Journal of the Neurological Sciences 395 (2018) 113–118

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Effects of continuous subcutaneous apomorphine infusion in Parkinson's disease without cognitive impairment on motor, cognitive, psychiatric symptoms and quality of life

Jean-François Houvenaghel[a,b,*], Sophie Drapier[a,b], Joan Duprez[a], Gabriel Hadrien Robert[a,c], Audrey Riou[a,b], Dominique Drapier[a,c], Paul Sauleau[a,d], Marc Vérin[a,b]

[a] "Behavior and Basal Ganglia" Research Unit (EA 4712), University of Rennes 1, Rennes, France
[b] Department of Neurology, Rennes University Hospital, Rennes, France
[c] Department of Psychiatry, Rennes University Hospital, Rennes, France
[d] Department of Neurophysiology, Rennes University Hospital, Rennes, France

A B S T R A C T

Introduction: Treatment optimization using continuous subcutaneous apomorphine infusion (CSAI) improves the control of motor fluctuations of patients with Parkinson's disease (PD). Although CSAI seems to be cognitively and behaviorally safe and to improve the quality of life, very few studies have investigated its influence in these domains, especially in patients without cognitive impairment. Methods: We estimated the impact of CSAI on motor symptoms, cognition, psychiatric domains and quality of life in parkinsonian patients without cognitive impairment by comparing the scores of 22 patients assessed before and 6 months after the start of add-on CSAI. Results: Optimized treatment with CSAI was associated with i) reduced motor fluctuations, ii) unchanged cognition, iii) unchanged psychiatric domains, and iv) improved quality of life in physical and psychological aspects. Conclusion: In PD patients without cognitive impairment, CSAI improves motor symptoms and quality of life and, as suggested by previous studies, alters neither cognition nor mental health.

1. Introduction

The addition of continuous subcutaneous apomorphine infusion (CSAI) to oral antiparkinsonian medication is considered to be an effective treatment for motor symptoms of patients with Parkinson's disease (PD) who are severely disabled by dyskinesia and/or motor fluctuations (for a review, see [1,2]). A randomized placebo-controlled study confirmed recently this widely accepted view [3]. CSAI is frequently considered to be cognitively safe, or even to have a potentially beneficial effect on cognition [4–6]. However, to our knowledge, very few studies have investigated these cognitive aspects with neuropsychological batteries, and most of them had small and heterogeneous patient samples [7–14]. The two studies that have so far been conducted in patients without severe cognitive impairment, as indicated by the fact that they were not contraindicated for subthalamic nucleus deep brain stimulation (STN-DBS), did not report any significant CSAI-induced changes [7,8,10]. In one study, executive, episodic verbal memory, and visuoperceptual performances remained stable in all seven patients 6 and 12 months after the introduction of CSAI [7]. In the other study, there was no significant change in either episodic verbal memory or visual working memory at 12 months for thirteen patients [10], or at 40 months for two patients [8]. However, since the exclusion criteria for STN-DBS rely on motor and/or neuropsychological symptom severity, we cannot know whether the patients in these studies had cognitive impairment. Similar results have been reported for patients with advanced PD who had more important motor and/or neuropsychological symptoms, and therefore underwent apomorphine infusion as an alternative therapeutic strategy [9,11,13,14]. A study evaluating the effect of 12 months of treatment in 23 patients found that executive functions were unaffected by CSAI, although a slight cognitive slowdown was observed, presumably induced by disease progression [11]. Similarly, a recent study failed to find any significant modulation of either overall cognitive efficiency (Mini-Mental State Examination, MMSE) or overall executive efficiency (Frontal Assessment Battery, FAB, or Scales for Outcomes in Parkinson's Disease-Cognition, SCOPA-COG) after a median follow-up duration of 26 months in 7–24 patients with cognitive disorders [13,14]. Lastly, one study reported a slight executive improvement in 12 patients after 6 months of add-on CSAI [9]. Thus, even if CSAI has frequently been reported to be cognitively safe, further evidence from neuropsychological assessments is needed, especially in patients with no cognitive impairment, who represent > 50% of all patients with PD [15].

In addition, research interest in quality of life is very recent, with only four studies published in international journals, all concerning

* Corresponding author at: Service de Neurologie, CHU Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex, France.
E-mail address: jeanfrancois.houvenaghel@chu-rennes.fr (J.-F. Houvenaghel).

https://doi.org/10.1016/j.jns.2018.10.010
Received 8 April 2018; Received in revised form 27 August 2018; Accepted 5 October 2018
Available online 07 October 2018
0022-510X/

Table 1
Levodopa equivalent daily dose (mean ± *SD*) of patients with PD before (M0) and after 6 months (M6) of add-on CSAI.

