm, patients used their individual combinations of medications present at baseline for both daytime and nighttime. All 24 patients used oral levodopa combined with a decarboxylase inhibitor. Other conventional oral drugs were the catechol-*O*-methyltransferase (COMT) inhibitors entacapone (n = 10) and tolcapone (n = 3), the dopamine agonists bromocriptine (n = 4), cabergoline (n = 4), pramipexole (n = 4), and ropinirole (n = 4), the monoamine oxidase-B (MAO-B) inhibi-

Table 1 *Patient demographics and clinical data at baseline*

	Group 1: Conventional/ Infusion		Group 2: Infusion/ Conventional	
Patients, no.	12		12	
Sex, no.				
Female	3		3	
Male	9		9	
Symptoms responsive to L-dopa, no.	12		12	
Wearing off of L-dopa effect, no.	10		11	
Start hesitation, no.	11		12	
Unpredictable "off" states, no.	11		11	
Dyskinesias in response to L-dopa intake, no.	12		12	
Dystonia in response to L-dopa intake, no.	11		9	
	Median	Range, min–max	Median	Range, min–max
Age, y	68	51–79	64	50–75
Age at onset of PD, y	56	38–67	50	37–63
Years with L-dopa treatment	13	6–18	13	5–21
UPDRS at baseline				
I	3.5	0–7	3.0	0–9
II	16.0	11–27	17.5	9–26
III	36.5	14–53	25.5	12–61
IV	9.5	3–12	10.0	6–12
Sum	66.5	37–82	59.0	36–92
Hoehn & Yahr at baseline				
Best	3	2–4	2	2–4
Worst	4	3–5	4	2–5

Conventional = conventional oral and subcutaneous pharmacotherapy; Infusion = intraduodenal levodopa/carbidopa gel infusion; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

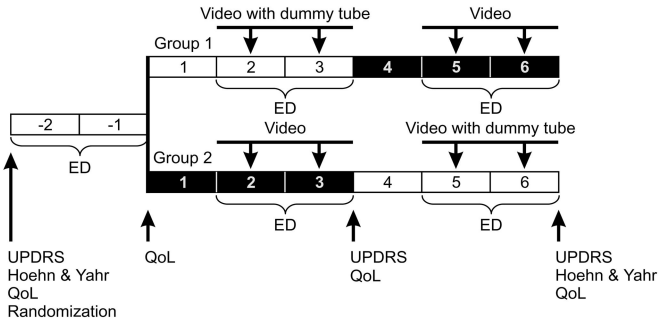

Figure 1. Study design. Black boxes denote duodenal levodopa/carbidopa gel infusion and white boxes conventional pharmacotherapy. Arrows pointing downward indicate video recording days with recordings for 1 to 2 minutes every 30 minutes for 8 hours. Arrows pointing upward indicate performance of different clinical tests. Numbers indicate weeks. ED = electronic diary; UPDRS = Unified Parkinson's Disease Rating Scale; QoL = quality of life.

tor selegiline (n = 4), and the glutamate antagonist amantadine (n = 3). The dopamine agonist apomorphine was used for subcutaneous injections (n = 4) and continuous infusion (n = 4) at baseline and in the Conventional arm. Median number of drug intakes per day was 10 (range 5 to continuous infusion). In the Infusion arm, the only antiparkinson medication allowed during daytime was intraduodenal infusion of levodopa/carbidopa. During nights, only levodopa tablets were permitted. Each morning, a bolus dose was given to rapidly reach an individually optimized level of motor function. The levodopa/carbidopa gel used was Duodopa (NeoPharma AB, Uppsala, Sweden). This formulation is an aqueous suspension containing 20 mg/mL levodopa and 5 mg/mL carbidopa as active ingredients in 2.92% carmellose sodium (carboxymethylcellulose). The levodopa/carbidopa ratio (4:1) is the same as in commonly used oral formulations. The gel was administered by a portable pump (CADD-Legacy Duodopa; Smiths Medical, Minneapolis, MN) into nasoduodenal Bengmark tubes (Nutricia, Switzerland). Nasoduodenal tubes were used in this short-term study to avoid unnecessary surgery. Long-term treatment with the levodopa/carbidopa gel infusion requires a transabdominal tube.[7] Dose adjustments for individual optimization were principally made in both treatment strategies during the first week of each treatment period and were allowed throughout the study, except during the 4 video recording days. The patients were allowed to use rescue medication, even on video recording days, if needed. During the Conventional arm, extra levodopa tablets or apomorphine injections could be used, if previously prescribed. During Infusion, bolus doses of 2 to 40 mg of levodopa could be self-administered via the pump.

