Continuous subcutaneous apomorphine infusion in the early phase of advanced Parkinson’s disease: A prospective study of 22 patients

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ABSTRACT

Introduction: Parkinson’s disease (PD) patients usually start treatment with apomorphine infusion (APO) in later stages of advanced PD (aPD). This timing limits the evaluation of its motor efficacy and other potential clinical benefits throughout the full course of aPD.

Methods: We prospectively analyzed the effect of APO on motor and non-motor symptoms, cognitive function and quality of life (QoL) in 22 PD patients with early stage aPD, defined as: age < 71 years and diagnosis of aPD for < 3 years.

Results: At baseline, mean (±SD) age and disease duration were 59.4 ± 6.1 and 8.7 ± 3.5 years, respectively. After 6 months of APO treatment, daily off-time decreased from 4.98 ± 2.37 to 1.48 ± 1.47 h (p < 0.001) and UPDRS IV scores from 7.00 ± 2.58 to 5.32 ± 2.48 (p = 0.018). Dyskinesia did not worsen with APO despite an overall increase in levodopa equivalent daily dose. Mean NMSS scores improved with APO, from 52.50 ± 27.24 to 38.68 ± 27.17 (p = 0.002), with particular improvements in apathy and sleep quality. Mean PDQ-39 score was reduced with APO from 31.96 ± 11.93 to 19.27 ± 11.86 (p < 0.001). Overall, cognition did not change after APO, while slight improvements were observed in executive functioning (attention and planning). All but one patient eventually underwent subthalamic deep brain stimulation.

Conclusion: In patients with early stage initial aPD, substantial benefit of APO was observed on motor symptoms, driven by a 70% reduction in off-time versus baseline, superior to that observed in previous prospective studies. APO also improved frontal dysfunction in PD patients.

1. Introduction

Advanced Parkinson’s disease (PD, aPD) starts when first line therapy, oral or transdermal, fails. This timing can be challenging and, then, should be individualized. Current thinking is that the efficacy of device-aided therapies may be optimal if these treatments are applied earlier in the course of the disease [1]. Apomorphine infusion (APO) is widely used to treat motor fluctuations in aPD. Studies show that APO treatment leads to a significantly reduction of the daily off-time [2,3], although its effect on dyskinesia is still unclear. It has been suggested that APO is more beneficial for dyskinesia the more the levodopa daily dose is reduced [4]. Retrospective studies have not observed worsening of dyskinesia with APO treatment, however their analysis is limited [5,6]. APO has a good effect profile for some non-motor PD symptoms, often particularly resistant to other treatments, such as mood, sleep, fatigue, urinary symptoms or pain [7,8].

APO is contraindicated in cases of dementia or severe neuropsychiatric symptoms. In contrast, APO is considered suitable for use in patients without cognitive impairment or even with mild-to-moderate decline [9,10]. In these cases, the progression of cognitive impairment or the presence of hallucinations have been linked to the natural course of PD rather than to APO treatment [6]. These data are derived from retrospective studies and are therefore based on clinical observations or non specific scales, and should be interpreted with caution. To date, few studies with APO have included a standardized neuropsychological evaluation in their analyses [11–13].

Over the last decade, results from about a dozen clinical studies of APO have been published (Table 1). In most of them, patients included in...
the analysis were of older age, had poorer dopaminergic response, sometimes with relevant axial symptoms, higher non-motor symptom burden and worse quality of life than those selected for subthalamic deep brain stimulation (STN-DBS), as the EUROINF 2 study shows [8].

We therefore undertook a study to examine the effect of APO treatment on patients in the earlier phases of aPD.

2. Patients and Methods

This prospective, non-randomised, observational study was conducted by the Movement Disorder Unit of the Hospital Clínico Universitario de Santiago de Compostela, Spain, from March 2017 to December 2020. Patients in the study met the following inclusion criteria: (1) specified criteria for treatment with STN-DBS (see Supplementary material), (2) aPD duration, defined by patient’s disabling fluctuations or dyskinesia more than 25% daytime, less than three years, and (3) informed consent obtained. Exclusion criteria were (1) Mattis Dementia Rating scale score under –1.5 standard deviation, (2) Hoehn and Yahr scale score over stage 3 in the on-state, and (3) patients previously treated with APO (intermittent apomorphine pen injection was permitted), levodopa infusion or STN-DBS.

Patients had clinical assessments at baseline and six months after the treatment with APO. Demographical data and medication use (levodopa and levodopa equivalent daily dose -LEDD-) were recorded. Motor state treatment with APO. Demographical data and medication use (levodopa

2.1. Statistical analysis

Data are expressed as a percentage for qualitative variables and as mean and standard deviation for quantitative variables. To determine statistical differences between the treatments, we applied paired t-test or the Wilcoxon test, depending on the parametric or nonparametric data distribution determined by Anderson-Darling normality test and Fligner-Killeen homoscedasticity test. Given the small sample size, we calculated the Bayes Factor to parametric variables and Effect Size to nonparametric variables to determine the magnitude of the change.