	N	M0	M6	M6 - M0	*p* Value
Dopamine agonists (mg/day)	22/22	278.7 ± 147.5	244.7 ± 146.8	−34.1 ± 86.9	0.11
L-DOPA (mg/day)	22/22	791.7 ± 409.7	479.5 ± 381.6	−312.1 ± 312.7	< 0.001
Total apomorphine dose (mg/day)	22/22		754.0 ± 209.7		
Total LEDD (mg/day)	22/22	1087.7 ± 485.5	1478.6 ± 552.7	391.9 ± 381.9	< 0.001

Note. LEDD = levodopa equivalent daily dose; *SD* = standard deviation.

patients with advanced PD [9,16–18]. Two of these reported a significant improvement in total scores on the Parkinson's Disease Questionnaire (PDQ-8; PDQ-39) [16,18], which was specifically built for PD, while a third found a trend towards an improvement [9]. The last one did not shown significant changes [17].

In this context, we conducted a retrospective study to investigate the influence of 6 months of add-on CSAI on the cognitive, motor and psychiatric domains, as well as on quality of life, in patients with no cognitive impairment at baseline. We hypothesized that add-on CSAI reduces motor symptoms and improves quality of life without disturbing cognitive or psychiatric aspects.

2. Methods

2.1. Participants

During the 2006–2015 period, the add-on CSAI treatment was introduced in 122 patients diagnosed with idiopathic PD according to the UK Brain Bank criteria at Rennes University Hospital. Among those 122 patients, 44 underwent motor and neuropsychological assessments before (baseline; M0) and 6 months (M6) after continuous add-on CSAI. Patients with dementia or mild cognitive impairment were excluded on the basis of the Level 1 diagnostic criteria recommended by the Movement Disorders Society [19], and the Mattis Dementia Rating Scale (MDRS; score > 137 [20] at baseline). Totally, 22 patients were included (8 men, 14 women) (Table 2). In addition to motor and neuropsychological assessments, most of them underwent psychiatric and quality-of-life assessments. Patients underwent the full assessment within the same week. All the patients were evaluated on dopaminergic medication both at baseline and during the follow-up assessments. At baseline, medication included both dopamine agonists and levodopa therapy in 21 patients, and levodopa alone in one patient. The study was approved by the local ethics committee of Rennes University Hospital and conducted in accordance with the Declaration of Helsinki and current French legislation.

2.2. Motor assessment

Disease severity was rated on the Unified Parkinson's Disease Rating Scale (UPDRS-II, III and IV), and the Hoehn and Yahr and Schwab and England scales.

2.3. Neuropsychological assessment

In addition to the MDRS, we administered a neuropsychological battery that mainly investigated executive functioning. This battery included the phonemic (letter *p*) and semantic (animals) verbal fluency tasks (2-min version), the Nelson's simplified version of the Wisconsin Card Sorting Test (MCST), the Trail Making Test (TMT) and the Golden's version of the Stroop Interference Test.

2.4. Psychiatric assessment

Apathy, depression and anxiety were assessed by an experienced psychiatrist using the Apathy Evaluation Scale (AES), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the AMDP-AT anxiety scale.

2.5. Quality-of-life assessment

Quality of life was assessed with the 36-item Short-Form Survey (SF-36), the 39-item PDQ (PDQ-39) and the Clinical Global Impression Improvement (CGI—I) scale.

2.6. Statistical analyses

Changes in dopaminergic treatment and motor, psychiatric, neuropsychological, and quality-of-life scores following add-on CSAI were compared using the Wilcoxon matched-pairs test. The significance threshold was set at $p = .05$ for all analyses. We did not correct the level of significance for multiple comparisons given the exploratory nature of our study to reduce the risk of type II error. However, we were mindful of the consecutively higher probability of a type 1 error.

3. Results

3.1. Treatments

The introduction of add-on CSAI was associated with a significant reduction in levodopa treatment of 38% (−312 ± 312 mg/d, $p = .0004$) and an increase in the total levodopa equivalent daily dose (LEDD) of 45% (392 ± 382 mg/d, $p = .0004$) (Table 1). At 6 months, the apomorphine treatment represented 55% of total LEDD. Daytime CSAI had a mean duration of 15.4 ± 2.1 h (range: 13–24) at a mean hourly rate of 4.7 ± 1.0 mg (range: 3.5–7) and a mean bolus number of 2.0 ± 1.8 per day (range: 0–5), with a mean dose of 2.9 ± 1.2 mg (range: 0–5) per bolus.

3.2. Motor assessment

Add-on CSAI significantly reduced motor fluctuations, as shown by the decrease in the UPDRS-IV Fluctuations score (sum of Items 36–39), which improved by −1.04 ± 1.8 points ($p = .005$). No other significant motor improvement was observed. In parallel, we observed a trend towards an increase in the UPDRS-III ON medication score (non-dopaminergic symptoms; $p = .09$) and the Schwab & England OFF medication score ($p = .09$), indicating potential disease progression (Table 2).

3.3. Neuropsychological assessment

Very few cognitive changes were observed at 6 months. Patients showed a slight slowdown, as measured by the Stroop Word score ($p = .04$). However, this slowdown was not reflected in the other scores, such as the Stroop Colour score ($p = .37$), or the TMT Part A which, on the contrary, tended to be faster ($p = .10$). The Stroop interference score also tended to be better at 6 months ($p = .10$) (Table 3).