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ORIGINAL ARTICLE

Experience with continuous levodopa enteral infusion (Duodopa®) in patients with advanced Parkinson's disease in a secondary level hospital ☆

D. Santos-García[a,*], M. Macías[a], M. Llaneza[a], L. Fuster-Sanjurjo[b], A. Echarri-Piudo[c], S. Belmonte[d], S. Blanco[d]

[a] *Sección de Neurología, Hospital Arquitecto Marcide, Ferrol (A Coruña), Spain*
[b] *Servicio de Farmacia, Hospital Arquitecto Marcide, Ferrol (A Coruña), Spain*
[c] *Sección de Digestivo, Hospital Arquitecto Marcide, Ferrol (A Coruña), Spain*
[d] *Nursing Staff, Duodopa expert from ABBOTT HEALTHCARE*

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KEYWORDS
Dyskinesias;
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Continuous enteral infusion;
Levodopa

Abstract
Introduction: Continuous levodopa delivery by enteral infusion (Duodopa®) is an alternative to deep brain stimulation and subcutaneous apomorphine to control motor fluctuations and dyskinesias in advanced Parkinson's disease (PD). We report our experience with Duodopa® therapy in 11 patients with advanced PD.
Methods: We retrospectively assessed clinical and quality of life changes in all patients with PD with severe motor fluctuations and dyskinesias who started continuous daily levodopa duodenal infusion through percutaneous endoscopic gastrostomy from September 2006 (Duodopa® was approved for advanced PD treatment in Spain at that date) until April 2010 at the A. Marcide Hospital of Spain.
Results: Nine patients received Duodopa® [62.7±10.6 (44-74) years, 63.6% male)]. Pre-Duodopa® clinical characteristics of patients were: disease duration 14.5±8.9 (3-34) years, oral levodopa dose 918.2±277.7 (450-1300) mg/day, and Hoehn and Yahr staging 3.7±0.5 (3-4). Nine patients are still receiving Duodopa®. Patients improved motor fluctuations (72.7% significant improvement), dyskinesia (55.5% significant improvement), daily off-time (90.9%) and daily duration dyskinesia (66.6%) after total infusion time of 170.5 months (3-31). The improvement in Parkinson's Disease Quality of Life Questionnaire-39 (PDQ-39) and Schwab&England Capacity for Daily Living Scale were 38.5±19.8 and 24±12.5 respectively ($P<0.05$). Equivalent daily dose of levodopa (April 2010) was 1683.4±295.8 (1234-2216) mg/day.

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*Corresponding author.
E-mail: diegosangar@yahoo.es (D. Santos-García).

Conclusions: Intraduodenal infusion of levodopa offers an important alternative in treating patients with advanced Parkinson disease

PALABRAS CLAVE
Discinesias;
Duodopa;
Enfermedad de Parkinson;
Fluctuaciones motoras;
Infusión continua enteral;
Levodopa

Experiencia con la infusión continua de levodopa intraduodenal (Duodopa®) en pacientes con enfermedad de Parkinson avanzada en un hospital de segundo nivel asistencial

Resumen
Introducción: La infusión continua de levodopa intraduodenal (Duodopa®) constituye una alternativa a la infusión subcutánea de apomorfina y a la cirugía en pacientes con enfermedad de Parkinson (EP) avanzada. Describimos nuestra experiencia con Duodopa® en pacientes con EP avanzada.
Métodos: Realizamos un estudio epidemiológico, observacional, no intervencionista, poblacional, descriptivo, y retrospectivo, en el que se incluyen todos aquellos pacientes con EP avanzada tratados con Duodopa® por parte de la Sección de Neurología del Hospital A. Marcide de Ferrol hasta abril de 2010.
Resultados: Once de un total de 12 pacientes seleccionados fueron tratados con Duodopa® [63,6% varones; edad media 62,7 ± 10,6 (44-74) años]. En el momento de ser seleccionados para recibir Duodopa® presentaban: tiempo medio de evolución de enfermedad de 14,5 ± 8,9 (3-34) años, dosis media de levodopa oral de 918,2 ± 277,7 (450-1300) mg/día, y un estadio de Hoehn y Yahr de 3,7 ± 0,5 (3-4). Nueve pacientes mantienen el tratamiento con Duodopa®. Hubo mejoría en las fluctuaciones motoras (72,7% gran mejoría) y discinesias (55,5% gran mejoría) con reducción del tiempo off/día (90,9%) y tiempo con discinesias/día (66,6%) después de un tiempo total de seguimiento con Duodopa® de 170,5 (3-31) meses. La mejoría en las escalas PDQ-39 y Schwab&England fue de 38,5 ± 19,8 y 24 ± 12,5 puntos respectivamente ($p < 0,05$). La dosis media equivalente oral de levodopa (abril 2010) fue de 1683,4 ± 295,8 (1234-2216) mg/día.
Conclusiones: Duodopa® pudiera ser un tratamiento efectivo, seguro, y bien tolerado alternativo a la cirugía y apomorfina subcutánea en pacientes con EP avanzada adecuadamente seleccionados.

