Parkinsonism and Related Disorders 23 (2016) 17–22

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Motor and non-motor outcomes of continuous apomorphine infusion in 125 Parkinson's disease patients

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form
30 October 2015
Accepted 16 November 2015

Keywords:
Apomorphine
Parkinson's disease
Motor fluctuations
Dyskinesia
Visual hallucinations

ABSTRACT

Introduction: Continuous apomorphine infusion (CAI) is an effective treatment in fluctuating Parkinson's disease (PD). However, long-term efficacy and safety data of CAI are scarce.
Methods: We retrospectively reviewed long-term outcomes of CAI on motor and non-motor symptoms in a Dutch cohort of 125 PD patients.
Results: Our cohort (age: 65.8 ± 9.8 years, disease duration: 11.9 ± 5.7 years) had a mean daily dose of apomorphine of 66 ± 30 mg, thereby reducing the levodopa-equivalent daily dose (LEDD) by 20%. The mean duration of treatment with apomorphine was 32.3 ± 31.9 months, ranging up to 139 months. Three-quarters of patients discontinued within the first four years. The main reason for discontinuation was a decreasing therapeutic effect. Patients who stopped apomorphine within four years had a lower LEDD reduction at hospital discharge and at last follow-up compared to patients who continued for a longer period. CAI showed good effects on motor fluctuations and dyskinesia, with better outcomes in patients with more pronounced LEDD reduction. CAI could be safely applied in patients with pre-existing visual hallucinations (30%).
Conclusion: CAI showed beneficial effects on motor and several non-motor symptoms, whereas the magnitude of LEDD reduction seems to be a positive predictive factor on the duration of CAI.

1. Introduction

Continuous apomorphine infusion (CAI) has been used as treatment for advanced Parkinson's disease (PD) patients with motor fluctuations and dyskinesia. The beneficial effect of CAI on motor fluctuations and dyskinesia has been shown in numerous open-label studies with a mean follow-up of two years [1]. Unfortunately, there have been no randomized controlled trials reported so far. A beneficial effect of CAI on non-motor symptoms has been observed as well. Non-motor symptoms, such as visual hallucinations (VH), sleeping problems, depression, cognitive deficits, and gastrointestinal and urinary dysfunction, improved with 6–12-month follow-up [2] and [3].

However, long-term data on the effect of CAI on motor and non-motor symptoms are scarce. Therefore, we reviewed our data on CAI treatment over the last 15 years to assess the effect of apomorphine on motor and non-motor symptoms.

2. Methods

2.1. Inclusion

This study included patients who were diagnosed with idiopathic PD according to the UK Brain Bank criteria [4], and who were treated with CAI at the University Medical Center Groningen, the Netherlands, between October 2000 and June 2014. Follow-up data were obtained by reviewing patients' medical records, and analyzed retrospectively. When patients were referred or moved to another hospital, patients' medical records were retrieved with permission.

2.2. Selection

Patients were selected for CAI treatment at the start of this cohort, if they had motor fluctuations, despite optimal oral treatment, and if they did not fulfill the selection criteria for deep brain stimulation (DBS) or did not want to be treated by DBS. Other indications for apomorphine were intolerance of oral dopaminergic medication and treatment with droxidopa due to severe orthostatic

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http://dx.doi.org/10.1016/j.parkreldis.2015.11.013
1353-8020/

hypotension. Droxidopa in combination with apomorphine (no decarboxylase inhibitor) proved to be the best combination to treat this hypotension successfully. DBS was and still is considered as first-choice advanced therapy, if possible and wanted by the patients, based on its long-term efficacy [5]. However, frequently registered contraindications for DBS were cognitive impairment, severe depression, frequent falling or dysarthria. Additionally, apomorphine was considered in patients who were on a waiting list for DBS, but had an urgent need for advanced treatment, because apomorphine was considered as an easy to administer, reversible therapy, which can be applied quite simply on the short term. The last ten years also levodopa-carbidopa intestinal gel (LCIG) was considered as an alternative, especially if there were contraindications for apomorphine infusion, like excessive daytime sleepiness and orthostatic hypotension, or if patients preferred the monotherapy with LCIG, because of compliance problems due to severe cognitive pathology or problems with swallowing. Apomorphine is less suitable in these cases, because very few patients are able to use apomorphine as a monotherapy [6].

