Duodopa pump treatment in patients with advanced Parkinson's disease

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ABSTRACT

INTRODUCTION: Patients with advanced Parkinson's disease (PD) often develop motor complications including fluctuations and involuntary movements (dyskinesias). In Denmark, treatment has comprised Deep Brain Stimulation (DBS) since the late 1990s, and as from 2002 use of a subcutaneous apomorphine pump. Monotherapy with continuous intestinal levodopa infusion to the duodenum (Duodopa) was introduced in 2004.

MATERIAL AND METHODS: A total of 14 PD patients were assessed for Duodopa pump therapy in the 2004-2008 period. After an initial test week, 12 of the patients had a permanent percutaneous endoscopic gastrostomy (PEG) tube inserted containing a smaller intestinal tube terminating in the duodenum. Before and after treatment initiation, we evaluated the patients using clinical rating scales and video recordings.

RESULTS: Objectively, all 12 patients experienced a significant reduction in fluctuations and dyskinesias while achieving a better gait function. Three patients received Duodopa as 24-hour treatment with good effect on severe nocturnal dystonic pain. One patient suffered a severe complication (peritonitis).

CONCLUSION: Duodopa has a symptom-relieving and stabilizing effect without side effects, but entails a risk of surgical complications (peritonitis).

ORIGINAL ARTICLE

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Currently, we have in our department evaluated 25 patients for Duodopa therapy. The treatment is costly and resource-consuming. Furthermore, it is a specialist task and multidisciplinary team cooperation is needed to ensure optimal patient care. The positive treatment effects include less fluctuations and side effects and therefore improved quality of life for patients, a reduction of the burden of care for families and home care services, and a decrease in the number of undesirable, acute hospital admissions.

Treatment of patients with advanced Parkinson's disease (PD) is a medical challenge. Despite optimal oral medication, patients usually develop motor complications in the form of fluctuations – so called "on-off" phenomena – and involuntary movements (dyskinesias) [1, 2]. The cause of this is longstanding unphysiological, pulsatile stimulation of postsynaptic dopamine receptors in the striatum as a result of the short half-life of levodopa, loss of dopaminergic cells and slower gastric emptying due to disease progression.

In Denmark, advanced treatment for PD patients with unsatisfactory effect of oral treatment has comprised Deep Brain Stimulation (DBS) since the late 1990s [3]. There may, however, be contraindications to surgery, e.g. advanced age, dementia or significant psychiatric illness/symptoms. Furthermore, some patients do not want to undergo surgery, and DBS also carries a risk of neuropsychiatric side effects [4].

Since 2002, a limited number of neurological departments in Denmark have also been treating advanced PD patients with continuous apomorphine using a pump for subcutaneous injection into the abdomen [5]. Apomorphine is a liquid dopamine agonist (DA). However, patients with significant psychiatric illness/symptoms usually do not tolerate apomorphine. Furthermore, psychiatrically healthy patients may develop psychiatric side effects (hallucinations or impulse control disorders). Disabling sedation and formation of subcutaneous nodules at the injection sites are not uncommon. Finally, treatment with apomorphine pump has only limited effect on dyskinesias [6].

Continuous intestinal levodopa infusion to the duodenum would theoretically reduce motor complications owing to a smoother intestinal drug uptake. This would produce more stable plasma concentrations [7] and a more sustained stimulation of the dopamine receptors.

As from September 2004, treatment with liquid sinemet (Duodopa) administered via a tube into the duodenum (**Figure 1** and **Figure 2**) has been possible in Denmark, using a method developed in Uppsala, Sweden, in the 1990s [8].

The treatment was initially introduced at Bispebjerg Hospital, but has now also been implemented at Glostrup Hospital, Roskilde Hospital, Aalborg University Hospital and Aarhus University Hospital. In all, approximately 75 patients have received this kind of treatment in Denmark. Throughout Europe, in excess of 1,500 patients have presently received Duodopa treatment.

An advantage of Duodopa is that it is usually administered as monotherapy during the patient's waking hours and accompanied by a night-time levodopa slow-

FIGURE 1

Duodopa pump kit.
A) Cassette for Duodopa medication; B) pump; C) connection; D) percutaneous endoscopic gastrostomy tube (outer tube to the stomach); E) inner tube (to the duodenum).