Introduction

The progression of Parkinson's disease (PD) and the use of dopaminergic pharmaceuticals is related to the long-term appearance of motor complications (motor fluctuations and dyskinesias) that are sometimes difficult to control.[1] In these patients, the alternatives to conventional symptomatic treatment are surgery —mainly deep brain stimulation of the subthalamic nucleus (DBS-STN)—and continuous infusion treatment through pumps (subcutaneous apomorphine and enteral infusion of levodopa).[2-4] The first results in patients with PD treated with Duodopa® (suspension of water-based levodopa/carbidopa formulated for intraduodenal infusion through an inserted PEG tube) date back to 1993.[5] In 2004, SOLVAY PHARMA obtained permission to use Duodopa® in patients with PD in various European countries.[6] In Spain, it was approved in January 2006 for patients with advanced PD and severe motor fluctuations not controlled with oral medication.[7]

In this study we describe our experience with patients with advanced PD treated with Duodopa® and we discuss the drug as a therapeutic alternative in these patients.

Material and methods

We carried out an epidemiological, observational, non-interventional, population-based retrospective descriptive study in which we included all patients with PD from the Ferrol healthcare area (Northern Spain) who had been or were being treated with Duodopa® by the Neurology Section at Hospital A. Marcide. The objective was to describe the effectiveness, tolerance, and safety of Duodopa® in our patients with advanced PD.

The selection of patients with PD who were candidates to receive treatment with Duodopa® was carried out by a neurologist expert in PD who was responsible for the Movement Disorders consultation (a monographic consultation held