For the neuropsychological battery, most of the tests used in our study have cut-off points adjusted for age and/or academic level, which helped to homogenize the variations between subjects. Standardized scores (Z) are available for the MDRS, RAVLT, WAIS III, BJLO, and Verbal Fluency tests.

3. Results

A total of 24 patients were included in the study. Two patients stopped APO treatment, one voluntarily and the other due to drug-induced psychosis (see discussion). For the remaining 22 patients (11 male, 11 women), mean age at inclusion was 59.4 ± 6.1 years and disease duration was 8.7 ± 3.5 years. At 6 months, mean daily APO dose was 73.6 ± 20.7 mg and mean daily time on APO was 15.9 ± 3.0 h (four patients had 24-hour infusion). For the patients who completed the study, adverse effects related to APO were all mild and all resolved satisfactorily. All but one patient ultimately received STN-DBS treatment.

Patient demographics and clinical scores at baseline and 6 months after initiation of APO treatment are shown in Table 2. APO improved almost all the motor and non-motor symptoms of PD compared with baseline values. APO treatment led to a significant decrease in mean daily hours of off-time (4.98 ± 2.37 to 1.48 ± 1.47, p < 0.001). UPDRS II scores in the on-state (8.27 ± 3.77 to 6.50 ± 3.64, p = 0.047) and UPDRS IV scores (7.00 ± 2.58 to 5.32 ± 2.48, p = 0.018). Dyskinesia scores did not worsen after APO initiation, despite an overall increase in LEDD (1446 ± 464 to 1676 ± 521 mg, p = 0.011). A subanalysis showed that dyskinesia trend even to worsen if APO treatment do not led to a significant reduction in levodopa intake (Fig. 1). Total levodopa daily dose was significantly reduced with APO treatment (1145 ± 436 to 856 ± 424 mg, p < 0.001). At baseline, levodopa accounted for 79.2% of the LEDD in contrast to the 51.1% following treatment with APO. Mean NMSS score was decreased significantly with APO (52.50 ± 27.24 to 38.68 ± 27.17, p = 0.002), and individual domains of sleep and fatigue, mood and miscellaneous all showed significant improvement (p = 0.014, p = 0.006 and p = 0.006, respectively). Urinary symptoms got better, close to statistical significance (p = 0.054). Apathy significantly improved with APO (7.00 ± 7.16 to 3.14 ± 2.85, p = 0.008), while depression did not. Sleep quality significantly improved with APO compared to baseline (22.75 ± 8.33 to 16.90 ± 8.63, p = 0.001). No cases of worsening impulsivity were observed in this series of patients. Mean PDQ-39 scores were reduced significantly with APO (31.96 ± 11.93 to 19.27 ± 11.86, p < 0.001). Individual domains for mobility (p ≤ 0.001), daily life activities (p ≤ 0.001), stigma (p = 0.020) and bodily discomfort (p = 0.002) reached the most significant improvements.

| Table 1 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| N | Age (years) | PD duration (years) | Off-time (hours) | LEDD (mg) | UPDRS III (on-state) | UPDRS IV | NMSS | PDQ-8 / PDQ39 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Martinez-Martín et al, 2011 | 17 | 59.5 | 12.1 | - | 1077 | 36.9 | 10.0 | 105.9 | 55.7 |
| Drapier et al, 2012 | 23 | 62.3 | 13.9 | - | 1372 | 18.3 | - | - | - |
| Martinez-Martín et al, 2015 | 43 | 62.3 | 14.0 | - | - | 30.8 | 10.0 | 82.4 | 49.9 |
| Drapier et al, 2016 | 142 | 66.7 | 11.6 | - | - | 1154 | 18.4 | 8.5 | 41.2 |
| Auffret et al, 2017 | 12 | 65.9 | 13.8 | - | 1227 | 17.7 | 8.1 | - | - |
| Sezar et al, 2017 | 93 | 67.3 | 11.9 | 5.4 | 1098 | 2.2 | - | - | - |
| Borgemeester et al, 2017 | 45 | 70.9 | 10.8 | 3.9 | 1269 | - | - | - | - |
| Houvenaghel et al, 2018 | 22 | 57.5 | 11.1 | - | 1088 | 11.1 | 7.0 | 38.8 |
| Katschnigler et al, 2018 | 55 | 63.9 | 11.8 | 6.7 | 1486 | 30.6 | - | - | 32.7 |
| Sezar et al, 2019 (group 1) | 18 | 63.0 | 12.9 | 5.4 | 1223 | 14.1 | - | - | - |
| Dufarici et al, 2019 (APO group) | 38 | 61.6 | 13.5 | - | 1198 | 29.5 | 9.0 | 76.4 | 43.5 |
| Present study | 22 | 59.4 | 8.7 | 5.0 | 1446 | 12.6 | 7.0 | 52.5 | 32.0 |