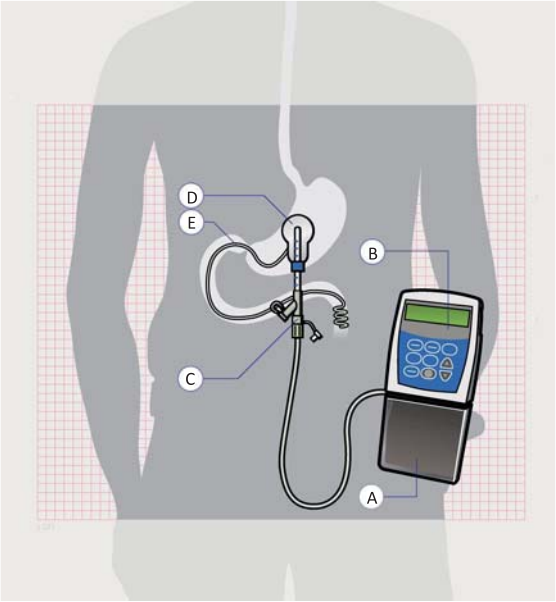

FIGURE 2

Duodopa pump.

release formulation. Treatment for any non-dopaminergic symptoms continues as scheduled. Some patients require 24-hour Duodopa pump treatment (the night-time dose constitutes approx. two thirds of the dose administered during the day).

To our knowledge, comparative studies on the efficacy of the three therapies have not yet been published, but a multicenter study to such effect is under preparation. The effect of the three modalities is probably comparable.

The aim of the present paper is to report the effect of Duodopa treatment on 14 PD patients' "on" state as measured by the Unified Parkinson Disease Rating Scale (UPDRS) III and their motor fluctuations and dyskinesias.

MATERIAL AND METHODS

Fourteen patients with advanced idiopathic PD (four men and ten women, mean age 64.9 ± 13.5 (mean ± standard deviation (SD)) years, Hoehn and Yahr Stage: 3.3 ± 0.7, disease duration: 16.2 ± 7.4 years) (**Table 1**) with unsatisfactory effect of oral medication were assessed for Duodopa treatment at the Neurological Department of Bispebjerg Hospital in the period 2004-2008. The patients were either followed at our Outpatient Clinic or Parkinson Day Hospital, or they were newly referred for evaluation at our Department.

All patients required advanced treatment, and neither DBS nor apomorphine pump treatment was possible: Four patients had insufficient effect of oral DA, four could no longer be adequately treated with apomorphine pump, four suffered side effects to DA and one young patient (no. 1 in Table 1) opposed to DBS. Furthermore, one patient (no. 3 in Table 1) initially received apomorphine pump treatment during admission, but developed visual hallucinations after a few days. The patient had dementia (Mini-Mental State Examination < 24). Only one of the other patients (no. 7 in Table 1) had clinical dementia.

Twelve of the 14 patients are still being treated with the pump and have been followed for 2-43 months (mean 16.3 ± 15.7 months) after treatment initiation.

Patients were switched directly from their previous treatment to Duodopa, but high-dose DA patients tapered out DA treatment before admission. On the first day of admission, patients were scored using the UPDRS III and recorded on video in the "on" and "off" state. Furthermore, patients or staff started to write Parkinson's diaries covering the whole day to document motor complications. Before discharge and after one month of treatment, the above measures were repeated. The best objective motor scores (UPDRS III) were compared before and after Duodopa initiation. The last three patients also completed a validated Quality of Life scale (SF36).

Duodopa (Solvay Pharmaceuticals GmbH, Hannover, Germany) is liquid Sinemet: a solution of levodopa in carboxymethyl cellulose 20 mg/ml and carbidopa 5 mg/ml. The medication comes in pre-mixed cassettes of 100 ml for approximately one day's consumption. The pump used is a portable CADD pump (Smiths Medical, Minneapolis, MN, USA) (size 9 × 19 cm, weight 500 g).

Before initiating treatment, the expected consumption of Duodopa was calculated on the basis of the patient's current total consumption of medication (l-dopa equivalent):

TABLE 1

Patient data.