Video scoring. Each of the 17 video sequences recorded on video recording days (see figure 1) contained the following tasks: finger tapping, alternating hand movements, rising from a chair, and walking.[7,15] Examples of the videos can be viewed on the *Neurology* Web site (www.neurology.org). Assessments of the video sequences were made by two blinded, independent senior neurologists after the study. The order of the recordings was randomized between days using a newly developed software program (NeuroRating; Animech, Uppsala, Sweden). All video recordings (>1,200 video sequences) were installed on two laptop computers together with a rating form for the items described below. The assessors were trained before the study, using video recordings from previous studies. The blinding of the video sequences was broken when all assessments were finalized. The operational definitions of the motor examination part of the UPDRS were used for finger tapping (item 23), rapid alternating movements of hands (item 25), arising from chair (item 27), gait (item 29), and bradykinesia (item 31). These items were considered to be the most relevant and convenient for the brief recordings. Percentages of ratings within the interval 0 to 1 of the five UPDRS items were calculated as secondary efficacy variables. Dyskinesias observed on the video recordings were reported using the definitions of the Dyskinesia Rating Scale.[18] A Treatment Response Scale (TRS) was used for a global assessment of clinical response. The TRS ranges from −3 (severe "off") to +3 ("on" with severe dyskinesia), where 0 is "on" without any dyskinesias. Some of the UPDRS items excluded above, such as tremor, posture, and facial expression, could thus be incorporated into the global assessment of the TRS. The primary efficacy variable was the percentage of ratings within the interval −1 to +1, that is, a clinically desirable, functional "on" state accepting mild parkinsonism or mild dyskinesia, and percentage of ratings within the intervals −3 to −2 (severe to moderate "off") and +2 to +3 ("on" with moderate to severe dyskinesia). In everyday practice, most patients prefer being dyskinetic before being "off." However, severe choreatic dyskinesia may be incapacitating and painful. Therefore, a secondary analysis of the interval −1 to +2, including moderate dyskinesia, was also used. Interrater reliability was assessed using percentage agreement between the raters and κ coefficients. Kappa coefficients between 0.60 and 0.80 are considered "good" and coefficients higher than 0.80 "very good." The simple κ coefficient for interrater reliability in the current study was 0.68, that is, "good," and the percentage agreement between raters was 90.9%, which is very satisfactory. A number of video recording days were selected for additional evaluation after an interval of several weeks to test the intrarater reliability. The mean simple κ coefficient was 0.83, and mean intrarater percentage agreement was 94.4%.

Self-assessments. For patient self-assessment of motor function and QoL in the home environment (figure 1), an electronic diary comprising a hand-held computer with integrated cellular phone for real-time data transfer was used as a secondary efficacy variable.[19] Patients were alerted by an alarm in the computer to respond to questions on the touch screen four times daily (at 8.00 AM, noon, 4.00 PM, and 8.00 PM) during the 2 baseline weeks and during the last 2 weeks of each treatment arm, except for the video recording days. The questions were to be responded to within 20 minutes. The responses were stored within the device and transferred to a centralized electronic database via the cellular phone. Seven day questions (DQs) were included in the electronic diary:

DQ1: Have you had problem walking 100 m the last 4 hours?