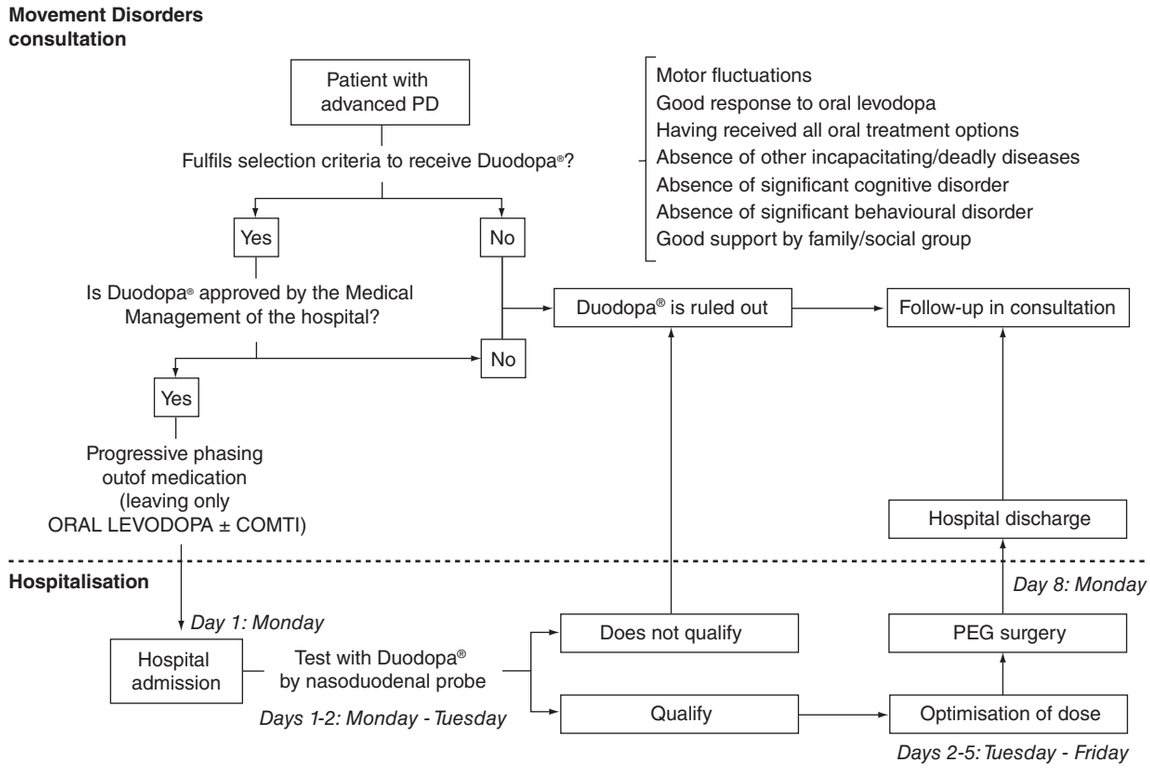

Figure 1 Action Protocol for Patients with PD Who Were Possible Candidates for Duodopa® Treatment.

once a week with a volume of 14 patients per consultation). This treatment option was always evaluated and approved by the Medical Management of the hospital.

Programming the hospital admission of patients to carry out the prior Duodopa® tests through nasoduodenal tube, dose adjustment, percutaneous endoscopic gastrostomy (PEG) surgery, monitoring and evaluation through intraduodenal tube and possible peri/postoperative complications was performed in accordance with the availability of nursing staff from ABBOTT HEALTHCARE, expert in the use of Duodopa®, the Gastroenterology section at our hospital and the patients themselves. The treatment was adjusted for each patient based on a protocol in the weeks prior to admission, ending treatment with dopamine agonists, monoamine oxidase B inhibitors, amantadine and/or anticholinergic drugs, so that the patient would only be receiving oral levodopa (± catechol-o-methyl transferase inhibitors, COMTI) at the time of admission. Patients were admitted on a Sunday, whereupon the Duodopa® dose was adjusted through a nasoduodenal tube in the 72-120 hours after admission. On Monday in the following week, PEG surgery took place (due to the schedule of the Gastroenterology section at our hospital), and discharge took place 24-72 hours after surgery in cases without complications. The following preoperative procedures took place in all cases: chest radiograph, analysis and ECG, outpatient anaesthesia, abdominal radiography to verify nasoduodenal tube placement and abdominal radiography to verify intraduodenal gastrostomy tube placement. Adjustment of the Duodopa® dose was performed according to the established protocols and in accordance with the assessment of the neurologist and ABBOTT HEALTHCARE nurse. The patient was monitored on an outpatient basis, with visits scheduled at 1 week, 15 days, 1 month, and 3 months after discharge, and subsequently every 3 or 4 months. If there were any complications, patients attended the Neurology service. Figure 1 shows the procedure protocol followed in cases of candidates liable to receive treatment with Duodopa®.

Patient data were obtained through the information available in their clinical histories. We quantified the improvement as: 1-Notable improvement, 2-Moderate improvement, 3-Mild improvement, 4-Without effect, and 5-Worsening. We quantified daily off time and dyskinesias time as: 0%, 0-10%, 10-25%, 25-50%, 50-75%, and 75-100% of the total time of the day (while awake). Different scales were used for the assessment of PD: Hoehn and Yahr stage classifications,[8] Schwab and England Activities of Daily Living Scale[9] and Parkinson's Disease Quality of Life questionnaire (PDQ-39).[10] We used the Clinical Global Impression Scale[11] to evaluate the degree of subjective improvement by the patients. Secondary effects and/or adverse occurrences were classified into 4 groups: 1) related to the treatment, 2) related to gastrostomy, 3) related to the device –technical aspects, and 4) others.

Statistical analysis

The data collected was analysed with the statistical program SPSS 16.0. The quantitative variables were expressed as a

mean (standard deviation) and qualitative variables as a percentage. To carry out the comparative analysis, the Student t test or the single factor ANOVA test were used for quantitative variables, and the chi square test was used for qualitative variables. Results with $P<.05$ were considered statistically significant.