Patient	Daily medication before Duodopa	LD-equiv., mg/day	Most common complaints	UPDRS III "on" before/ after Duodopa	Reduction in UPDRS III "on" after one month, %	Duodopa doses	LD consumption per day, morning + cont. + SR, mg/day	LD consumption, change, %	Clinical effect	Complications	Side effects	Help
1	675 mg LD/CD Pergolide 3.9 mg	1,065	Fluctuations "Off" periods Difficulties in the morning	68/10	85	Morning: 5.2 ml Cont.: 4.5 ml/hour Bolus: 2.0 ml	1,744	+ 64	Overall marked improvement	Inner tube slid out and also into the stomach, but with unchanged effect	Depression Antidepressants in 5 months	Personal assistant 10 hours daily stopped Managed by herself
2	Selegiline 5 mg LD/CD, SR 125 mg LD/CD 350 mg Tolcapone 300 mg	475	Dystonic pain in left side Fluctuations	27/15	44	Morning: 0.8 ml Cont.: 3.5 ml/hour No bolus	1,336	+ 281	Marked improvement, especially concerning dystonic pain Better gait function (walker)	After 1 month: inner tube slid into the stomach After 18 months: admitted with clogged inner tube	After 1 year: Admitted with hallucinations (good response to clozapine)	Unchanged private home care service
3	LD/BE, SR 100 mg LD/BE 800 mg EN 1,600 mg	900	Dystonic pain and cramps in "off" Dementia with confusion in "off"	48/25	48	No morning dose 4.9 ml/hour as 24-hour treatment Bolus: 2 ml	2,352	+ 261	"New life" No dystonic pain Increased level of function Less confused Sleeps at night	None	Mild hallucinations (demented patient)	Spouse
4	LD/CD 400 mg LD/CD, SR 1,000 mg Amantadine 200 mg	1,400	Reduced effect of the medication "Off" periods with tremors Hyperkinesias Falls	37/25	32	Morning: 4.0 ml Cont.: 2.7 ml/hour Bolus: 7 ml	1,144	–18	Fewer hyperkinesias Better gait function Fewer "off" periods	Secretion of gastric juice because of hyperkinesias After 2 months: inner tube slid into the stomach After 4 months: new tube with new entry Inner tube slid out × 3	None	Spouse + unchanged home care service
5	LD/CD/EN 800 mg Pram 4.2 mg	1,080	Fluctuations Hyperkinesias Wearing-off "Bad thoughts"	37/24	35	Cont.: 5 ml/hour 24-hour treatment because of pain in legs Bolus: 3 ml	2,400	+ 222	Fewer fluctuations Less pain in the legs (can walk to the toilet at night) Fewer hyperkinesias	After 4 months: inner tube occluded After 5 months: inner tube slid out	None	Spouse and now home care service
6	LD/CD, SR 300 mg LD/BE, Quick 50 mg LD/BE 850 mg Apomorphine pump 5.5 mg/hour	1,200 (+ apomorphine = 1,760) = 2,960	Sedation Hyperkinesias Fluctuations	20/16	20	Morning: 9 ml Cont.: 4.5 ml/hour Bolus: 2 ml	2,020	–53	Less sedation Fewer fluctuations Fewer hyperkinesias	None	None	Only spouse
7	LD/CD 200 mg Pergolide 1 mg	300	"Off" periods Fluctuations Many hyperkinesias	43/35	19	Morning: 2.4 ml Cont.: 3.7 ml/hour Bolus: 1.5 ml	1,432	+ 477	Stabilized Fewer hyperkinesias	Inner tube slid into the stomach × 4 Admitted once with crack in the tube	None	Home care service unchanged

TABLE 1

Table 1. Continued.

Patient	Daily medication before Duodopa	LD-equiv., mg/day	Most common complaints	UPDRS III "on" before/ after Duodopa	Reduction in UPDRS III "on" after one month, %	Duodopa doses	LD consumption per day, morning + cont. + SR, mg/day	LD consumption, change, %	Clinical effect	Complications	Side effects	Help
8	Patient decided against PEG											
9	LD/CD 1,400 mg Pram 2.1 mg LD/BE Quick 200 mg	1,740	Periods with tremor Gait problems "Off" periods	38/17	55	Morning: 9 ml Cont.: 5.9 ml/hour Bolus: 4 ml	2,168	+25	No longer "walker" Mentally better (no anxiety)	After 1 week: operated for acute peritonitis (perforation in the stomach)	None	Spouse and home care service unchanged
10	Apomorphine pump 5.5 mg/hour LD/CD 400 mg LD/CD SR 100 mg	500 (+ apomorphine = 1,760) = 2,260	Fluctuations Sedation Hallucinations	28/21	25	Morning: 3 ml Cont.: 4.5 ml/hour Bolus: 2 ml	1,600	–29	Fewer fluctuations No sedation No hallucinations	None	None	Spouse (home care service educated in use of the pump)
11	Amantadine 150 mg LD/BE 800 mg	800 mg	Fluctuations "Off" periods Hyperkinesias	58/41	29	Morning: 5.7 ml Cont.: 2.3 ml/hour Bolus: 0.5 ml	950	+19	Fewer fluctuations Fewer hyperkinesias Only "off" periods while eating	Tube placed × 2 (in generalised anaesthesia)	None	Spouse (home care service educated in use of the pump)
12	Patient decided against PEG											
13	Pram. 1.4 mg Tolcapone 300 mg LD/BE 375 mg	468 mg	Low level of function Reduced effect of the medication Fluctuations and hallucinations	35/13	63	Morning: 11 ml Cont.: 5.4 ml/hour Bolus: 3 ml	2,048	+438	Better gait function The patient was now able to manage by himself Dancing	None	Irritated skin around the tube insertion site	Spouse, but less strain
14	LD/BE 350 mg EN 1,400 mg Apomorphine pump 6.25 mg/hour + 3.75 mg as bolus	350 mg (+ apomorphine pump = 2,000) = 2,350	Dystonic pain and cramps, especially at night Sudden "off" periods	2/3	50 (worsening)	Cont.: 5.5 ml/hour in daytime From afternoon: 5.7 ml/hour At night: 3.7 ml/hour Bolus : 4 ml 24-hour treatment	2,500	+6	Less dystonia, but 24-hour treatment necessary More stable	None	None	The patient was now able to manage by himself

