CONTINUOUS INTESTINAL INFUSION OF DUODOPA CAN AMELIORATE THE MOTOR AND NON-MOTOR COMPLICATIONS ASSOCIATED WITH ADVANCED PARKINSON'S DISEASE

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Abstract

Advanced Parkinson's disease (PD) is associated with significant motor and non-motor complications. Motor complications include fluctuations, dyskinesias and unsteadiness and falls, whereas non-motor complications include dysarthria, dysphagia, dysautonomia, psychosis and cognitive decline. In advanced Parkinson's disease continuous intestinal infusion of levodopa/carbidopa (Duodopa) gel has been approved for ameliorating PD-related motor complications. Here, we present the data from five patients who underwent placement of Duodopa pump for advanced PD and were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) prior to and two days after Duodopa pump initiation. These patients met the typical criteria for intestinal Duodopa infusion. This analysis revealed that the overall performance and ability to perform activities of daily living were significantly improved, and motor complications were significantly ameliorated with Duodopa treatment as compared to per os treatment. None of the patients presented a serious complication following Duodopa placement. Continuous intestinal infusion of Duodopa is therefore beneficial and acceptably safe in advanced Parkinson's disease given that the indications and contraindications for this method are considered.

Keywords: Advanced Parkinson's disease, levodopa/carbidopa (Duodopa), motor complications, fluctuations, dyskinesias

Η ΣΥΝΕΧΗΣ ΕΝΔΟΝΗΣΤΙΔΙΚΗ ΕΓΧΥΣΗ DUODOPA ΜΠΟΡΕΙ ΝΑ ΒΕΛΤΙΩΣΕΙ ΤΙΣ ΚΙΝΗΤΙΚΕΣ ΚΑΙ ΜΗ ΚΙΝΗΤΙΚΕΣ ΕΠΙΠΛΟΚΕΣ ΠΟΥ ΣΧΕΤΙΖΟΝΤΑΙ ΜΕ ΤΗΝ ΠΡΟΧΩΡΗΜΕΝΗ ΝΟΣΟ PARKINSON

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Περίληψη

Η προχωρημένη νόσος Parkinson σχετίζεται με σημαντικές κινητικές και μη κινητικές επιπλοκές. Οι κινητικές επιπλοκές περιλαμβάνουν τις διακυμάνσεις, τις υπερκινησίες και αστάθεια και πτώσεις, ενώ οι μη κινητικές επιπλοκές περιλαμβάνουν δυσαρθρία, δυσφαγία, δυσλειτουργία του αυτονόμου, ψύχωση και νοητική έκπτωση. Στην προχωρημένη νόσο Parkinson η συνεχής ενδονηστιδική έγχυση γέλης levodopa/carbidopa

(Duodopa) είναι εγκεκριμένη θεραπεία για την αντιμετώπιση των κινητικών επιπλοκών. Σε αυτό το άρθρο, παρουσιάζουμε τα δεδομένα από πέντε ασθενείς με προχωρημένη νόσο Parkinson που υποβλήθηκαν σε τοποθέτηση αντλίας Duodopa και εκτιμήθηκαν με την Unified Parkinson's Disease Rating Scale (UPDRS) πριν και δύο ημέρες μετά την έναρξη ενδονηστιδικής έγχυσης Duodopa. Οι ασθενείς πληρούσαν τα κριτήρια τοποθέτησης αντλίας Duodopa. Αυτή η ανάλυση έδειξε ότι η θεραπεία με Duodopa οδήγησε σε βελτίωση της γενικής επίδοσης και της ικανότητας επιτέλεσης καθημερινών δραστηριοτήτων, και σε ελάττωση των διακυμάνσεων και των υπερκινησιών, συγκριτικά με την αγωγή από το στόμα. Κανένας από τους ασθενείς δεν παρουσίασε σοβαρή επιπλοκή. Η συνεχής εντερική έγχυση Duodopa είναι συνεπώς αποτελεσματική και σχετικά ασφαλής στην προχωρημένη νόσο Parkinson, εάν τηρηθούν οι ενδείξεις και οι αντενδείξεις της μεθόδου.