Results

The number of patients included was 11, of which 63.6% were males with a mean age of 62.7±10.6 (44-74) years. One patient was rejected by the Medical Management of the hospital (fig. 2).

Table 1 reflects the basal characteristics of patients in relation with their PD. The mean evolution time of PD was 14.5±8.9 (4-34) years, and the span of time with levodopa was 12.7±7.6 (2-30). The Hoehn and Yahr stage was 3.7±0.5 (3-4). With respect to motor complications, all patients presented motor fluctuations (100%deteriorated at the end of dosage; 36.4% on-off phenomenon). As for non-motor symptoms (NMS), the most frequent were depression (100%), anxiety (72.7%), pain (54.5%), and insomnia (54.5%). None of the patients presented cognitive deterioration (MMSE 27.3±1.4). The daily dose of oral levodopa was 918.2±277.7 (450-1.300) mg/day. Two of the patients had been treated previously through a subcutaneous apomorphine continuous infusion pump, and another had undergone DBS-STN.

The mean hospital stay was 11.8±4.6 (7-22) days. The mean time to ascertain an adequate response to Duodopa® and adjustment of the corresponding dose was 3.4±0.7 (3-5) days. There were no complications except problems with probe migration in Case 7 in relation with constipation and intestinal motility deficiency, plus a migration of the probe in Case 11, in which the probe had to be relocated. The equivalent dose of oral levodopa on discharge was 1,796.7±487.1 (1,160-2,670) mg/day.

The evolution of patients treated with Duodopa® is shown in table 2. The total accumulated Duodopa® follow-up time was 170.5 months (3-31). A total of 9 patients are currently undergoing treatment. Case 4 resulted in death from autolysis after 3 months of follow-up. Case 9 interrupted the treatment after 3 months due to lack of expected improvement. One patient (Case 2) received continued infusion during 24 hours. A great improvement in motor fluctuations was reported by 72.7% and in dyskinesias by 55.5% (reduction of off-time in 90.9% and of dyskinesias time in 66.6%). As for NMS, 81.8% presented some degree of improvement (36.6% notable improvement and 45.5% moderate improvement). There was also a significant improvement in quality of life and autonomy (reduction of 42.5±16.1 points in PDQ-39 and increase of 25.6±10.1 in the Schwab/England scale; $P<.05$). The mean equivalent dose of oral levodopa was 1,683.4±295.8 (1,234-2,216) mg/day as of 15th April 2010.

Complications during the follow-up period were: 1) related to the treatment: dyskinesias (Cases 3 and 11) and dizziness (Case 9); 2) related to gastrostomy: 6 patients presented granuloma and 2 local stoma infections; 3) related to the device-technical aspects: 3 patients suffered a gastric migration of the probe, 2 from knotting, 1 from kinking, and 1 had rupture of the external probe; 4) others: autolysis (Case 3), cholecystitis (Case 5), and mild axonal polyneuropathy associated with B12 deficiency and weight loss (Case 9). The total number of radiological tests was 46 abdominal Rx, 15 digestive tract endoscopies, 4 abdominal CT scans, and 3 abdominal ultrasound scans (including digestive endoscopy for PEG and 2 abdominal Rx controls included in the protocol).

Discussion

The present study is a retrospective analysis of the use of Duodopa® in a series of 11 patients with advanced PD. This

