Use of levodopa-carbidopa intestinal gel to treat patients with multiple system atrophy

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Short communication – *Parkinsonism and Related Disorders*
Title Page

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Abstract

Background: Levodopa-carbidopa intestinal gel (LCIG) is an effective treatment for late-stage Parkinson's disease (PD) but had not been evaluated in levodopa-responsive patients with the parkinsonian variant of multiple system atrophy (MSA-P) and motor fluctuations. We aimed to assess the safety of LCIG in MSA-P patients.

Methods: In a retrospective, single-center study, we analyzed clinical and treatment-related data for all patients with MSA-P or PD treated with LCIG between December 2004 and November 2017. Adverse events (AEs) were classified into three classes: AEs related to gastrointestinal effects or to the PEG-J procedure, AEs related to the device, and AEs related to the pharmacological effect of LCIG.

Results: 7 MSA-P and 63 PD patients had been treated with LCIG for a median [interquartile range] period of 31 [16;43] and 19 [8;45] months, respectively. There were no significant intergroup differences in safety. Enteral nutrition was introduced at the same time as LCIG treatment in 4 (57%) MSA-P patients. In the MSA-P and PD groups, LCIG was associated with a better Global Clinical Impression score and discontinuation of oral anti-parkinsonian drugs (in 43% and 27% of cases, respectively).

Conclusions: LCIG treatment is feasible in MSA-P patients with severe motor complications. The safety profile is similar to that seen in PD.

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Main text

INTRODUCTION

Multiple system atrophy (MSA) is a severe neurodegenerative disorder characterized by autonomic dysfunction and either predominant parkinsonism (MSA-P) or cerebellar ataxia (MSA-C). Although the MSA-P variant is usually considered to be poorly levodopa-responsive[1], 31% of patients show a lasting response to levodopa before the development of motor complications (in 68% of cases) and/or dyskinesia (in 11 to 44%)[2,3]. Three types of continuous dopaminergic therapy are currently available for late-stage Parkinson's disease (PD): deep brain stimulation (DBS), subcutaneous apomorphine pump therapy, and levodopa-carbidopa intestinal gel (LCIG). In France, LCIG is usually accepted by PD patients as a last-line therapy when subcutaneous apomorphine and DBS are ineffective, not tolerated, or contraindicated. In MSA-P, these second-line treatments are generally not recommended, and there is a lack of clinical data other than case reports[4]. By providing more stable plasma levodopa concentrations, LCIG improves quality of life, increases the frequency of "on" periods, and decreases the frequency of "off" periods in PD patients with severe levodopa complications[5]; we therefore reasoned that LCIG might be of value in the treatment of MSA-P with severe motor levodopa complications. Hence, the primary objective of the present study was to assess LCIG's safety profile in levodopa-responsive MSA-P patients with motor complications vs. patients with PD. The secondary objective was to assess the patient's motor outcome in the MSA-P population treated with LCIG.

METHODS

We performed a retrospective study of successively included patients having undergone a gastrostomy for the initiation of LCIG treatment in the Movement Disorders Department at Lille University Medical Center (Lille, France) between December 2004 and November 2017. All the patients in our database were diagnosed as having MSA-P or PD before introducing LCIG treatment., according to the respective diagnostic criteria[1,6]. Clinical diagnosis was supporting by MRI findings in MSA-P patients.

In line with the French legislation on retrospective studies of clinical practice, the study protocol was approved by a hospital committee with competency for research not requiring approval by an institutional review board (reference: 1372959). Patient data were consulted until November 2020.

The analysis was performed in two steps. Firstly, the LCIG-treated MSA-P population was described in terms of (i) epidemiologic variables (sex, age at symptom onset, time with motor fluctuations before LCIG initiation, and age at LCIG initiation), (ii) clinical variables (motor symptoms, autonomic failure, imaging, etc.), and (iii) LCIG-related variables (the levodopa response before LCIG initiation, oral-levodopa-induced complications, previous dopaminergic medications, duration of LCIG therapy, and the status at last follow-up). The levodopa response before LCIG initiation was evaluated with administration of 1.5-fold the morning dosage of levodopa. Levodopa responsiveness was defined as a 30% or more improvement in the Unified Parkinson's Disease Rating Scale motor score during the test[7]. Secondly, the MSA-P and PD group were compared with regard to the characteristics of the LCIG treatment (the levodopa equivalent daily dose (LEDD) at LCIG initiation and at last follow-up, the presence or absence of enteral feeding, and the duration of LCIG therapy). Adverse events (AEs) in each group were classified into three classes: gastrointestinal AEs or AEs related to percutaneous endoscopic gastrostomy with placement of a jejunal tube (PEG-J), AEs related to the device, and AEs related to the pharmacological effect of LCIG. Data for the PD patients have been reported previously[8]. AEs were recorded on a systematic retrospective evaluation from medical records by the investigators. The total number of AEs were recorded in each category and their incidence in the MSA-P and PD populations were compared.