Λέξεις Ευρετηρίου: Προχωρημένη νόσος Parkinson, λεβοντόπα/καρβιντόπα (Duodopa), κινητικές επιπλοκές, διακυμάνσεις, υπερκινησίες

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by progressive dysfunction and loss of dopaminergic neurons that reside in substantia nigra pars compacta (SNc) and project to the striatum (nigrostriatal pathway) which is the input nucleus of basal ganglia[1,2]. This degeneration greatly impairs the balance between excitation and inhibition in basal ganglia neuronal circuits, resulting in loss of spontaneous movements and hypokinesia[3]. Despite that idiopathic PD responds to dopaminergic therapy at early stages, at advanced stages PD presents with progressively lower response to levodopa and presents with motor fluctuations, dyskinesias, truncal symptoms that include unsteadiness and falls, dysarthria and dysphagia as well as psychosis and cognitive decline[4]. Motor complications of advanced PD result from fluctuating levels of per os administered levodopa, which when it is present at high levels can lead to dyskinesias and when it is present at low levels can lead to "OFF state". In addition, in PD patients, gastric emptying is delayed, impacting directly the absorbance and bioavailability of orally administered medications that have intestinal absorption. As a result, with disease progression fluctuations and dyskinesias are difficult to manage and become refractory to per os therapeutic manipulations[4]. The continuous intestinal infusion of Duodopa through a portable infusion pump has been approved as a standard of care for advanced PD when certain indications are met, with the most important of these being the good response to levodopa (satisfactory "ON state"), in the absence of contraindications. Levodopa/ carbidopa enteral suspension is marketed as Duodopa outside the United States (U.S.) and it was approved by the European Medicines Agency in 2004, while in the U.S. it is marketed as Duopa and it was approved by the U.S. Food and Drug Administration (FDA) on January 12th 2015; the latter was based on a Phase 3, 12-week, double-blind, double-placebo, multi-center trial that compared the efficacy and safety of Duopa to oral levodopa-carbidopa tablets in advanced Parkinson's disease patients. Here, we present the data from five patients who were placed on Duodopa intestinal infusion for advanced PD at our tertiary center and emphasize the multifaceted clinical benefit of this method in these patients.

Methods

Patients: Five patients with advanced PD who have had good prior response to levodopa and at late disease stages displayed motor fluctuations and dyskinesias despite optimal per os treatment, and without major non-motor disease complications, underwent placement of Duodopa intestinal infusion pump at our hospital, in a collaborative effort by Parkinson's disease outpatient center, the Neurology Clinic, and the Gastroenterology Department. Advanced PD patients met the '5-2-1' criteria for advanced PD[5]. Patients underwent neurologic evaluation before and after the placement of Duodopa infusion pump, which included quantification of PD-associated symptoms and signs with the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS total scores and sub-scores for UPDRS parts I (UPDRS-I), II (UPDRS-II), III (UPDRS-III) and IV (UPDRS-IV) of this scale, which evaluate mood/cognition/ behavior, daily living, motor examination and motor complications, respectively, are presented for two time points, before the placement of the pump and two days after Duodopa initiation. All evaluations were performed at the "ON state" for both per os treatment and for Duodopa. "ON" state is defined as the state in which PD patients have good mobility, as this has been defined previously[6,7]. After Duodopa initiation, all PD medications were discontinued except for dopamine receptor agonists.

Endoscopic procedure: The placement of nasojejunal tube (NJ) and percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) were performed at the endoscopic department following standard procedures. All patients underwent rigorous cardiological and anesthetist evaluation before PEG-J. The

patients had no contraindications for endoscopic PEG tube placement. Prior to the procedure, written informed consent was obtained from all patients and detailed information regarding the procedure itself and the post-procedure tube care was given to both patients and caregivers. All five patients underwent placement of a temporary nasojejunal tube as a treatment evaluation test for a period of three days before the placement of the permanent gastrojejunal tube. The latter consisted of the placement of a 15 French Freka PEG tube via the "pull" technique, through which a 9 French Freka J-tube was inserted during the same procedure. The jejunal tube was placed into the distal duodenum/proximal jejunum by grasping the tube tip with a forceps and then advancing the endoscope. The scope was slowly withdrawn into the stomach while the forceps were advanced to hold the tip of the J-tube in place. Once the endoscope was in the stomach, the forceps were opened, releasing the jejunal tube. One patient presented desaturation at the beginning of the endoscopic procedure and was intubated, followed by detubation at the end of the procedure with immediate and complete recovery.