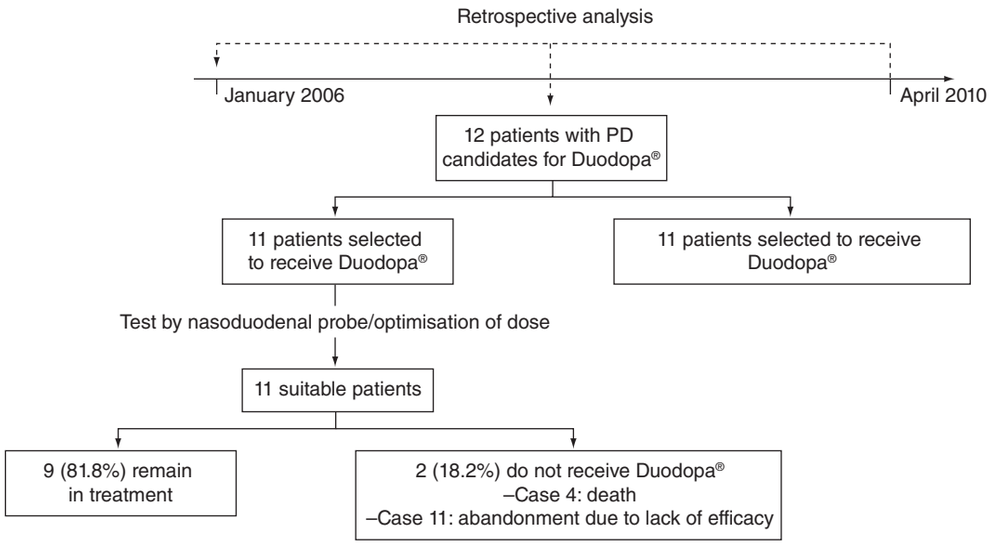

Figure 2 Patients Treated with Duodopa®: Selection and Monitoring.

Table 1 Baseline Characteristics of Patients with PD (Pre-Treatment) Selected for Duodopa® Treatment

	Gender	Age	Years of PD evolution	Years with oral levodopa	Total no. of PD drugs	Current no. of PD drugs	Oral LD dose (mg/day)	MMSE	H&Y (on)	FM	Ds	Non-motor symptoms, other symptoms	APO	Su
Case 1	Male	59	15	11	9	2	1,300	27/30	4	Yes	No	Anxiety, VH, depression, pain, nausea	No	No
Case 2	Female	61	34	30	7	5	750	NE	3	Yes	Yes	Headache, depression, pain, insomnia, dizziness	No	No
Case 3	Male	44	10	10	6	4	750	NE	4	Yes	Yes	Jealousy, depression, insomnia, orthostatism	No	No
Case 4	Male	65	28	22	9	3	700	25/30	4	Yes	Yes	Anxiety, VH, depression, insomnia, orthostatism, psychosis	Yes	No
Case 5	Female	65	13	12	9	2	700	28/30	3	Yes	Yes	Anxiety, constipation, depression, pain, paresthesias	No	No
Case 6	Female	44	4	2	6	5	850	28/30	3	Yes	Yes	Anxiety, depression, dyspepsia, insomnia, dizziness	No	No
Case 7	Male	67	10	9	8	2	1,150	29/30	4	Yes	Yes	Anxiety, depression, constipation, pain	No	No
Case 8	Male	74	14	14	10	4	450	28/30	4	Yes	Yes	Depression, dysphagia, pain, somnolence, cluttering	No	No
Case 9	Male	74	10	9	4	3	1,000	28/30	4	Yes	Yes	Anxiety, depression, insomnia	No	No
Case 10	Female	74	7	7	4	1	1,200	25/30	4	Yes	No	Anxiety, constipation, depression, pain	No	No
Case 11	Male	63	14	12	8	3	1,250	28/30	4	Yes	Yes	Anxiety, VH, constipation, depression, insomnia, cluttering	Yes	Yes
		62.7±10.6	14.5±8.9	12.7±7.6	7.3±2.1	3.1±1.3	918.2±277.7	27.3±1.4	3.7±0.5					

APO: continuous subcutaneous apomorphine infusion; MMSE: Mini-mental State Examination; NE: not evaluated (Cases 2 and 3, clear absence of cognitive impairment); Su: surgery (deep brain stimulation); VH: visual hallucinations.