DQ2: Have you been "off" (stiff, slow, or shaking) the last 4 hours?

DQ3: Have you been hyperkinetic the last 4 hours?

DQ4: Have you had difficulties with your daily chores the last 4 hours?

DQ5: Have you had any muscular cramps or spasms the last 4 hours?

DQ6: Have you felt depressed the last 4 hours?

DQ7: Have you been satisfied with your overall functioning the last 4 hours?

At 8.00 AM, the seven DQs were asked with respect to "this morning" instead of "the last 4 hours." Two additional morning questions (MQs) were asked:

MQ1: How did you sleep last night?

MQ2: Could you turn over in bed last night?

As the patients' medication during nights was different than during daytime (oral medication only), the MQs are reported separately. Each question had five response alternatives from 1 = severe disability (i.e., not able to walk, "off" all the time, hyperkinetic all the time, difficulties with chores all the time, dystonia all the time, very depressed, not at all satisfied) to 5 = no disability (i.e., fully able to walk, not at all "off"/hyperkinetic/difficulties with chores/dystonic/depressed, completely satisfied). The scores at noon, 4.00 PM, and 8.00 PM for each DQ for each patient were averaged over the 14-day baseline and the 12 days during each treatment period as a measure of her/his experiences. Increased scores indicate improvement. The Parkinson's Disease Questionnaire (PDQ-39)[20] and the generic 15D Quality of Life Instrument[21] were used to evaluate the health-related QoL. These instruments were applied at baseline and at the end of each treatment arm as secondary efficacy variables.

Safety evaluation. Adverse events were queried using open-ended questions at all visits. Routine clinical laboratory tests, EKGs, and physical examination were conducted at enrollment and at the end of each treatment arm.

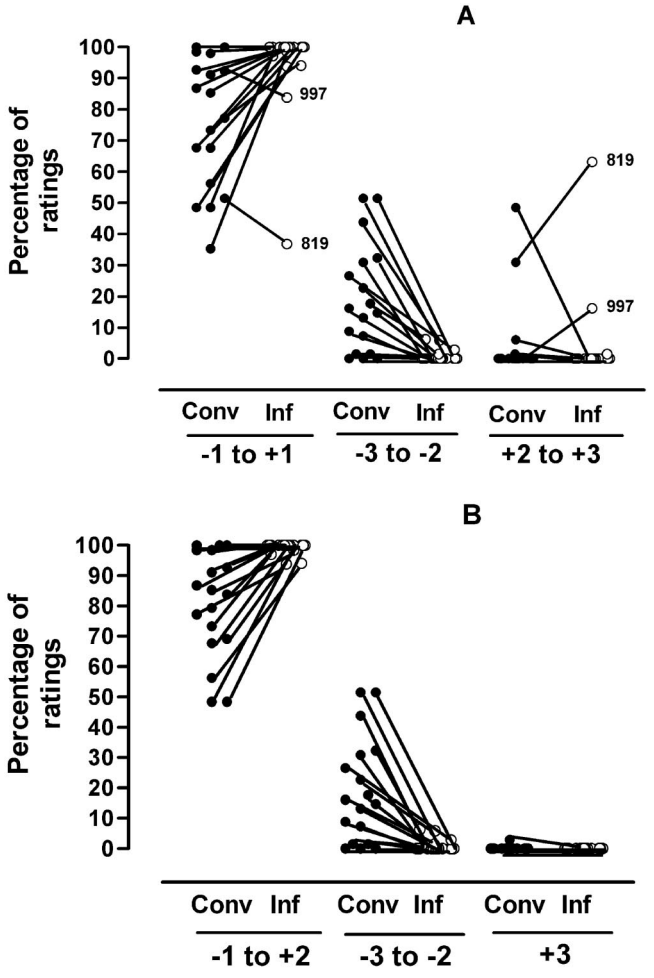

Figure 2. Individual percentages of ratings in different motor states on the Treatment Response Scale. (A) Desired functional "on" interval including mild "off" and mild dyskinesia (−1 to +1). (B) Extended functional "on" interval including mild "off" and moderate dyskinesia. Patients 819 and 997 are marked to show that their decrease in the desired "on" interval on Infusion was explained by an increase in moderate dyskinesia. Data are from the per-protocol population (n = 18). Conv = conventional oral and subcutaneous pharmacotherapy; Inf = intraduodenal levodopa/carbidopa gel infusion.

