BAOJ Neurology

Alvaro Sanchez-Ferro, et al., BAOJ Neuro 2015 1: 2
1: 007

Short Communication

Effectiveness of Gastric Levodopa Infusion on Motor Fluctuations in a Series of Advanced Parkinson's Disease Cases

Alvaro Sanchez-Ferro[1,2,3,4*], Jaime Herreros-Rodríguez[1,2,3], Jaime Hernando-Alvarez [5], Fernando Canga Rodriguez-Valcarcel[6] and Jose A Molina-Arjona[1,2,3]

[1]Department of Neurology, Hospital Universitario 12 de Octubre, Madrid, Spain

[2]Department of Medicine, Facultad de Medicina, Universidad Complutense de Madrid, Spain

[3]HM Hospitales – Centro Integral en Neurociencias HM CINAC, Spain

[4]Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge, USA

[5]Department of Nuclear Medicine, Hospital Universitario 12 de Octubre, Madrid, Spain

[6]Department of Gastroenterology, Hospital Universitario 12 de Octubre, Madrid, Spain

Abstract

Background

Enteral (duodenal or jejunal) levodopa-carbidopa gel infusion is increasingly used for the treatment of patients with fluctuating advanced Parkinson's disease (PD). It has been argued that delayed and inconsistent gastric emptying cause erratic absorption of oral levodopa and may play a role in the loss of efficacy of oral therapy. However, the experience with therapeutic strategies in the advanced phase of the disease is still limited.

Methods

Three patients with technical problems and transient gastric levodopa infusions were retrospectively evaluated. A motor examination (on status) and gastric motility studies (off status) were performed. Gastrointestinal motility was assessed by scintigraphy with $^{(99m)}$Tc-DTPA-labeled meal.

Results

Two women aged 74 years and one man aged 66 years with advanced PD were treated with transient continuous levodopa infusion into the stomach due to technical problems. No changes in the Unified Parkinson's Disease Rating Scale (UPDRS) scores, Hoehn and Yahr stage, or global score of the Clinical Global Impression (CGI) scale were documented. Adverse effects were not observed. Two of the patients had a lower gastric emptying on scintigraphy.

Conclusion

Gastric levodopa infusion could be as effective as enteral levodopa infusion without significant adverse outcomes in certain cases. Impairment of gastrointestinal motility appears to be unrelated to the effectiveness of infusion levodopa therapy in some patients with fluctuating advanced PD. Further studies are needed to confirm these results.

Keywords: Advanced Parkinson's disease; Continuous Dopaminergic Stimulation; Duodenal Levodopa Infusion; Gastric Emptying; Gastric Levodopa Infusion.

Financial disclosures

ASF has received travel grants and Honoraria from Abbott Healthcare. JHR, FCRV and JAM have received honoraria from Abbott Healthcare. Dr. Alvaro Sanchez-Ferro is currently enjoying a research fellowship grant from the Madrid-MIT M+ Vision Consortium (Comunidad de Madrid)

Introduction

Parkinson's disease (PD) is a clinical syndrome characterized by bradykinesia accompanied by rigidity, tremor, or postural instability. The disease has a typical progressive clinical course leading to a state in which motor symptoms increasingly fluctuate throughout the day (or on-off fluctuations) after a variable period from the initial diagnosis (usually three to five years). Motor fluctuations and other non-motor complications in patients with advanced PD become increasingly challenge to manage over time.

Continuous enteral (duodenal or jejunal) levodopa-carbidopa gel infusion is an effective and feasible alternative to reduce daily off-time and to improve other motor and non-motor symptoms of the disease [1, 2]. However, technical issues related to problems with

***Corresponding author:** Centro Integral de Neurociencias AC, Avenida del Emperador Carlos V, 70, E-28938 Madrid, Spain, Tel: +34 91 2673200; Fax: +34 912673197; E-mail: asferro@mit.edu

Sub Date: October 1 2015, **Acc Date:** October 5 2015, **Pub Date:** October 7 2015.

Citation: Alvaro Sanchez-Ferro, Jaime Herreros-Rodríguez, Jaime Hernando-Alvarez, Fernando Canga Rodriguez-Valcarcel and Jose A Molina-Arjona (2015) Effectiveness of Gastric Levodopa Infusion on Motor Fluctuations in a Series of Advanced Parkinson's Disease Cases BAOJ Neuro 1: 007.

the infusion device have been reported to occur in up to 70% of patients [3], particularly dislodgement and blockade of the inner tube, with the need of removal and replacement of the portable pump. Although many patients with advanced PD have impaired gastric motility [4] and this has been cited as a potential reason of motor fluctuations due to erratic absorption of drugs given to treat the disorder [5], no previous study has addressed the influence of gastric emptying and the use of the currently employed continuous levodopa infusion into the stomach in patients with fluctuating advanced PD. A pilot study conducted in 1988 evidenced in 10 PD patients that duodenal and gastric infusions improved motor function compared with standard oral therapies. In the overall comparison, the duodenal delivery was preferable, but it was reported that in some of the cases the effect of a gastric infusion was similar to a duodenal one [6].

