Movement Disorders
Vol. 23, No. 8, 2008, pp. 1130–1136

Efficacy of Long-Term Continuous Subcutaneous Apomorphine Infusion in Advanced Parkinson's Disease with Motor Fluctuations: A Multicenter Study

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Received 4 October 2007; Revised 18 February 2008; Accepted 29 February 2008

Published online 28 April 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22063

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Abstract: Continuous subcutaneous apomorphine infusion (CSAI) is, at present, an alternative option for advanced Parkinson's disease (PD) with motor fluctuations. We studied the evolution of patients with PD and severe motor fluctuations long-term treated with CSAI. We reviewed data from 82 patients with PD (mean age, 67 ± 11.07; disease duration, 14.39 ± 5.7 years) and severe motor fluctuations referred to 35 tertiary hospitals in Spain. These patients were long-term treated (for at least 3 months) with CSAI and tolerated the procedure without serious side effects. We compared the baseline data of these 82 patients (before CSAI) with those obtained from the last follow-up visit of each patient. The mean follow-up of CSAI was 19.93 ± 16.3 months. Mean daily dose of CSAI was 72.00 ± 21.38 mg run over 14.05 ± 1.81 hours. We found a statistically significant reduction in off-hours, according to self-scoring diaries (6.64 ± 3.09 vs. 1.36 ± 1.42 hours/day, $P < 0.0001$), total and motor UPDRS scores ($P < 0.0001$), dyskinesia severity ($P < 0.0006$), and equivalent dose of antiparkinsonian therapy (1,405 ± 536.7 vs. 800.1 ± 472.9 mg of levodopa equivalent units $P < 0.0001$). CSAI is an effective option for patients with PD and severe fluctuations, poorly controlled by conventional oral drug treatment. © 2008 Movement Disorder Society

Key words: apomorphine; Parkinson's disease; subcutaneous infusion; motor fluctuations; levodopa-induced dyskinesias

Apomorphine was the first dopamine receptor agonist used to treat Parkinson's disease (PD).[1,2] It is a short-acting dopamine D1 and D2 receptor agonist,[3,4] and its potency, in pharmacological studies, is qualitatively and quantitatively similar to levodopa (L-dopa).[3–5] Subcutaneous apomorphine is currently used for the management of sudden, unexpected, refractory, L-dopa-induced "off" states in fluctuating PD and for the treatment of dopa-related dyskinesias. Other indications include the challenge test for determining the dopaminergic responsiveness, and finding the appropriate dose of the drug in intermittent subcutaneous administration.[3–31]

The efficacy of intermittent subcutaneous apomorphine injection has been confirmed in several controlled studies.[26–31] Furthermore, the efficacy of continuous subcutaneous apomorphine infusion (CSAI) has been evaluated in monotherapy or as an add-on to L-dopa therapy in advanced PD through several open-label studies, including more than 400 patients. These clinical experiences are summarized in Table 1.[6–24]

These studies confirmed that CSAI is efficacious in patients with motor fluctuations. It reduces off periods, improves dopa-related dyskinesias, and usually reduces oral drug therapy.[8,13,16,23] However, CSAI is not devoid of side effects, including cutaneous reactions and neuropsychiatric complications. Today, the real impact of CSAI in advanced PD is still a matter of debate, and since other useful alternatives are already available, including deep brain stimulation (DBS), large, well-designed, randomized, multicenter, controlled, long-term, and prospective clinical trial is needed in order to properly evaluate the pros and cons of each technique.

We analyzed clinical data of 82 patients, studied in a large number of tertiary care centers, long-term treated with CSAI, and who had achieved a stable response.

PATIENTS AND METHODS

We identified 166 PD patients who had received CSAI over the last 5 years. This included all patients

TABLE 1. *Summary of the main findings of open-label studies using continuous subcutaneous apomorphine (APO) infusions in the long-term treatment of advanced Parkinson's disease*