EN = entacapone; LD/BE = levodopa, benserazid; LD/CD = levodopa, carbidopa; PEG = percutaneous endoscopic gastrostomy; Pram = pramipexole; SR = slow-release; UPDRS III = Unified Parkinson Disease Rating Scale III.

- As morning dose: 80% of oral l-dopa equivalent morning dose.
- As continuous dose: 90% of the remaining days l-dopa equivalent dose spread over 16 hours.
- As extra dose: Start with 1 ml (20 mg l-dopa).

All patients participated in a 4-7-day test period in which Duodopa was administered through a nasoduodenal test tube and adjusted as needed. Upon observation of a satisfactory effect during the test period, experienced surgeons at our Endoscopic Department inserted a percutaneous endoscopic gastrostomy (PEG) tube containing a jejunal inner extension, the point of which was placed at the ligament of Treitz. The location of the point of the inner tube in the duodenum was confirmed radiographically before the patient left the Endoscopic

Department. The vast majority of patients were discharged one week after insertion of the permanent tube. Prior to discharge, the patient along with his or her relatives and home care nurses were trained in the handling of the the pump by staff at the Department and a nurse from Solvay.

After discharge, patients were followed at our Parkinson Day Hospital by a specialised Parkinson nurse and/or physician at 1-2 month intervals as needed.

RESULTS

Two patients discontinued Duodopa treatment after the test period at their own request. Three patients received Duodopa as 24-hour treatment with good effect on severe nocturnal dystonic pain. None of these patients experienced the decrease in effect which might have been expected due to continuous treatment (tolerance). No patients developed hallucinations. There was good agreement between subjective and objective assessments as well as video recordings.

For nine patients the total consumption of levodopa was significantly higher after changing to Duodopa; The mean increase constituted 199% (range: 6-477%). Three patients experienced a reduction in levodopa consumption: 33% (range: 18-53%). Motor condition was stabilised within the first month.

The mean reduction in the UPDRS III was 34% (from 85% improvement to 50% deterioration) (Table 1). Quality of life assessment using the SF-36 demonstrated a reduction in the score of one patient from 118 to 74 after one month and to 45 after two months (62% reduction). The maximum score (worst possible condition) is 149. Another patient had scores of 81, 89 and 91, respectively, representing a score increase; but during the test period, the patient was psychosocially burdened by issues other than his PD.

Complications: One patient suffered from continued hyperkinesias causing secretion of large quantities of gastric juice, which irritated the skin around the tube insertion site and resulted in several tube shifts.

In two patients, the inner tube slipped out. One patient underwent surgery for acute peritonitis one week after PEG because the tube had perforated the stomach. The tube was not replaced, as the patient died some months after surgery. The cause death was unrelated to the surgery. In three patients, the tube slid into the stomach, leading to reduced and more varying medication effects. The tube was returned to its correct position at our Endoscopic Department under X-ray guidance.

DISCUSSION

All twelve patients experienced significant improvement after switching to Duodopa treatment. Most patients described a decrease in motor fluctuations (six patients) and dyskinesias (five patients) and improved gait function (five patients) (Table 1). These findings are in accordance with the results achieved by other groups [9-11]. A total of four patients reported reduced dystonic pain. This symptom is not scored in the UPDRS III.

The total consumption of levodopa per day increased significantly in most patients, while their hyperkinesias simultaneously decreased. This phenomenon indicates that it is the pulsatile stimulation of dopamine receptors by oral medication that causes motor complications rather than the total quantity of medication per day. Pulsatile stimulation up-regulates the glutamate receptors in the postsynaptic GABAergic neurons in the striatum, which overstimulates the neurons leading to dysfunction and dyskinesia [12-14].