*Only levodopa. A PDQ-8 and PDQ39 are both expressed as a percentage.
Baseline characteristics of PD patients included in most recent apomorphine infusion studies.

|                     | Baseline | APO     | p-value | Effect size |
|---------------------|----------|---------|---------|-------------|
| Age (years)         | 59.41 ± 6.12 | –       |         |             |
| PD evolution (years)| 8.73 ± 3.52   | –       |         |             |
| APO dose (mg/hour)  | –         | 4.81 ± 1.17 |         |             |
| APO (hours by day)  | –         | 15.87 ± 3.03 |         |             |
| off time (hours)    | 4.98 ± 2.37   | 1.48 ± 1.47 | ≤0.001 | large       |
| UPDRS II on         | 8.27 ± 3.77   | 6.50 ± 3.64 | 0.047 | small       |
| UPDRS III on        | 12.64 ± 5.53  | 11.77 ± 1.05 | 0.492 | ns          |
| UPDRS IV            | 7.00 ± 2.58   | 5.32 ± 2.48 | 0.018 | large       |
| Dyskinesia score    | 2.77 ± 2.20   | 3.09 ± 2.24 | 0.432 | ns          |
| LEDD (mg)           | 1446 ± 464   | 1676 ± 521 | 0.011 | moderate    |
| Levodopa (mg)       | 1145 ± 436   | 856 ± 424  | ≤0.001 | large       |
| NMSS                | 52.50 ± 3.88  | 38.68 ± 0.02 | 0.002 | large       |
| Cardiovascular      | 27.24 ± 0.73  | 27.17 ± 0.73 |         |             |
| Sleep/fatigue       | 10.41 ± 5.69  | 7.23 ± 5.28 | 0.014 | moderate    |
| Mood                | 13.18 ± 9.32  | 9.32 ± 0.06  | 0.001 | large       |
| Perceptual/          | 0.18 ± 0.85   | 0.27 ± 1.28 | 1 ns    |             |
| Hallucinations      |           |         |         |             |
| Gastrointestinal    | 4.50 ± 5.54  | 4.59 ± 5.43 | 0.925 | ns          |
| Urinary             | 6.36 ± 5.13  | 4.91 ± 4.77 | 0.054 | ns          |
| Sexual              | 5.62 ± 6.44  | 4.23 ± 5.42 | 0.092 | ns          |
| Miscellaneous       | 10.23 ± 8.84  | 7.05 ± 8.29 | 0.006 | large       |
| MADRS               | 13.00 ± 11.73 | 9.25 ± 0.253 | 0.253 | ns          |
| SAS                 | 10.73 ± 9.17  |           |         |             |
| QUIP-RS             | 7.00 ± 7.16   | 3.14 ± 2.85 | 0.008 | large       |
| PDSS-2              | 2.00 ± 5.15   | 2.41 ± 6.45 | 1 ns    |             |
| PDQ-39              | 22.75 ± 8.33  | 16.90 ± 0.001 | 0.001 | large       |
| Mobility            | 45.45 ± 21.93 |           | ≤0.001 | large       |
| Daily life activities| 39.76 ± 20.27 |           | ≤0.001 | large       |
| Emotional wellbeing | 37.48 ± 28.98 |           | 0.059 | ns          |
| Stigma              | 19.46 ± 19.27 |           |         |             |
| Social support      | 4.92 ± 11.68  | 5.68 ± 20.48 |         |             |
| Cognition           | 11.86 ± 9.96  | 13.94 ± 0.754 | 0.754 | ns          |
| Communication       | 19.31 ± 15.06 |           |         |             |
| Bodily discomfort   | 37.12 ± 19.32 |           | 0.002 | large       |
|                     | 23.55 ± 20.48 |           |         |             |

Results from neuropsychological evaluation are shown in Table 3 (see Supplementary material for the absolute scores for each test). Evaluation at 6 months showed slight improvements in some frontal tasks. Time used to resolve the 3-piece and 4-piece Tower of Hanoi was significantly lower with APO (94.95 ± 71.08 to 73.14 ± 43.86 s, p = 0.029 and 240.70 ± 110.32 to 167.05 ± 74.73 s, p = 0.014, respectively), as well as attention subscale of MDRS (-0.05 ± 0.73 to 0.26 ± 0.52, p = 0.047). Phonemic fluency, another sensitive test for frontal dysfunction commonly used in PD, improved with APO treatment compared to baseline, to near statistical significance when evaluating direct scores (p = 0.065). Overall cognition did not change with APO treatment.