Patient characteristics				APO treatment			Change (vs. APO treatment)			
n	Age (yr)	Duration of disease (yr)	Hoen and Yahr stage	Duration of follow up (mo)	Duration of infusion (hr/day)	Total dose per day (mg)	Daily time in off. (%)	Dyskinesia intensity (%)	Daily levodopa dose (%)	Reference
25	58.8	17.8	4.1	22	20.1	89	−55		−22	Frankel et al.[6]
25	64.7	16	4.5	44	24	112.5	−50	−14	−50	Pietz et al.[7]
22	60.6	19.2		36.5	12.7	70	−59		16	Hughes et al.[8]
19				34.8	12	77.6	−72	−65	−80	Colzi et al.[9]
11	56	14.4		8	14	77	−62		−73	Stibe et al.[10]
10	60	11.5	3.7	12	12	38	−58	−40	−48	Stocchi et al.[11]
18	60.2	12.4	3.8	20.6	24	160	−58		−78	Poewe et al.[12]
16	60	11	3–5	57	24	162	−55		−55	Wenning et al.[13]
30	62	14	4.2	60	12	52			−50	Stocchi et al.[14]
12	64.3	14.4	4.5	24		31	−80		−23	Kanovský et al.[15]
64	60.3	15.7		33.8	12–24	98	−49	−57	−63	Manson et al.[16]
7	59	17	3–5	11	8–12	29.7	−85	−45	−39	Chaudhuri et al.[17]
9	52	15	5	10	12–24	93	−67	−20	−53	Pollak et al.[18]
14	60.2	12.4	3.8	26	24	151.7	−77		−81	Kreczy-Kleedorfer et al.[19]
7	61.1	17.6	4	3		50.4	−58		−50	Gancher et al.[20]
12	54	10	3.7	24		100	−60	−48	−52	Morgante et al.[21]
80	50.9	10		25.1	13.5	69.8			−24	Tyne et al.[22]
12	61.3	14.5	4	6	13.4	75.2	−38	−31	−55	Katzenschlager et al.[23]
13	59	10	3–5	12		74.78	−51	0	−29	De Gaspari et al.[24]
82	67	14.39		19.93	14.05	72	−79.51	−32.14	−32.9	Present study
406	59.1	14.1	4.1	24.7	17.1	84.8	−60.8	−35.6	−47.5	Synopsis

who had started therapy since 2003 but were still on treatment at follow-up in March 2007, when this audit was initiated. They were referred to tertiary care centers in Spain because of advanced PD associated with motor fluctuations, not adequately controlled with oral antiparkinsonian therapy. All of them met the clinical criteria for the diagnosis of PD.[32] Of these patients, we excluded 68 from analysis after they dropped out of CSAI before March 2007 for different reasons, including:

a. change of treatment: DBS (13 patients) and duodenal infusion of L-dopa (4 patients);
b. incomplete or insufficient response (8 patients);
c. lack of collaboration, caregiver support, and/or poor acceptance of CSAI (9 patients);
d. secondary side effects: psychosis (9 patients), subcutaneous skin nodules (4 patients), impairment or previous cognitive decline (4 patients), hemolytic anemia (HA) (1 patient), and severe chronic headache (1 patient);
e. medical problems not related with CSAI (11 patients); and, finally,
f. unknown reasons: loss to follow-up/case-notes unavailable (4 patients).

In addition, we excluded 16 patients who had been on CSAI for less than 3 months when this audit started.

Finally, for analysis we selected 82 patients (age: 67 years [23–85]; gender [M-F]: 34–48; duration of PD [years]: 14.3 ± 5.7) who tolerated the procedure for long-term use (at least for 3 months) and were under CSAI when collection of data started.

These 82 patients were started on CSAI because of the presence of severe on–off fluctuations (79 patients; 96%), dopa-related dyskinesia (39 patients; 48%), and other causes (13 patients; 16%) despite optimum oral treatment.

Twenty-two patients presented hallucinations before CSAI treatment (13 mild, 8 moderate, 1 severe), and 27 patients had cognitive impairment (19 mild, 7 moderate, 1 severe).

Table 2 depicts the reasons to choose CSAI over other techniques in these 82 patients. Most patients (52%) were discarded as candidates for DBS when evaluated for this purpose.

Once apomorphine acute challenge was considered positive, apomorphine was given subcutaneously as CSAI. Apomorphine hydrochloride 10 mg/mL (Britan-

TABLE 2. *Reasons to select continuous subcutaneous apomorphine infusion over other therapeutic strategies (n = 82)*

	n	%
Not suitable for neurosurgery	42	52
Patient preference	16	20
Neurosurgery failure	7	9
Neurosurgery not available	5	6
Others	12	15

TABLE 3. *Main outcomes of subcutaneous apomorphine continuous infusion therapy (n = 82)*