We hypothesize that gastric emptying may not be as relevant as previously suspected in some subjects and that continuous gastric levodopa infusion may be as effective as continuous enteral levodopa infusion in the management of certain patients with fluctuating advanced PD. Here, we describe three patients in which gastric levodopa infusion was transiently established for different reasons. None of the patients had a change in their clinical status as a result of gastric delivery of levodopa.

Methods

All the patients gave written informed consent and were attended at the Movement Disorder Unit of the Department of Neurology of Hospital Universitario 12 de Octubre, in Madrid, Spain. Data of the patients were retrospective collected from their medical records by three of the authors (ASF, JHR, JAM). The diagnosis of PD was made according to the UK PDS Brain Bank Criteria [7]. Clinical assessment was performed at two different time points based on the location of the infusion system (stomach or duodenum). During intragastric and intraduodenal continuous delivery of levodopa, the following were assessed: a) motor status, b) device position, c) gastric motility, and d) efficacy of treatment.

Motor status included data of the Unified Parkinson's Disease Rating Scale (UPDRS) section III scores (maximum score 68) [8] and Hoehn and Yahr stage [9] both in the on status during duodenal and gastric levodopa infusion. The disease phenotype was also documented and the cause and duration of gastric levodopa treatment were also registered. The precise position of the infusion system was confirmed visually during the upper gastrointestinal endoscopic examination and further assessed by abdominal X-ray studies. Symptoms of gastrointestinal motility impairment were evaluated by the non-motor items of constipation, salivation, and swallowing of the UPDRS [8] and the Non-Motor Symptom Scale (NMSS) [10]. Gastric motility was objectively evaluated with a 2 mCi $^{(99m)}$Tc-DTPA labeled meal, acquiring dynamic scintigraphy images for 1 hour. It was performed in the off status after an overnight fast (drugs affecting gastric motility, e.g., prokinetics, were stopped for 48 h prior the test) [11]. Slowed or delayed gastric emptying was defined as an elimination less than 50% of the radiolabeled food thirty minutes post-intake. [11].

The efficacy of treatment was evaluated in a different clinical visit during the gastric and duodenal levodopa therapy using the global score of the Clinical Global Impression (CGI) [12]. Patients were asked if any change in the treatment outcome or adverse events for the two infusion sites were noticed.

Results

Description of Cases

Case #1 was a 74-year-old woman with a history of PD of 20 years' duration (tremoric phenotype) who was referred to our unit because of uncontrollable motor fluctuations. The clinical evaluation showed response to oral levodopa treatment with persistent off time despite different oral drug combinations, and moderate dyskinesia. Continuous duodenal levodopa-carbidopa gel infusion was started in September 2010; a mild-to-moderate cognitive impairment was not considered a contraindication for the procedure. An improvement in off/on times with some persistent dyskinesia was obtained. However, 18 months after percutaneous endoscopic gastrostomy, the inner tube was dislodged and expelled with the stools. An immediate replacement of the infusion system was not feasible and there was no change in the patient's motor symptoms. The patient was scheduled for a change in the up-coming months based on the current recommendations for replacement and the fact that she already underwent an endoscopic procedure to solve another complication. Four months later, the programmed replacement was carried out, leaving the system in the duodenum. Once again, we noticed that the motor situation was similar to that of the drug administered directly into the stomach. A Hoehn & Yahr stage IV was confirmed in both treatment periods. UPDRS III section was only registered in the duodenal period with a value of 20 points. In the gastrointestinal symptoms assessment, mild dysphagia and moderate sialorrhea were reported. In the scintigraphy, 31% of the gastric content was eliminated after 30 min, reflecting a moderate slowing of gastric emptying. No differences in the overall CGI score between both routes of levodopa infusion were observed, and neither the patient nor the family reported any relevant clinical change or adverse events related to gastric levodopa infusion.

Case #2 was a 74-year-old woman with a long-standing history of PD (17 years) and tremoric phenotype in whom continuous duodenal infusion of levodopa-carbidopa gel was indicated in March 2011 due to uncontrollable motor fluctuations. A favorable response to treatment was observed. In August 2011, an obstruction of the inner tube during 5 consecutive days occurred. Conservative measures including the administration of dromperidone 10 mg every 8 h and fiber-rich diet resulted in reversal of the occlusion, and the duodenal access could be re-used. There was no evidence

of changes in the patient's motor condition, with a Hoehn & Yahr stage III and UPDRS motor scores of 19 and 20 during the duodenal and gastric levodopa infusion, respectively. No subjective gastrointestinal symptoms were reported. A slight impairment of 46% in the gastric motility was documented in the scintigraphy. No adverse events were recorded. The patient's clinical condition and the overall CGI scores were similar during duodenal and gastric levodopa infusion periods.