Graphs and statistics: Data collection and generation of graphs were performed in

GraphPad Prism. Figure assembly was performed in Adobe Illustrator. Formal statistical analysis was not performed for these five patients because of the small size of the sample that would make the power of statistical analysis quite low. Descriptive statistics is provided. Data are presented in three types of graphs: one graph shows all patients on per os treatment and on Duodopa in which absolute values of each sub-scale are presented (a dashed line connects the two values for each patient), one graph shows the change between per os treatment and Duodopa for each patient (each patient is denoted by a different symbol) and an improvement is reflected in negative values, and another graph shows the response rate for each patient (each patient is denoted by a different symbol) and an improvement is reflected in positive values. Response rate % is calculated as the ratio $\Delta UPDRS/UPDRS_{initial}$ ($UPDRS_{initial}$, per os treatment) x100.

Results

Effect of Duodopa on overall performance of patients with advanced Parkinson's disease

Five patients with advanced PD were placed in treatment with Duodopa intestinal infusion pump, while per os treatment for PD was discontinued (see Methods). The overall motor and non-motor performance and the ability to perform activities of daily living were evaluated with the UPDRS before and two days after Duodopa initiation. Evaluations at both time points were performed at the "ON state". Despite the small size of our sample that prevents a detailed statistical analysis, there seems to be a beneficial effect of Duodopa on the overall state and performance of PD patients, compared to their respective state while receiving optimal oral treatment (Figure 1). This is reflected in the lower total score of UPDRS (Figures 1A-C) and the lower sub-score of UPDRS-II (Figures 1D-F) achieved with Duodopa treatment compared to oral treatment. Of note, there also seems to be a positive effect of Duodopa on mood and behavior during the "ON state", as compared to per os treatment (Figure 2).