2.3. Data

Follow-up data were collected by R.B and M.D. according to a predefined list of endpoints, including clinical indications for CAI, adjustments of medication over time, duration of CAI treatment, occurrence of side-effects, reasons for discontinuation, reasons to switch to other advanced therapies and frequency of switching, effect of CAI on motor fluctuations, dyskinesia, VH, nighttime sleeping problems, weight and blood pressure. To evaluate dopaminergic medication, a levodopa-equivalent daily dose (LEDD) was calculated [7]. Cholinesterase inhibitors (ChEI) were grouped and equalized to oral rivastigmine. An oral dose of 12 mg rivastigmine was equal to a rivastigmine patch of 9.5 mg and 24 mg galantamine [8]. The clinical effect of CAI on motor and non-motor symptoms (i.e. motor fluctuations, dyskinesia, VH and nighttime sleeping problems) was scored by means of a 5-point clinical global impression of improvement (CGI-I) as much improvement, some improvement, no improvement, some worsening or much worsening of the therapeutic effect. Much improvement was scored if patients had no symptoms left after initiation of CAI. Some improvement was scored if patients partially improved, but still had some symptoms left. Worsening was scored if a moderate or severe increase of symptoms was observed. Insomnia and parasomnia were grouped together as nighttime sleeping problems.

2.4. Titration of apomorphine

Apomorphine was started in all patients with an infusion rate of 1 mg/h, which was given on top of the existing dopaminergic medication. The apomorphine dose was increased with 0.5–1 mg/h, until dyskinesia appeared or worsened. At that time the other dopaminergic medication was tapered off. In patients with VH, dopamine agonists (DA) were tapered off first. In patients without VH, in whom DA's were well-tolerated, levodopa was tapered off first (see Supplementary file 1). If off-periods appeared or worsened after reduction of the oral drugs, apomorphine was increased again with steps of 0.5–1.0 mg/h. There was no predefined minimal infusion rate of apomorphine, which could mean that the addition of apomorphine of just 1–2 mg/h was considered as sufficient for the patient, whereas optimal reduction of off-time and/or dyskinesia-time were the final endpoints.

2.5. Statistical analysis

Data analysis was performed using SPSS 22.0 (SPSS, Chicago, USA). Variables were checked for normality using Shapiro–Wilk test. For comparison of normally distributed continuous variables an independent T-test was used, whereas a Mann–Whitney U test was used for continuous variables that violated the normality assumption. For comparison of ordinal variables a Chi-square test was conducted. The Chi-square test was also used to evaluate the relative change in LEDD. The duration of CAI treatment was visualized using the Kaplan–Meier method. P-values less than 0.05 were considered as statistically significant, and a Benjamini-Hochberg correction was applied for multiple comparisons [9].

3. Results

3.1. Patient characteristics

One-hundred-twenty-five PD patients were included (77 male and 48 female patients). At initiation of CAI, the mean age of our cohort was 65.8 ± 9.8 years with a mean disease duration of 11.9 ± 5.7 years. Rigidity, tremor and postural instability were present in 78%, 22%, and 10% of the patients respectively. The prevalence of dystonia at initiation was 30%, whereas 15% of our cohort was demented at the start of CAI.

3.2. Indications

The main indication was motor fluctuations (92%), whereas 78% had levodopa-induced dyskinesia as well. Other indications were intolerance of oral dopaminergic medication (6%), and apomorphine was started in two patients (2%) with severe orthostatic hypotension, in combination with droxidopa (Table 1).

3.3. Dose

The daytime apomorphine dose after initial titration was 3.9 ± 1.8 mg/h, infused over 16.6 ± 3.2 h/day. Fifteen patients (12%) received 24 h infusion without developing any tolerance. The mean daily dose of apomorphine was 66 ± 30 mg. The addition of apomorphine made it possible to reduce the LEDD with 20% after the first titration period in the hospital (from 1287 ± 660 mg/day at baseline to 1029 ± 615 mg/day at hospital discharge). Only three patients (2%) were able to continue on apomorphine monotherapy. The mean daily dose of apomorphine at last follow-up (or at discontinuation) had increased slightly with 11% towards 74 ± 30 mg/day. The LEDD reduction had increased to 32% (873 ± 465 mg/day) over time.

3.4. Concomitant medication

Before the start of CAI, all patients were pre-treated with domperidone. Baseline dopaminergic medication and adjustments during the course of apomorphine infusion are illustrated in Supplementary file 2, as well as the use of clozapine and ChEI's.

3.5. Duration of CAI

The mean duration of treatment with apomorphine was 32.3 ± 31.9 months. In June 2014, 37 patients were still on CAI treatment with a mean duration of 56.1 ± 40.5 months (range 2–139). Fifty-nine patients discontinued CAI after a total follow-up of 19.3 ± 21.7 months (range 0–92). Twenty-eight patients died during CAI treatment after a mean treatment of 28.2 ± 15.7 months (range 3–68). Common causes of death were aspiration pneumonia and cardiovascular diseases. None of the deaths was directly related to CAI treatment. The patients who died were significantly older at initiation of apomorphine as compared to the patients still alive