Table 2 Data Related to Monitoring of Patients with Duodopa®

	Infusion time (months)	Improvement of MF	Off/day before Duodopa®	Off/day post-Duodopa®	Improvement of Ds	Ds/day before Duodopa®	Ds/day post-Duodopa®	CGI scale	Improvement of NMS	Baseline PDQ-39	ΔPDQ-39 Post-Duodopa®	Baseline S&E	ΔS&E Post-Duodopa®	Dose e.q. oral LD (mg/day)
Case 1	31	1	50-75%	0-10%	NE	0%	0%	1	1	114	-60	50	40	1,948
Case 2	29	1	25-50%	0-10%	1	10-25%	0%	1	2	82	-68	40	40	1,712
Case 3	23	1	10-25%	0-10%	5	25-50%	50-75%	2	2	80	-54	60	30	1,234
Case 4	3	X	50-75%	X	X	25-50%	X	X	X	103	X	30	X	X
Case 5	21	1	10-25%	0-10%	3	75-100%	50-75%	2	1	73	-30	60	10	1,658
Case 6	18	1	25-50%	0-10%	1	10-25%	0%	1	2	108	-45	80	20	1,324
Case 7	13	1	10-25%	0-10%	1	10-25%	0-10%	1	2	103	-40	50	20	1,76
Case 8	13	1	75-100%	0-10%	1	10-25%	0-10%	1	1	60	-41	40	30	1,702
Case 9	12	1	10-25%	0%	1	50-75%	10-25%	1	1	74	-21	50	20	1,596
Case 10	4.5	2	75-100%	10-25%	NE	0%	0%	2	2	87	-24	20	30	2,216
Case 11	3	X	50-75%	X	X	10-25%	X	X	X	105	X	50	X	X
	170.5	72.7% notable improvement		↓ 90.9%*	55.5% notable improvement		↓ 66.6%	54.5% much better	36.4% notable improvement	88.6±179	-42.5±16.1*	50±15.6	+25.6±10.1*	1,683.4±295.8

Ds: dyskinesias, MF: motor fluctuations; NE: not evaluated (cases 1 and 10 due to absence of prior dyskinesias); NMS: non-motor symptoms.
Improvement in MF, dyskinesias, and NMS: 1-notable improvement, 2-moderate improvement, 3-mild improvement, 4-no effect, 5-worsening.
Clinical Global Impression Scale (CGI, Clinical Global Impression): 1-much better, 2-moderately better, 3-slightly better, 4-no change, 5-slightly worse, 6-moderately worse, 7-Much worse.
X: no data due to inadequate monitoring.
* $P < .05$.

analysis shows that Duodopa® is an efficient, well-tolerated and safe treatment. However, this must be interpreted in the context of the corresponding methodological limitations.

There are various interesting observations about the epidemiological characteristics of our sample. The mean age is relatively low (62.7 years) if we take into account that the recommended age for surgery is below 70 years.[12] In any case, in other series the mean age is not too high and ranges from 59 (45-83),[13] 60 (39-79),[6] 66 (57-78),[14] 68 (57-74)[15] and 72.7 (36-87)[16] years. Our time of evolution and treatment with levodopa was similar to other series.[13-17] All of our patients presented motor complications that could not be controlled through other oral drugs that they had used during the evolution of their disease. Another important aspect is the presence of many NMS. It is especially relevant that all patients presented depression associated to PD, and that more than half of them also presented anxiety. The fact that these are patients at an advanced stage of PD with very significant limitations probably explains this datum, which is higher than usual (a recent meta-analysis showed a prevalence of depression of 50%[17%major depression, 22% minor depression, and 13% dysthymia] in patients with PD).[18]

Response to treatment was encouraging. There was a significant improvement in relation with motor fluctuations and dyskinesias, with reductions in off-time and total daily time with dyskinesias. Patients also experienced improvement in their quality of life and in their ability to perform normal everyday activities. This was accompanied by a subjective improvement in all cases evaluated through the CGI scale. These data are consistent with previous publications that have reported a reduction in off-time,[6,13-17,19-21] reduction in length and severity of dyskinesias,[12,14] and improvement in the quality of life and autonomy of patients with advanced PD treated with Duodopa®.[14,16,22,23] As for NMS, all the patients who followed the treatment presented some degree of improvement (mostly in depression, anxiety, pain and insomnia). Recent studies have shown an improvement in diverse NMS in patients with PD treated with Duodopa®.[23]