4. Discussion

Treatment with APO resulted in a substantial improvement in motor fluctuations in this population of patients in the early stages of aPD. Mean daily off-time was reduced by almost 70% (-3.50 h) compared to baseline. This improvement is much greater than the reductions of 33% [11] and 53% [14], reported in previous prospective studies of APO. Nevertheless, our result is similar to the reduction of 74% found in our retrospective analysis of data from patients treated with APO before STN-DBS [15], and the figures of 79% and 78% reported in the largest retrospective series to date [2,6]. UPDRS IV scores were also reduced...
after APO, as observed in other studies [8,13,16]. However, this cannot be attributed to an improvement in dyskinesia, as dyskinesia score was unchanged compared to baseline. Dyskinesia did not worsen with APO treatment despite the substantial increase in LEDD increase. This is probably due to the decrease in the pulsatile dopaminergic stimulus. However, in animal models of PD, a compensatory D1 receptor functional hypersensitivity of the direct pathway in the context of chronic levodopa intake, was demonstrated as a key factor in the development of a prodyskinetic state [17,18]. Apomorphine, contrary to other dopamine agonists, had a high affinity for this receptor [19]. Historically, it has been suggested that APO has greater benefit in terms of dyskinesia the more the levodopa dose is reduced [4,20]. Levodopa reduction in this study was similar to others [3,6,13,15].

Non-motor symptoms, assessed using the NMSS, improved with APO. Sleep and fatigue, mood and miscellaneous were the items that showed the most improvement. The convenience of APO to treat non-motor symptoms of aPD has been demonstrated in a previous study [7], however, its results have not been replicated [8,21]. In our study, the non-motor symptom burden at baseline was low as the patients were in a relatively early phase of the aPD. In fact, cardiovascular or cognitive symptoms were scarcely represented in NMSS scores. Depression and apathy were evaluated in this study using specific scales. APO improved apathy in this study, but not depression similar to the results found in another study using specific scales (Lille Apathy Scale and MADRS) [12]. Sleep quality, assessed by the PDSS-2, was improved with APO. In this study, only four patients used APO during the night. Therefore, it seems that this improvement in sleep quality is not due to the improvement in night-time off-state, a key observation in patients receiving overnight APO [22,23]. We did not identify any worsening or onset of impulse control disorder. APO was discontinued in one patient who developed a psychotic episode with hospitalization. Although APO was stopped and the patient put on neuroleptic treatment, symptoms remained the same.

Overall cognition did not show changes after APO in our study. Although mean scores for short verbal memory, visual memory and visuospatial skills were lower compared to baseline, they did not reach statistical significance. By contrast, we found a slight improvement in executive functions. Patients with APO were faster completing the Tower of Hanoi, even 4-piece Tower of Hanoi, more complex and less conditioned to learning effect than the 3-piece Tower of Hanoi.

Fig. 2. Comparison between baseline and APO mean scores for frontal tasks and apathy (frontal dysfunction).
findings support the efficacy of APO improving PD frontal dysfunction.

Patients enrolled in this study were in an early phase of aPD. Compared to APO-treated patients in other series, they had a shorter PD duration, predominantly levodopa-responsive motor fluctuations and a reduced non-motor symptom burden. In comparison, APO patients in other series are in more advanced disease with worse dopaminergic response and more severe non-motor symptoms. In fact, baseline characterisitics of these patients are quite similar to the frequently-cited EARLYSTIM study which evaluated the early use of STN-DBS [29]. In our study, PD patients had less advanced disease than than usually be considered for infusion treatment, and the effect of APO on motor fluctuations was more substantial than previously reported.

Our study has some limitations. The sample size was relatively small, however it is similar to other APO prospective studies. The majority of our patients were on APO while waiting for DBS. We have not analyzed a group of more advanced patients treated with APO to compare.

Advanced PD is a challenging condition for which, despite its name, several effective treatment options are available, either surgery or infusion therapies. When conventional therapies begin to fail and are no longer able to control motor symptoms of PD, a shift to device-aided therapies is mandatory. The earlier we start such treatment, the better the patient’s quality of life will be. As we have shown in this study, APO is very effective in early phases of aPD, which makes it a good treatment option to adequately control disease symptoms in this stage.

Ethics approval

The study has been approved by the Research Ethics Committee of Santiago (Project identification code 2018/339). Informed consent was obtained from each patient or from their relatives, after a full explanation of the procedures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100129.

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