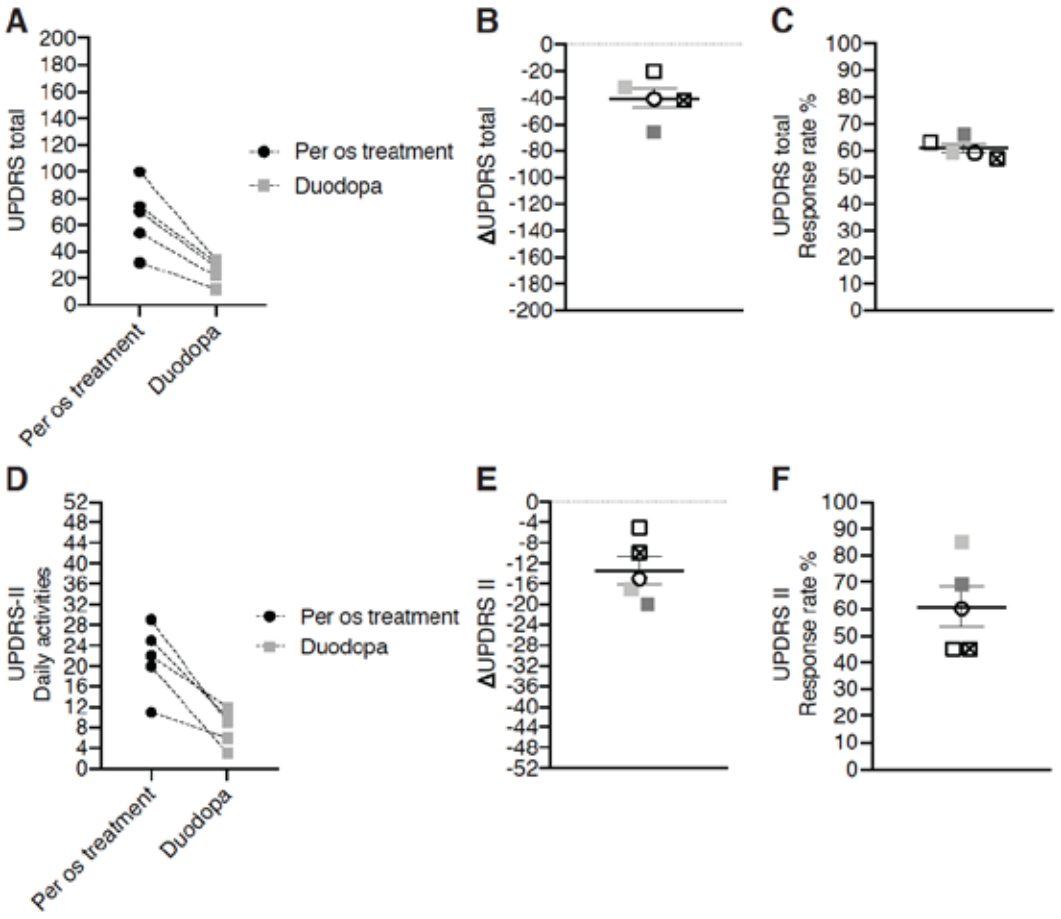

Figure 1. Effects of treatment with Duodopa intestinal infusion on overall performance and state of patients with advanced PD.

(A-C) Duodopa may improve overall performance of PD patients. (A) UPDRS total score before and two days after Duodopa placement for each of the five patients analyzed. Y axis extends up to 199, which is the maximum total UPDRS score. For each treatment category, each dot represents a different patient; the same patients are presented for per os treatment and for Duodopa. (B) All patients present a decrease in UPDRS total score (ΔUPDRS total) while on Duodopa compared to optimal per os treatment, which is reflected in negative values. Data are presented in a scatter dot plot with mean ± S.E.M. (S.E.M., standard error of the mean). Mean decrease is 40.2. Each patient is depicted in a different symbol, which is the same for each patient across all graphs presenting a change (Δ) in this article. (C) Total UPDRS response rate, expressed as %, is calculated as the difference between final and initial total UPDRS score divided by the initial score x100 (see Methods).

(D-F) Duodopa may improve the ability to perform activities of daily living, as reflected in UPDRS-II subscale. (C) UPDRS-II score before and two days after Duodopa placement. Y axis extends up to 52, which is the maximum UPDRS-II score. (D) All patients present an improvement in their daily activities with Duodopa treatment compared to per os treatment. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 13.4. (F) UPDRS II response rate, calculated as explained above.

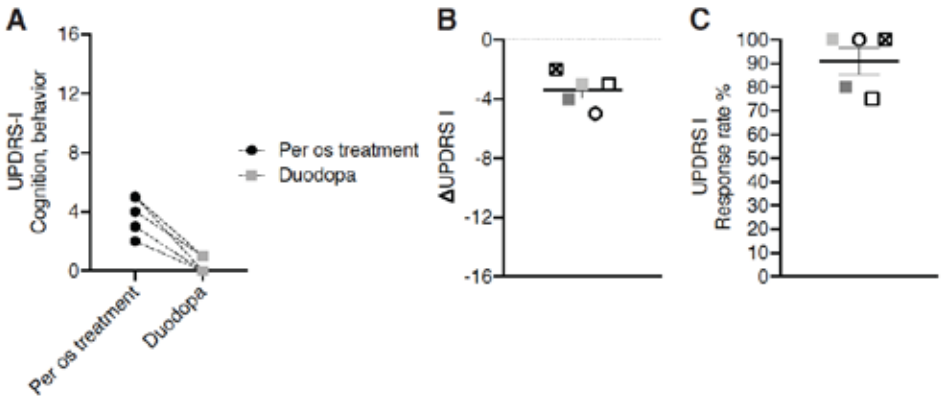

Figure 2. Effects of treatment with Duodopa intestinal infusion on emotional and behavioral deficits associated with advanced PD.

(A-C) Duodopa may ameliorate emotional and behavioral symptoms associated with advanced PD. (A) Mood and behavior, as reflected in UPDRS-I subscale, before and two days after Duodopa placement. Y-axis extends up to 16, which is the maximum UPDRS-I score. (B) All patients display an improved behavioral and emotional profile following Duodopa treatment compared to per os treatment. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 3.4. (C) UPDRS I response rate, calculated as explained above.