Case #3 was a 69-year-old man with a history of PD of 15 years' duration (akinetic phenotype) who started continuous duodenal infusion of levodopa-carbidopa gel in March 2012. In the initial optimization process, the nasointestinal tube could not progress and the levodopa infusion treatment had to be started from the stomach because endoscopic/fluoroscopic placement was not readily available. The patient showed a good response to gastric levodopa infusion, with a Hoehn & Yahr stage III and UPDRS motor score of 24. Subjectively, he reported a great improvement of his motor symptoms, so the optimization phase continued until the system was placed into the duodenum 2 days later. He did not notice any relevant clinical change or adverse events during gastric infusion of levodopa as compared with duodenal infusion therapy. The UPDRS motor score was 28 when the device was in the duodenum. Subjective complaints of gastrointestinal impairment were only reflected by a moderate constipation. In the scintigraphy a normal gastric emptying of 60% was observed.

Clinical characteristics of these patients are shown in Table 1 and results of scintigraphy studies in Figure 1. None of the patients required levodopa dose adjustments.

Discussion

This limited clinical experience in three patients with long-standing fluctuating advanced PD shows that continuous gastric levodopa infusion may be as effective as the conventional enteral route in patients without any documented contraindication for treatment. The study also shows that the beneficial effects of treatment cannot be related to differences in gastric emptying as two of the three patients presented gastrointestinal motility impairment in the scintigraphy evaluation. However, there are some methodological concerns that made us to be cautious with the present results. Firstly, this is an open descriptive retrospective study carried out

Table 1. Main clinical and demographic variables in three patients with fluctuating advanced PD

Variable	Case #1	Case #2	Case #3
Age	74	74	66
Gender	Female	Female	Male
PD phenotype	Tremoric	Tremoric	Akinetic
Years since PD diagnosis	20	17	15
Hoehn & Yahr stage (*on*) Intragastric Intraduodenal	 IV IV	 III III	 III III
UPDRS-III score (*on*) Intragastric levodopa infusion Intraduodenal levodopa infusion	 Unknown 20	 19 20	 24 28
Levodopa-Equivalent Dose during gastric and duodenal administrations (mg)	1348	1404	1312
Gastrointestinal symptoms*	Mild dysphagia Moderate sialorrhea	None	Moderate constipation
Scintigraphy†	31	46	60
Clinical Global Improvement (CGI)	No change	No change	No change

*Based on NMSS and UPDRS items related to gastrointestinal function.

†Percentage of gastric emptying based on the amount of radiotracer outside the stomach at 30 min.