	Baseline	Last follow-up	*P* value
Total UPDRS score (off oral medication)	68.13 (SD ± 21.14)	44.70 (SD ± 24.63)	<0.0001
Motor UPDRS score (off oral medication)	42.28 (SD ± 14.05)	28.62 (SD ± 15.84)	<0.0001
Daily off-time (hr/waking day)	6.64 (SD ± 3.10)	1.36 (SD ± 1.42)	<0.0001
Number of daily off episodes	4.55 (SD ± 1.70)	1.36 (SD ± 1.63)	<0.0001
Dyskinesia severity	1.67 (SD ± 1.01)	1.15 (SD ± 0.86)	<0.0006
Daily levodopa dose (mg/day)	989.4 (SD ± 420.1)	663.8 (SD ± 403.2)	<0.0001
Daily LEU dose (mg/day)	1,405 (SD ± 536.7)	800.1 (SD ± 472.9)	<0.0001
Gait imbalance	1.41 (SD ± 0.99)	1.04 (SD ± 0.99)	0.0066
Cognitive impairment	0.47 (SD ± 0.72)	0.58 (SD ± 0.83)	0.0314
Hallucinations	0.41 (SD ± 0.73)	0.49 (SD ± 0.74)	0.3823

nia Pharmaceuticals, Surrey, UK) was administered, diluted with normal saline to 5 mg/mL via the Canè Crono Apo-Go portable pump for ambulatory use connected to a subcutaneously inserted cannula. Domperidone was routinely used in the early stages of therapy.

The common strategy of this study was to improve motor fluctuations; dopa-related dyskinesias was not the main goal unless they were severe enough to interfere with activities of daily living. There was no specific common strategy for withdrawing oral antiparkinsonian drugs; this was left to each investigator's clinical practice.

Before CSAI treatment was initiated, these 82 patients were evaluated at baseline by means of the Unified Parkinson's Disease Rating Scale (UPDRS) total score, and motor subscale.[33] Evaluation was carried out in the morning, before the first oral medication whenever possible. Cognitive impairment, neuropsychiatric disturbances, and gait imbalance were evaluated in the "off" state. Dyskinesia severity was assessed on a five-point scale (0–4) in accordance with UPDRS items 1, 2, 29, and 33 during the "on" period. In addition, patients completed an "on/off" diary during the waking day, the week prior to CSAI treatment.

We compared the baseline parameters with data obtained from the last visit (mean follow-up: 19.93 ± 16.3 months). Every patient was evaluated with the same protocol as baseline (assessment early in the morning, before the first oral medication but CSAI running), including UPDRS (total score and motor subscale) and dyskinesia evaluation. We also calculated the L-dopa equivalent units (LEU) under baseline conditions and post-CSAI treatment. Calculation of daily LEU was based on theoretical equivalence to L-dopa of antiparkinsonian therapy according to previous reports.[23]

Data were analyzed for normality using the Shapiro–Wilks and Kolmogorov–Smirnov tests. Mean values before and after treatment were compared using Wilcoxon's rank paired *t* tests, as appropriate.

RESULTS

Efficacy data are shown in Table 3. As already noted, most parameters improved after CSAI, including total and motor UPDRS, daily off-time, and number of daily off-episodes. Gait imbalance and dyskinesia scores also improved. The reduction of antiparkinsonian medication achieved with CSAI was statistically significant (Tables 3 and 4). Full data on concomitant medication for selected patients were collected (Table 4). Only 3 patients achieved complete withdrawal of other antiparkinsonian medication (CSAI on strict monotherapy). There was a trend toward increased cognitive decline, although the differences did not reach statistical significance.

The daily dosage of apomorphine infusion ranged from 35 to 160 mg (72.00 ± 21.38 mg), run over a mean time of 14.05 hours (SD ± 1.81) each day (range, 10.0–16.5 hours). The mean hourly rate of apomorphine was 5.03 mg (SD ± 1.34).

Overall, CSAI was well tolerated in these patients. From 148 adverse events collected, 93 (62.8%) were mild, 44 (29.7%), moderate, and 11 (7.4%) severe, but did not lead to treatment dropout. Moreover, no case of HA was reported in these 82 long-term-treated patients.

Adverse events considered by investigators to be related to CSAI are presented in Table 5. Many

TABLE 4. *Concomitant antiparkinsonian medication (n = 82)*

	Baseline		Last follow-up	
	n	%	n	%
Levodopa	81	99	79	96
Dopamine agonist	69	84	33	40
Apomorphine (intermittent injections)	44	54	14	17
COMT inhibitors	33	40	13	16
MAO inhibitors	6	7	8	10
Anticholinergics	1	1	1	1
Amantadine	19	23	15	18

TABLE 5. *Adverse drug reaction profile related to the 82 long-term-treated patients under continuous subcutaneous apomorphine infusion (n = 82)*