Statistics. The primary efficacy variable for each patient, that is, the percentage of ratings spent within the interval −1 to +1 (functional "on") was calculated for the treatments by averaging results from each rater and treatment day. The change in percentage of ratings spent in the −2 to −3 ("off") and the +2 to +3 ("on" with dyskinesia) interval was also calculated. Treatment success was defined as a significant increase in percentage of ratings spent in the interval −1 to +1. Mean and median values of the percentage of ratings were calculated for each treatment period together with mean and SDs as well as median, quartiles, and range of the within-subject differences. Analyses were performed on the within-subject differences for the intention-to-treat (ITT) population and the per-protocol (PP) population. The ITT population consists of all patients who started to receive Infusion treatment, but only 21 patients received Infusion during the video recording days. Twenty patients received Conventional therapy during the video recording days. The PP population consists of all patients correctly included, fulfilling at least 82% of each video recording day per 3-week period and receiving study treatment according to the study design. In the ITT analyses, a within-subject difference of 0 was assigned to patients with data from only one of the treatments. All comparisons were performed as two sided, at the 5% significance level, using the Wilcoxon signed rank test.

Results. Six patients dropped out from the study, and 18 patients qualified for the PP population. One patient did not enter the crossover part because of relapse of inguinal hernia, and two patients withdrew their consent on the first day of Infusion because they could not tolerate either the nasoduodenal tube or the pump. Two patients had confusion during the Infusion procedure: One withdrew his consent after pulling the tube out twice, and the other was removed from the study because of severe insomnia. One patient withdrew his consent after the Infusion period because he was so satisfied with the infusion that he did not want to return to his conventional therapy. One patient was excluded from the PP analysis because he continued his previous treatment with bromocriptine into the Infusion treatment phase, thus violating the protocol that stipulated Infusion as monotherapy. Two other patients changed levodopa treatment 2 to 28 days before baseline, violating the protocol's request of 4 weeks of unchanged medication before baseline, but were accepted for the PP analysis. The baseline demographic and clinical characteristics are shown in table 1.

Video scoring. The results of the primary variable are shown in table 2 (ITT population) and figure 2 (PP population). Moderate to severe "off" state (−2 to −3) was markedly reduced in all patients during treatment with Infusion. Moderate to severe dyskinesia (+2 to +3) was uncommon in both treatment arms. The median difference of ratings in the desired, functional "on" interval −1 to +1 on the TRS between the Infusion and Conventional treatments for the PP population was 14% (range −15 to 63%; n = 18, $p < 0.01$). The two patients (Patients 819 and 997) who had negative difference, that is, less ratings in the functional "on" state on Infusion, both had a significant

Table 2 *Percentage of ratings in different motor states on Treatment Response Scale*

	Conventional, n = 20			Infusion, n = 21			
	Median	Range	Mean ± SD	Median	Range	Mean ± SD	*p* Value
−1 to +1 (functional "on")	81.3	18–100	74.5 ± 24.6	100	37–100	90.7 ± 19.2	<0.01
−3 to −2 ("off")	15.4	0–51	19.2 ± 17.9	0	0–22	1.8 ± 5.0	<0.01
+2 to +3 ("on" with dyskinesia)	0	0–49	6.3 ± 14.6	0	0–63	7.5 ± 17.3	1

The *p* values are based on the intention-to-treat population (n = 24), where the difference between the treatments was set to zero for patients with data from only one treatment arm.