Effect of Duodopa on motor deficits associated with advanced Parkinson's disease

Evaluation of PD patients with motor examination for motor performance and motor complications, showed that there is a positive effect of Duodopa on motor performance at the "ON state", compared to per os treatment at the "ON state" (Figures 3A-C). The more modest effect of Duodopa on motor performance as this is reflected in UPDRS-III is attributed to the optimization of per os treatment before Duodopa initiation and also to the timely placement of Duodopa pump in late-stage PD. In addition to evaluating the motor performance overall, we assessed the patients for motor complications including fluctuations and dyskinesias, as these are reflected in UPDRS-IV. This assessment showed that there is a strong effect of Duodopa treatment on motor complications compared to per os treatment (Figures 3D-F). Next, we assessed the effect of Duodopa separately on fluctuations and dyskinesias. This analysis revealed that both fluctuations and dyskinesias may be ameliorated with continuous intestinal Duodopa infusion, compared to per os treatment (Figures 4A-F).

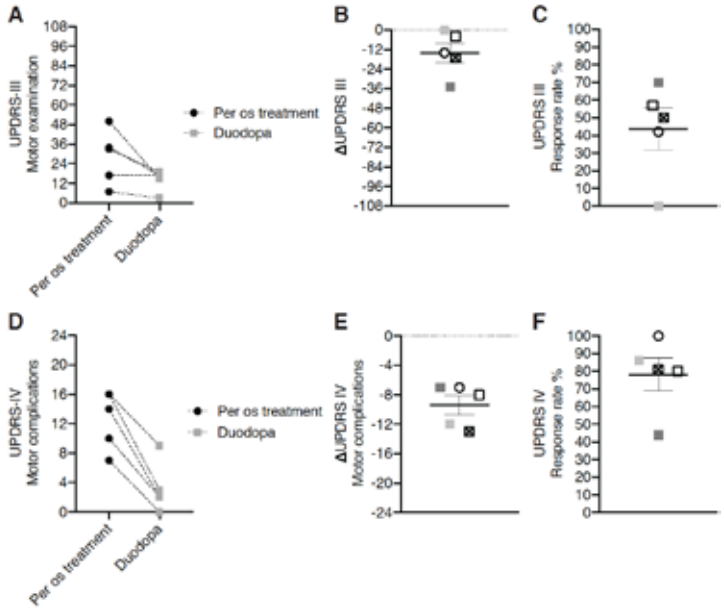

Figure 3. Effects of Duodopa intestinal infusion on motor performance and motor complications in advanced PD.

(A-C) Duodopa may improve motor performance, compared to optimal per os treatment, in advanced PD patients. (A) Motor skills, reflected in UPDRS-III sub-scale, before and two days after Duodopa placement. Y axis extends up to 108, which is the maximum UPDRS-III score. (B) All patients display improved motor skills following Duodopa treatment compared to optimal per os treatment, as reflected in the decrease in UPDRS-III score. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 14. (C) UPDRS III response rate.

(D-F) Effects of Duodopa on PD-associated motor complications (both fluctuations and dyskinesias). (C) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 23, which is the maximum UPDRS-IV score. (D) All patients display diminished PD-related motor complications following Duodopa treatment compared to optimal per os treatment, as reflected in the decrease in UPDRS-IV score. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 9.4. (F) UPDRS IV response rate.