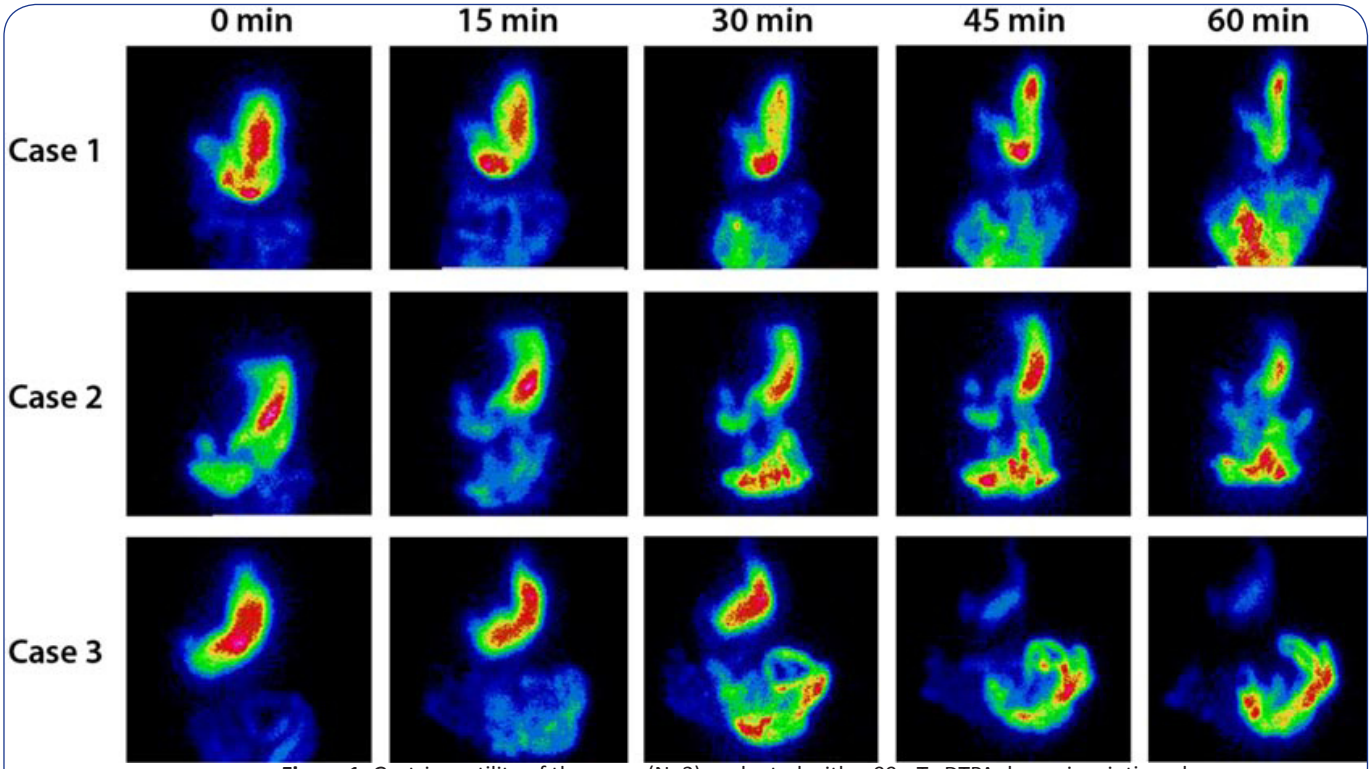

Figure 1. Gastric motility of the cases (N=3) evaluated with a 99mTc-DTPA dynamic scintigraphy.

in only three PD patients, so that it was clearly exposed to different sources of bias, which could influence our results. Secondly, the duration of follow-up is also limited. Thirdly, these cases were already therapeutically optimized patients, so other problems related to this optimization process could not be addressed except in one case where even when the treatment was started in the stomach the motor situation was objectively and subjectively better than when it was began in the duodenum. Lastly, the scintigraphy was performed in the off status, preventing us from controlling any potential beneficial effects that enteral levodopa might exert on gastric motility.

On the other hand these findings are of the utmost importance as most of the technical issues with this type of treatment are related to the inner duodenal tube. If the effect of treatment is proved to be equally effective and safe when placed directly into the stomach, even with concomitant prokinetic treatment, a simplification of the procedure could be achieved and an improvement in the morbidity-related outcomes could be expected in patients where gastric emptying is not playing a role in motor fluctuations. Prospective studies including subjects under continuous duodenal levodopa infusion (which is the approved administration) requiring temporary gastric infusion because of technical problems with the device system could help to clarify the role of gastric emptying, scintigraphy (on/off studies) and the effect of this therapy in motor fluctuations.

Acknowledgments

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

References

1. Fernandez HH, Vanagunas A, Odin P, Espay AJ, Hauser RA, et al. (2013) Levodopa-carbidopa intestinal gel in advanced Parkinson's disease open-label study: Interim results. Parkinsonism Relat Dis19:339-45.
2. Honig H, Antonini A, Martinez Martin P, Forgacs I, Faye GC, et al. (2009) Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. Mov Disord 24:1468-74.
3. Nyholm D, Lewander T, Johansson A, Lewitt PA, Lundqvist C, et al. (2008) Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure. Clin Neuropharmacol 31:63-73.
4. Pfeiffer RF (2003) Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 2:107-16.
5. Djaldetti R, Baron J, Ziv I, Melamed E (1996) Gastric emptying in Parkinson's disease: patients with and without response fluctuations. Neurology 46:1051-4.
6. Kurlan R, Nutt JG, Woodward WR, Rothfield K, Lichter D, et al. (1988) Duodenal and gastric delivery of levodopa in parkinsonism. Ann Neurol 23:589-95.
7. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181-4.

8. Fahn S, Elton RL (1987) Unified Parkinson's Disease Rating Scale (UPDRS). In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. Recent developments in Parkinson's disease. Vol 2. Macmillan Health Care information: Florham Park, NJ pp 153-64.

9. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427-42.

10. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, et al. (2007) The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord 22:1901-11.

11. Early PJ, Bruce Sodee D (1995) Gastric empitying imaging. Principles and practice of nuclear medicine 59: 522 – 525.

12. Guy W (1976) Clinical Global Impressions ECDEU Assessment Manual for Psychopharmacology, Revised (DHEW Publ. No. ADM 76-338). National Institute of Mental Health: Rockville MD pp 218–22.