	None		Mild		Moderate		Severe		Any grade	
	n	%	n	%	n	%	n	%	n	%
Local adverse reactions										
Skin nodules	26	32	31	38	18	22	7	9	56	68
Panniculitis	66	80	12	15	4	5	0	0	16	19
Neuropsychiatric adverse reactions										
Confusional Status	68	83	8	10	5	6	1	1	14	17
Hallucinations	67	82	10	12	5	6	0	0	15	18
Hypersexuality	75	91	5	6	1	1	1	1	7	8
Systemic adverse reactions										
Sedation/Drowsiness	58	71	15	18	8	10	1	1	24	29
Nausea	77	94	4	5	1	1	0	0	5	6
Orthostatic hypotension	77	94	4	5	1	1	0	0	5	6
Hemolytic anemia	82	100	0	0	0	0	0	0	0	0
Others	76	93	4	5	1	1	1	1	6	7

patients exhibited at least one, including subcutaneous nodules, the most prevalent problem. 13/82 (15.9%) patients did not report any side effect.

DISCUSSION

At present, CSAI has an established role in advanced PD with motor fluctuations. We have examined our experience of CSAI over the last 5 years to assess indications, pattern of use, efficacy, and side effect profile.

According to our data and previous studies,[6–24] CSAI improves motor parameters in fluctuating patients, including the number of daily off-periods. Gait imbalance and dyskinesia scores also improved, although the differences were not as striking as other measures. An important reduction in antiparkinsonian medication is possible in most patients, which probably explains the improvement in dopa-related dyskinesias. However, most patients were not able to completely discontinue their concomitant oral antiparkinsonian medication. Only 3 patients were able to maintain strict monotherapy with CSAI, while 20 others needed only L-dopa, mainly as an early-morning dose of standard L-dopa and/or a nocturnal controlled-release formulation. These data apparently contrast with those from the study by Manson et al.,[16] where monotherapy was achieved in the majority of patients. However, they considered a patient to be under monotherapy if a kick-start of L-dopa was received in the morning before starting the pump, and/or a single dose of controlled-release LD after stopping the pump before bedtime. We rather preferred the strict application of the term "monotherapy."

Daily apomorphine dose and duration of infusion (hours/day) are lower compared with some previous reported series (Table 1).[6–24] This could be explained because, at present, there is a dose restriction for apomorphine for continuous infusion in Spain; health authorities rarely approve greater dosages than 100 mg/day. This dose restriction could also partially explain the small number of patients on monotherapy.

Previous reported data show that CSAI can be maintained in some subjects for extended periods of time. Of the 82 patients studied, 27 had been under CSAI for more than 2 years at the time the audit was performed, and 9 patients for at least 4 years. In these selected cases, the results were striking (including almost disappearance of dyskinesias in some of them).

Our findings support the belief that subcutaneous apomorphine infusions as an add-on to L-dopa or monotherapy are successful in aborting "off" periods, reducing dyskinesias, and improving PD motor scores with a substantial L-dopa-sparing effect, consistent with replacement of short-acting oral antiparkinsonian medication with continuous dopamine receptor stimulation.[7,9,15,16,23]

CSAI is not devoid of side effects, and most patients sooner or later face one. In clinical practice, skin nodules are the most common. Neuropsychiatric adverse reactions are not infrequent, but we must take into account that patients with advanced PD are frequently suffering from cognitive decline, and many have hallucinations and dopamine-related psychoses.[34] Thus, it is not surprising that patients treated with CSAI may have cognitive-psychiatric disturbances. Although we did not have any case of HA in those patients chronically treated with CSAI, we had a case of HA in a patient who withdrew prematurely.

No direct comparison has been carried out between CSAI and other antiparkinsonian techniques, such as

DBS, except for some nonrandomized studies.[24,35] It is quite difficult to collect information to compare these techniques because of the lack of proper randomized, controlled trials. In spite of these limitations, it seems that DBS is probably superior to CSAI in terms of dyskinesia improvement and reduction in antiparkinsonian medication.[24,36–38] On the other hand, CSAI is a relatively nonaggressive technique, easy to perform, and relatively easy to control. Certainly, patient and family must have some skills in handling the device, and meticulous hygiene must be maintained, but this can be accomplished easily in the majority of patients. Experience, availability, and patient preference will lead the physician and patient to choose the best technique in individual cases.

Although limited by the use of retrospective data and the complexity of evaluation by more than 40 physicians at 35 centers, our study confirms again that CSAI is efficacious for the management of advanced PD, and the improvement can be maintained over several years.

In conclusion, CSAI is an effective and well-tolerated option for those patients with PD and severe fluctuations, who are poorly controlled by conventional treatment.

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