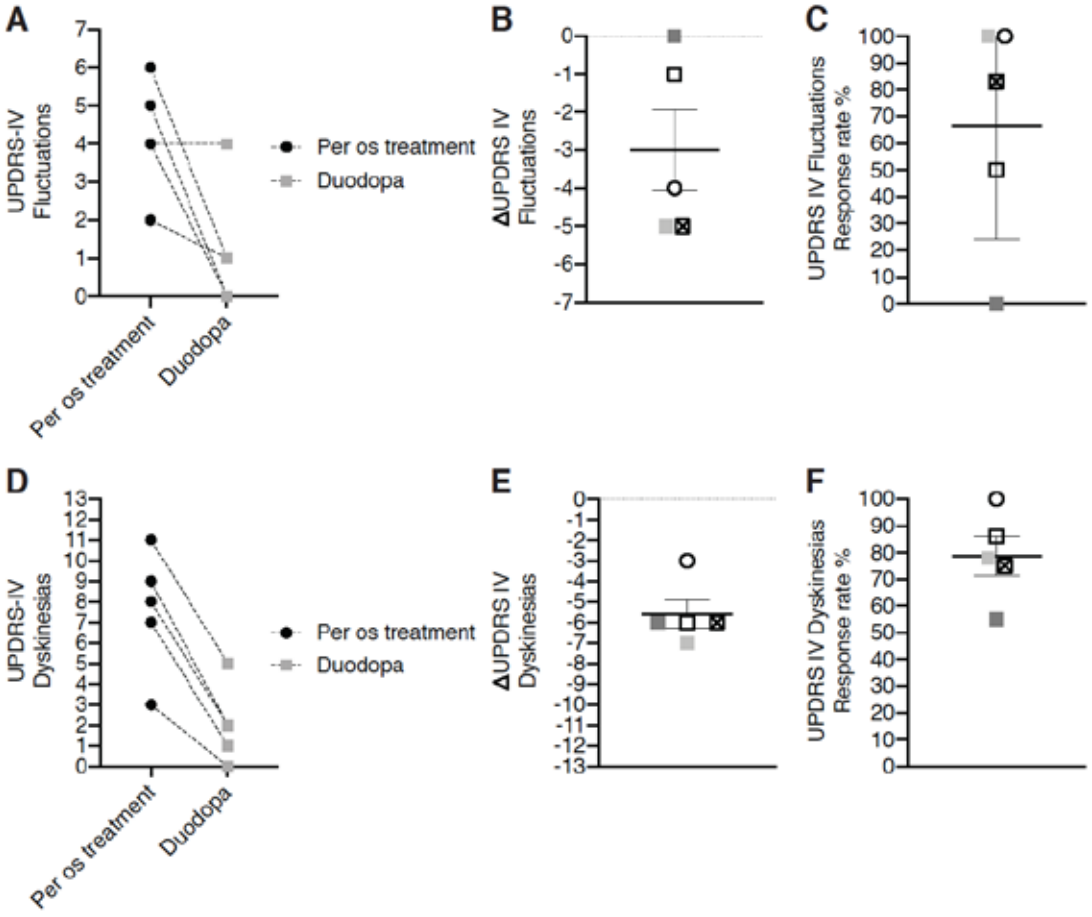

Figure 4. Effects of Duodopa intestinal infusion on fluctuations and dyskinesias in advanced PD.

(A-C) Effects of Duodopa on PD-associated motor fluctuations. (A) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 7, which is the maximum UPDRS-IV sub-score for motor fluctuations. (B) All patients display diminished PD-related motor fluctuations following Duodopa treatment compared to optimal per os treatment. Data are plotted in a scatter dot plot with mean ± SEM; Mean decrease is 3. (C) UPDRS IV response rate of fluctuations.

(D-F) Effects of Duodopa on PD-associated dyskinesias. (C) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 13, which is the maximum UPDRS-IV sub-score for dyskinesias. (D) All patients display diminished PD-related dyskinesias following Duodopa treatment compared to optimal per os treatment. Data are plotted in a scatter dot plot with mean ± SEM; Mean decrease is 5.6. (F) UPDRS IV response rate of dyskinesias.

Optimization of Duodopa intestinal infusion

Duodopa is usually administered with a 16-hour infusion during daytime. Less frequently, Duodopa

infusion is maintained during the night in case it is needed. Of the five patients placed on Duodopa that are presented here, one needed 24-hour infusion to avoid dystonia and freezing associated with the "OFF state" during the night. This is in agreement with previous studies reporting the need for all-day Duodopa administration in a select subset of patients[8]. Moreover, given that most PD patients have worse status in the afternoon and at night, our experience has shown that biphasic titration can work for optimal Duodopa dosage for controlling motor fluctuations and dyskinesias, given the inherent diurnal variability of disease-related symptoms. Moreover, the "dose failure" effect usually seen with per os treatment, was seen intensely in one of our patients, which was surpassed with the administration of an extra dose half an hour before a rich meal.

Safety of Duodopa infusion pump

Duodopa pump treatment may have short-term and long-term complications and/or side-effects. These may be associated with the procedure or the infusion of Duodopa. The vast majority of PEG-J-related complications occur in the first month. Given the short follow-up of our patients (a few months long) following Duodopa initiation, only short-term complications can be presented here. Among our patients with Duodopa pump, one presented with local skin infection around the tube's entry site that resolved with local application of mupirocin cream and another one presented with pneumoperitoneum that resolved after a couple of days with a short course of antibiotics. Moreover, all of our patients presented a transient increase in serum markers of inflammation, mostly asymptomatic. Therefore, percutaneous endoscopic gastrostomy-mediated Duodopa administration seems to be quite safe, in accordance with previous reports[9]. These data are reassuring for advanced PD-affected individuals that choose to follow this type of treatment at the late stages of their disease.