The efficacy of Duodopa was unchanged in the follow-up period. Several patients' doses were reduced by approximately 5% at follow-up, as also described in other studies [15].

We have currently evaluated 25 patients for Duodopa. Treatment is costly and a specialist task. It should therefore only be offered at main centers for Parkinson's patients in Denmark. It is important that the treatment team comprises neurologists, gastroenterologists, nurses as well as an outbound contact to cooperate in the care of the patient. Thorough training of the patient and any relatives and caregivers is important to ensure that everyone feels capable of handling the pump after discharge.

The average daily treatment cost (DDD) for Duodopa is 339 DKK (a Euro is approximately equivalent to 7.5 DKK) including the pump. Apomorphine treatment costs are 102 DKK per day plus an additional pump cost of 12,850 DKK, and the cost of tubing, needles, etc. is 2,000 DKK. DBS is associated with one-off costs in the order of 250,000 DKK, to which should be added the cost of battery change every 4-5 years (80,000 DKK). Under the assumption of a long life expectancy, DBS is the most inexpensive of the three treatment options currently available.

Conversely, Duodopa treatment is associated with substantial savings owing to fewer hospital admissions, a reduced need for home care and personal assistance services as well as residential care facilities and finally less strain on the spouse and other family members. It is well-documented [16] that motor complications such as nocturnal akinesia and dyskinesias affect quality of life substantially.

CONCLUSIONS

Duodopa pump treatment is an expedient offer for selected patients with advanced PD who have experi-

enced unsatisfactory effect of oral treatment, and for whom the DBS and apomorphine pump treatment are not possible. The disadvantages of being "tied" to a rather bulky pump, and any stomach tube discomfort experienced were clearly outweighed by Duodopa's symptom-relieving and stabilising effect with few side effects, but the risk of surgical complications, especially in the form of peritonitis, should be taken into consideration. Duodopa pump treatment is difficult to implement successfully without the assistance of a care system based on home care or relatives. Further technical development leading to a smaller pump and an optimized PEG-tube system is desirable.

In the light of the positive results, it would be expedient to offer Duodopa pump treatment to fluctuating PD patients earlier in the disease course.

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REFERENCES

1. Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol 2000;47(suppl 1):2-11.
2. Golbe LI. Young-onset Parkinson's disease: a clinical review. Neurology 1991;41:168-73.
3. Marconi R, Landi A, Valzania F. Subthalamic nucleus stimulation in Parkinson's disease. Neurol Sci 2008;29 Suppl 5:S389-91.
4. Voon V, Kubu C, Krack P et al. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord 2006; 21(Suppl. 14):S305-27.
5. Stocchi F. Use of apomorphine in Parkinson's disease. Neurol Sci 2008;29 Suppl 5:S383-6.
6. DeGaspari D, Siri C, Landi A et al. Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus. J Neurol Neurosurg Psychiatry 2006:77:450-53.
7. Nyholm D, Askmark H, Gomes-Trolin C et al. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003;26:156-63.
8. Bredberg E, Nilsson D, Johansson K et al. Intraduodenal infusion of a water-based levodopa dispension for optimisation of the therapeutic effect in severe Parkinson's disease. Eur J Clin Pharmacol 1993;45:117-22.
9. Antonini A, Isaias I, Canesi M et al. Duodenal levodopa infusion for advanced Parkinson's disease: 12-months treatment outcome. Mov Disord 2007;22:1145-9.
10. Westin J, Nyholm D, Groth T et al. Outcome prediction of enteral levodopa/carbidopa infusion in advanced Parkinson's disease. Parkinsonism and related Disorders 2006:12; 509-13.
11. Odin P, Wolters E, Antonini A. Continuous dopaminergic stimulation achieved by duodenal levodopa infusion. Neurol Sci 2008;29 Suppl 5: S387-8.
12. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006;5:677-87.
13. Nyholm D, Lewander T, Johansson A et al. Intraduodenal infusion of a gel suspension of levodopa/carbidopa, Duodopa, in advanced Parkinson's disease: safety, tolerability, efficacy and dosage. Mov Disord 2004;19(Suppl.9):S177.
14. Nyholm D. The rationale for continuous dopaminergic stimulation in advanced Parkinson's disease. Parkinsonism Rel Disord 2007;13:S13-17.
15. Nyholm D, Lewander T, Johansson A et al. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term Exposure. Clin Neuropharmacol 2008;31:63-73.
16. Chapuis S, Ouchchane L, Metz O et al. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord 2005; 20:224-30.