Conventional = conventional oral and subcutaneous pharmacotherapy; Infusion = intraduodenal levodopa/carbidopa gel infusion.

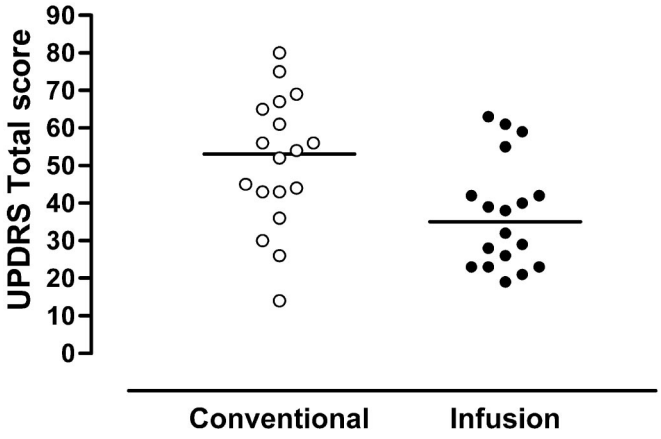

Figure 3. Individual total scores of Unified Parkinson's Disease Rating Scale (UPDRS) at the end of each treatment arm. Horizontal bars represent median values. The difference is significant in favor of Infusion. Data are from the per-protocol population (n = 18). Conventional = conventional oral and subcutaneous pharmacotherapy; Infusion = intraduodenal levodopa/carbidopa gel infusion.

decrease in the "off" state and increased number of ratings in +2 (moderate dyskinesia) (see figure 2). The preplanned analysis of the broader TRS interval −1 to +2 showed a median percentage of ratings of 84.6% (range 49 to 100%) with Conventional and 100% (range 75 to 100%) with Infusion (ITT population). Median percentage of ratings in +3 was 0% (range 0 to 3%) for both treatments in the ITT population. Although patients fulfilled the inclusion criteria with motor fluctuations and dyskinesias, five of the ITT patients had >98% of ratings within the functional "on" interval (−1 to +1) on Conventional. The median percentages of scores within 0 to 1 (no or mild symptoms) of the five UPDRS items assessed from the video tapes were all significantly increased with Infusion vs Conventional (see table E-1 on the *Neurology* Web site). The median difference between treatments was largest for bradykinesia (21%) and smallest for rising from chair (2%). Video assessment of dyskinesias revealed no significant differences between the treatments (see table E-1 on the *Neurology* Web site). Dystonia represented a small part of the dyskinesias; the median value was 0 for both treatments.

Rating scales. Median total UPDRS score at the end of each treatment arm was 53 with Conventional and 35 with Infusion (n = 18, $p < 0.05$) (figure 3; see table E-2 on the *Neurology* Web site). Infusion provided lower median scores in all parts of the UPDRS; Parts I, II, and IV showed a significant improvement, whereas improvement in Part III was not significant ($p = 0.06$) (see table E-2 on the *Neurology* Web site). Median PDQ-39 summary index was 35 (range 16 to 55) with Conventional and 25 (range 10 to 42) with Infusion, that is, higher QoL with Infusion (n = 18, $p < 0.01$). Median scores of seven of the eight dimensions of the PDQ-39 were significantly decreased with Infusion (mobility, $p < 0.01$; activities of daily living, $p = 0.03$; emotional well-being, $p = 0.03$; stigma, $p = 0.03$; cognitions, $p = 0.01$; communication, $p = 0.03$; bodily discomfort, $p = 0.01$). The remaining dimension "social support" was unchanged ($p = 0.16$). PDQ-39 summary index and two of the most relevant dimensions for patients on Infusion treatment are shown in figure E-1 on the *Neurology* Web site. Median total score of the generic QoL instrument 15D was increased from 0.72 (range 0.58 to 0.88) to 0.78 (range 0.64 to 0.95) with Infusion (n = 18, $p < 0.01$), meaning higher QoL with Infusion. Table 3 shows results from the electronic diary. Among the DQs, dyskinesia was reported to be unchanged, whereas the other six questions were improved on Infusion.