Discussion

Late stage PD is difficult to manage because of the multitude of non-motor symptoms that are variably responsive to treatment, and because of the motor symptoms that result from the advanced degeneration of the dopaminergic system and the non-continuous levodopa administration per os, which both account for peak-dose and end-of-dose side-effects[4]. Duodopa intestinal infusion pump is an approved treatment for motor complications of late stage PD. Our data support the notion that continuous intestinal infusion of Duodopa can mitigate advanced PD-associated morbidity and in particular fluctuations, dyskinesias, and mood and behavioral deficits related to the "OFF state", in accordance with the results of similar studies reported elsewhere[10–14]. This is due to the fact that Duodopa pump reduces L-dopa level fluctuations in plasma leading to reduced motor complications. Our results are in accordance with the results of the largest international, prospective, 54-week, open-label LCIG study. In addition, it has been shown a significant benefit for the quality of life of PD patients and their caregivers[16].

According to our experience, rigorous titration is needed in order to achieve maximal clinical benefit of Duodopa. This includes optimization of continuous dose, which may be different during the day and in the afternoon until Duodopa shutoff, optimization of the morning dose, optimization of extra doses to achieve best motor performance tailored to the needs of individual patients in the absence of debilitating dyskinesias, regulation of the infusion interval (16-hour or 24-hour), and manipulations to minimize dose failure following protein-rich meals.

In our analysis, it is evident that besides motor complications, non-motor symptoms of advanced PD, as these are reflected in UPDRS-I scores, can also be ameliorated with continuous Duodopa intestinal infusion. Although this could be a direct result of the elimination of "OFF states" or be due to the fact that non-motor symptoms were mild, given that UPDRS scoring for both pre-Duodopa and on Duodopa periods was performed at the "ON state", it is possible that effects of Duodopa on brain circuitry controlling mood and behavior account for this non-motor improvement. The latter could be explained by the robust anatomical and functional bidirectional coupling of the circuits that control motor performance with the circuits that control cognition and emotional states[17–19]. In particular, functional disconnection between cognitive control networks and basal ganglia networks has been associated with freezing of gait in patients who were walking and at the same time were performing a cognitive task[19]..Similarly, in PD patients who perform dual task, cognitive and motor, a cognitive error may lead to loss of balance, which is not observed in healthy control subjects [20]. Further, reduced function in executive-attention network and in visual network at resting state has been associated with freezing of gait[21]. Of note, PD patients with freezing of gait who respond to levodopa have a better executive function than PD patients with freezing of gait unresponsive to levodopa[22]. It is therefore likely that continuous intestinal levodopa infusion exerts effects on the feedback loop between motor performance and cognitive states.

Chronic Duodopa intestinal treatment has been associated with the development of polyneuropathy, at least partially accounted for by the malabsorption of complex B vitamins[23]. It is prudent that patients placed on Duodopa treatment are followed up for

signs of polyneuropathy and levels of vitamins.

Given the therapeutic benefit of continuous Duodopa infusion, there have been taking place intense efforts to develop levodopa/carbidopa administered continuously via the subcutaneous route. It seems that this method can achieve good levodopa levels and similar therapeutic benefit[24]. Moreover, subcutaneous levodopa administration is associated with better tolerance because it has fewer side-effects since it is minimally invasive and does not have the high weight of Duodopa pump that the patients need to carry. Provided that PD is a chronic and progressive debilitating disease, the endeavors that point toward the development of continuous subcutaneous Duodopa administration should be intensified with the aim to reduce the burden related with the treatment of advanced PD.

Conflict of interest

The authors declare no conflict of interest related to the work presented here.

Ethical requirements statement

All clinical and laboratory procedures were performed according to the ethical principles for human medical research established by the Declaration of Helsinki (1964 and subsequent amendments) and in line with the "Code of Medical Ethics" (Article 62 N. 2071/1992) and "The Rights of the Nosocomial Patient" (Article 47 N. 2071/1992) of the Greek National Council on Medical Ethics (article 61 N. 2071/1992) as well as in accordance with the institutional policies of Attikon Hospital. Each and every patient has signed a written informed consent.

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