We also observed an increase in the equivalent dose of daily oral levodopa with respect to the dose prior to Duodopa®. Results in other series oscillate between those where an increase was observed and those with no variations. However, most importantly, there was no tolerance phenomenon and dyskinesias did not worsen at higher doses,[6] which could be explained by a more constant plasma concentration of levodopa.[24] In comparison with other continuous dopaminergic stimulation (CDS) options (surgery and subcutaneous apomorphine), Duodopa® usually achieves monotherapy, consequently avoiding the pulsed administration of other additional medications.[25] One patient received 24-hour infusion. Previous studies have reported that a continuous 24-hour infusion of Duodopa® is well tolerated and produces an improvement in sleep.[23,26]

A total of 9 patients (81.8%) are currently following treatment with Duodopa®. The maintenance rate is higher than in other series (57.1%,[13] 73%,[16] 76.9%,[15] and 77.8%[4]), although the length of the follow-up period must be taken into account (170.5 versus 92,[14] 1,045,[13] and more than 1,250[16] months in other series), as should the number of cases treated (11 versus 9,[14] 15,[15] 28,[13] and 91[16] in other series). Case 4 resulted in death due to suicide consummated 3 months after having started treatment.[27] The presence of complications related to gastrostomy and the device were frequent. The number of radiological tests performed was equally high.

Treatment with Duodopa® offers some advantages compared to surgery and apomorphine: there is no associated mortality (1% with DBS-STN), there are no irreversible secondary effects (cerebral haemorrhage with DBS-STN), reversibility, monotherapy in most cases, tolerability similar to oral levodopa, proved effectiveness, fewer exclusion criteria than DBS-STN (age), a "cleaner" therapeutic mechanism similar to the physiological one, and individual regulation of infusion rhythm with the possibility of administration of additional doses. Furthermore, patients can be controlled at units or services of small hospitals, such as in our case, as opposed to the larger facilities required for surgery. The main disadvantages are the need for PEG and daily care of the stoma, the need for support from a family member or caregiver, possible stigma from the need to carry an external infusion pump, adverse effects related to the infusion system, an increase in the number of radiological explorations, and a higher economic cost. There are no defined criteria to select a patient with advanced PD as candidate for one type of therapy or the other (it will depend on many factors such as the characteristics of the patient, family support, preferences of the patient/family, availability of the centre, experience of said centre, etc.) but it is clear that proper selection is fundamental for optimal response.[28] The ideal candidate for Duodopa® is a young patient with an optimal response towards oral levodopa and a good cognitive-behavioural-emotional situation.[28] However, patients rejected for surgery or apomorphine treatment can sometimes be treated satisfactorily with Duodopa®.[29] In our series, Duodopa® was considered as the primary treatment option in 7 of the 11 cases (63.6%). Cases 3 and 6 rejected the possibility of surgery, Case 4 was treated with apomorphine (good response but the treatment had to be abandoned due to adverse effects) and discarded for DBS-STN, and Case 11 had been unsuccessfully treated with apomorphine and DBS-STN. In these cases (4 and 11) Duodopa® was considered as the last treatment option, and these were precisely the two cases with non-optimal response/evolution. Data from other series varies. Recently, Duodopa® was used as the last option after surgery and apomorphine in up to 98% of cases in France (*French DUODOPA Study Group).*[16] In Spain, from January 2006 to January 2010, 246 patients with advanced PD were considered for treatment with Duodopa®. Around 12% of them did not receive the treatment after having been considered unsuitable following the nasoduodenal probe test. Out of the 217 patients treated, 82% were following treatment as of January 2010 (information provided by ABBOTT HEALTHCARE).

Our study has many important limitations. It is a retrospective analysis and not a prospective study, designed specifically to evaluate the effectiveness and safety of Duodopa®. Unified Parkinson Disease Rating Scale (UPDRS)

data is not collected, since that information was not available in all cases. The daily off-time and dyskinesias time is stated in percentages of daily time and not in hours. Lastly, the data referring to pain, depression or anxiety is based on the data collected from the clinical history, symptomatology manifested by the patient or treatment received, with no scales being used for its identification and quantification.

In conclusion, we consider that Duodopa® could be an effective, safe and well-tolerated alternative to surgery and subcutaneous apomorphine in adequately selected patients with advanced PD. A longer follow-up period and a higher number of patients are necessary for more definitive conclusions. We believe that an analysis of all patients treated with Duodopa® in Spain (similar to the study performed in France) would be very interesting.

Conflict of interest

The authors declare no conflict of interest.

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