Table 3 *Electronic diary*

	Morning					Day				
	Conventional		Infusion			Conventional		Infusion		
Question	Median (range)	Mean	Median (range)	Mean	*p* Value	Median (range)	Mean	Median (range)	Mean	*p* Value
MQ1: Sleep last night?	3.5 (2.8–4.8)	3.7	3.9 (2.8–4.4)	3.8	0.23	—	—	—	—	—
MQ2: Able to turn in bed?	3.1 (1.0–4.0)	2.8	3.2 (1.7–4.1)	3.1	0.04	—	—	—	—	—
DQ1: Difficult walking 100 m?	2.9 (1.2–4.0)	2.8	3.6 (2.5–4.3)	3.4	<0.01	3.5 (2.2–4.2)	3.4	4.0 (2.5–5.0)	4.0	<0.01
DQ2: Been "off"?	2.9 (2.1–4.8)	3.0	3.8 (2.4–4.9)	3.6	<0.01	3.3 (2.4–4.2)	3.3	4.0 (2.7–4.8)	3.9	<0.01
DQ3: Been dyskinetic?	4.6 (3.3–5.0)	4.5	4.4 (3.3–5.0)	4.4	0.62	4.2 (2.4–4.8)	4.1	4.0 (2.0–5.0)	3.9	0.26
DQ4: Difficulty with chores?	3.2 (2.0–4.0)	3.2	3.7 (2.2–4.3)	3.6	0.02	3.8 (2.5–4.3)	3.6	3.9 (2.8–4.9)	4.0	0.01
DQ5: Muscular cramps/spasms?	3.9 (1.9–5.0)	3.7	4.1 (2.0–5.0)	4.0	0.09	4.0 (2.4–5.0)	3.9	4.2 (2.6–5.0)	4.1	0.09
DQ6: Depressed?	4.0 (2.8–5.0)	4.0	4.0 (2.8–5.0)	4.1	0.27	3.9 (2.5–5.0)	4.0	4.3 (2.6–5.0)	4.2	0.12
DQ7: Satisfied with functioning?	3.0 (1.0–3.9)	2.7	3.4 (1.3–4.6)	3.4	<0.01	3.2 (1.0–4.0)	2.9	3.5 (1.3–4.8)	3.4	<0.01

Data are from the per-protocol population (n = 18). The questions are abbreviated for the table. Complete questions are given in Methods. Morning questions (MQs) were posed at 8 AM daily during 12 days during each treatment arm. Daily questions (DQs) were posed at noon, 4 PM, and 8 PM during 12 days during each treatment arm. The daily questions were also posed at 8 AM (morning) but are presented separately. Each question had five response alternatives: 1 = severe disability to 5 = no disability.

Conventional = conventional oral and subcutaneous pharmacotherapy; Infusion = intraduodenal levodopa/carbidopa gel infusion.

Table 4 *Adverse events experienced by two or more patients*

	Conventional: no. of patients, n = 21	Infusion: no. of patients, n = 24
Dyskinesia/hyperkinesia	7	4
Constipation	6	2
Depression	5	3
Insomnia	5	1
Somnolence	4	3
Dystonia	3	0
Palpitation	3	0
Anxiety	3	3
Dizziness	2	0
Headache	2	4
Agitation	2	2
Diarrhea	1	2
Sweating increased	1	2
Anorexia	0	2
Confusion	0	2
Accident NOS (falling)	0	2

Conventional = conventional oral and subcutaneous pharmacotherapy; Infusion = intraduodenal levodopa/carbidopa gel infusion; NOS = not otherwise specified.

Medication. Levodopa infusion rates were on average 94 mg/h (range 26 to 196 mg/h; n = 18) on video recording days. The morning bolus doses ranged between 20 and 200 mg of levodopa. Bolus doses administered with the pump as rescue medication were used on average once per 8-hour video recording period (range zero to five times). The bolus doses were generally small, a mean of 24 mg (range 12 to 40 mg), but one patient used 140 mg on one occasion. Infusion times were on average 16.5 hours (range 14.2 to 19.3 hours). Infused daily levodopa doses ranged between 456 and 3,556 mg.

Adverse events. Safety, as judged from adverse events, laboratory findings, vital signs, and EKG, did not differ between the two treatments. Adverse events occurred in 16 patients on Conventional and in 17 patients on Infusion and were mostly mild. All adverse events affecting more than one patient are listed in table 4. There were three serious adverse events. One 75-year-old patient developed insomnia and confusion on Infusion and was withdrawn from the study. One 59-year-old patient needed hospitalization because of deterioration of depression after discontinuation of an antidepressant while on Infusion. One 65-year-old patient had syncope and commotio cerebri while on Conventional treatment. The two latter cases were regarded as probably unrelated to medication.

Follow-up. After the study, 16 of the 24 patients (67%) in the ITT population chose to be treated with continuous daytime enteral infusion by a permanent tube system.

Discussion. We compared monotherapy with continuous intraduodenal infusion of a new stable formulation of levodopa/carbidopa with individual combinations of conventional pharmacotherapy. Because this new drug delivery system is not easily investigated in a placebo-controlled, double-blind, double-dummy design, we introduced blinded rating using video recordings (to be published separately) and self-rating using newly developed electronic home diaries.[19] Comparing this drug delivery system with best possible conventional treatment is also more clinically relevant than using a placebo control. The risk of encountering the placebo effect should be taken into account in this short-term study where a new medication is compared with a combination therapy that is well known for the patients (unchanged for at least 4 weeks). However, it seems unlikely that patients with very advanced PD would be improved for 3 weeks only because of the placebo effect. The use of blinded neurologists for the assessment of motor function has removed a possible rater bias in this study. The interrater reliability and the percentage agreement of the two raters were good, which underscores the robustness of the study. The use of real-time data capture within the electronic patient diary provides more reliable data as compared with paper diaries, with respect to compliance, that is, missing data or retrospective data entry.[22] All patients were reported to be individually optimized with regard to conventional treatment at baseline. The median frequency of drug intakes in various combinations of levodopa, COMT inhibitors, MAO-B inhibitor, amantadine, and dopamine receptor agonists was 10 times per day, which illustrates the complex therapeutic situation for many patients with advanced PD. The blinded assessment of motor fluctuations using video recordings revealed a difference in favor of Infusion in percentage of ratings in the TRS. The results of the assessment are supported by significant differences in favor of Infusion on simultaneous assessments of the five UPDRS items and other secondary outcome measures. Thus, Infusion provided lower median scores in all parts of the UPRDS, and several important items ("off" time, walking, satisfaction with overall functioning) in the electronic home diary were improved. Further, patients reported significantly improved scores in the two QoL instruments PDQ-39 and 15D in favor of Infusion. The appreciation of the Infusion procedure is also illustrated by the fact that 16 of the 24 patients randomized in the study later chose to have treatment by a permanent infusion system. The adverse events were typical for patients with PD treated with levodopa and dopamine receptor agonists and were reported approximately equally for Infusion and Conventional. There was one serious adverse event in a 75-year-old patient (insomnia and confusion), which was probably related to the nasoduodenal infusion. The results are in accordance with earlier studies,[7,10] which show that levodopa infusion is well tolerated and that complications are less frequent than reported for DBS.[4,23] Intraduodenal infusion of the levodopa/carbidopa gel thus represents a good alternative for patients with fluctuating PD before options such as DBS need to be considered

or for patients in whom DBS is considered not suitable. The patient population in this study had advanced disease, with motor fluctuations and dyskinesias in spite of individually optimized combinations of conventional pharmacotherapy. Eight patients were either previously or currently treated with apomorphine, but none had tried apomorphine infusion as monotherapy. Dyskinesias were mild in most patients. This probably reflects the aim to keep dopaminergic therapy as low as possible to prevent side effects such as dyskinesias and hallucinations. Thus, the main problem for these fluctuating patients was frequent "off" episodes. On Infusion, "off" episodes were dramatically reduced without causing more dyskinesia. Alleviation of interdose trough disability is important for increased "on" time.[24] We have previously demonstrated that significantly lower variability in plasma levodopa can be achieved with infusion of the levodopa/carbidopa gel suspension compared with oral sustained-release tablets.[15] The therapy is thus consistent with the advantages offered by continuous dopaminergic stimulation.[25] The pharmacokinetic study also showed significantly improved motor performance during infusion.[15] A number of open-label studies on small numbers of patients have suggested that enteral levodopa infusion is effective against motor fluctuations and dyskinesias, but these studies did not fit into the Level I criteria of the evidence-based review performed by the Movement Disorders Society.[2] One double-blind, placebo-controlled study of intraduodenal levodopa infusion has been published, showing significant decrease in plasma levodopa variability and significant increase in "on" time.[13] The outcome of our study is consistent with previous studies of the effects of enteral levodopa infusion on motor fluctuations and dyskinesias, although a broad variety of study designs have been used. Blinded motor assessment has not been performed previously, however. The selection of patients for our study excluded patients with dementia and severe psychiatric disorders and is hence not fully representative for the population with advanced, fluctuating PD. However, the results can probably be generalized to the rest of that population, because of the wide spectrum of age (50 to 79 years) and age at onset of PD (37 to 67 years) in this study. The size and duration of this trial require follow-up of a longer duration of infusion treatment, which has been performed and will be reported separately. For long-term therapy, monotherapy with levodopa/carbidopa gel infusion is recommended because it facilitates both the adjustments in dosage and the assessment and management of adverse events. Education of physicians, nurses, patients, and relatives is needed to initiate levodopa infusion therapy. Long-term treatment requires a permanent infusion system with an intestinal tube inserted via gastrostomy. A team involving a neurologist/geriatrician, a specialized nurse, and a surgeon or a radiologist is needed for proper follow-up. Technical complications due to the infusion system occur but are generally mild.[7,10] The gel infusion concept is feasible in the home environment, as proven in this short-term study and in previous long-term observations.[7] The practicality, cost, efficacy, and side effect profile of levodopa infusion therapy should be compared with other invasive strategies in advanced PD, for example, apomorphine infusion monotherapy and DBS. Today, such a comparison can be based on only a few cases. We conclude that continuous intraduodenal levodopa/carbidopa gel infusion as monotherapy is clinically superior to a number of individually optimized combinations of conventional medications in patients with PD with motor fluctuations and dyskinesias.

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Correction

Prevalence of multiple sclerosis in a residential area bordering an oil refinery

The Introduction of "Prevalence of multiple sclerosis in a residential area bordering an oil refinery" (*Neurology* 2004;63:1796–1802) by Neuberger et al. should have stated: "The initial description and results of this study were written by the authors and published as a peer reviewed final report by the Agency for Toxic Substances and Disease Registry (ATSDR). In addition to information from that Final Report, this manuscript provides more details concerning the study."

Reference

Agency for Toxic Substances and Disease Registry, Final Report: Multiple Sclerosis Prevalence: Independence and Sugar Creek, Missouri. Atlanta, GA: US Department for Health and Human Services, Public Health Service, February 2004.

In addition, the acknowledgment should have included the statement: "The contents of this article are soley the responsibility of the authors and do not necessarily represent the official views of ATSDR."

Prevalence of multiple sclerosis in a residential area bordering an oil refinery

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