The clinical profiles during LCIG therapy in the MSA-P population and a subgroup of PD patients were assessed at last follow-up on the Clinical Global Impression (CGI) scale based on the investigators' non blinded interpretation of improvement in motor symptoms and reduction in time with motor fluctuations. The CGI scale is divided in 7 categories from very much improved (1) to very much worse (7).

Statistical analyses were performed using GraphPad Prism® software (version 7, GraphPad Software Inc. San Diego, CA). Qualitative variables were quoted as the frequency (percentage), and quantitative variables were quoted as the median [interquartile range (IQR)]. Pairwise intergroup comparisons were performed with the Mann-Whitney U-test (for quantitative variables) or Fisher's test (for qualitative variables). The threshold for statistical significance was set to $p<0.05$.

RESULTS

Characteristics of the MSA-P patient population

Between 2004 and 2017, a total of 70 patients had been treated with LCIG. Of these, 7 (10%) had been diagnosed with MSA-P prior to the initiation of LCIG treatment (**Table 1**). The brain MRI findings were suggestive of MSA-P in six patients; MRI was contraindicated in the remaining patient. LCIG was initiated because of severe motor fluctuations and/or dyskinesia (even with combinations of antiparkinsonian drugs). The response to an acute levodopa challenge was evaluated before LCIG initiation in 5 patients. Three of the 7 LCIG-treated MSA-P patients (43%) had previously been treated with an apomorphine pump. Reason for apomorphine pump discontinuation was lack of efficacy in the 3 patients.

PD patients and MSA-P patients treated with LCIG

The demographic and LCIG-related characteristics of the PD and MSA-P groups are summarized in **Table 2.** LCIG therapy was initiated sooner after diagnosis in the MSA-P group population than in the PD group (median [IQR] time interval: 7 [7;9] and 15 [11;18] years, respectively, $p<0.001$).

The frequencies and prevalences of the main AEs in the MSA-P and PD groups are summarized in **Table 2.** The proportion of patients with at least one AE was similar in the PD and MSA-P groups. Of the 7 MSA-P patients, 4 (57%) had gastro-intestinal AEs or AEs related to the PEG-J procedure (n=16 events). Local effects (such as leakage, granuloma or stoma dermatitis) occurred in 4 patients (57%), digestive effects (such as pneumoperitoneum or intestinal obstruction) occurred in 2 patients (29%), and infectious complications occurred in 3 (43%, including one case of peritonitis). Furthermore, 4 of the 7 patients (57%) experienced device-related AEs (n=11 events): the most common were accidental device removal, device occlusion, external tube deterioration, and gastric loop formation. Lastly, 4 patients (57%) had AEs related to dopaminergic therapy (n=7 events), such as hallucinations (in 2 patients), psychosis and worsen orthostatic hypotension (in 1 patient) and worsening of dyskinesia (in 1 patient).

At last follow-up, 14% of the MSA-P patients and 57% of the PD patients were still being treated with LCIG. The reasons for discontinuation are detailed in **Table 2**. Four MSA-P patients dead during the follow-up, none of the death was due to an AE related to the LCIG treatment. The proportion of deaths was significantly higher in the MSA-P group than in the PD group, although none of the deaths was related to the LCIG treatment. In contrast, the death followed an AE linked to the PEG-J in 2 patients with PD (3%). None of the MSA-P patients discontinued the LCIG treatment because of an AE.

The effectiveness of treatment with LCIG had been initially tested over a 1-week period via administration through a nasojejunal tube in 57 (90%) PD patients and 6 (86%) MSA-P patients. All patients then underwent PEG-J. Enteral nutrition was introduced most frequently at the same time as LCIG treatment in MSA-P than in PD patients (57% vs 8%; p=0.004).

The calculation of the initial LEDD for the LCIG was based on each patient's previous dose level of oral medication[9]: the calculated intake and the clinically effective intake after adjustment did not differ significantly. Prior to LCIG initiation, all patients were taking at least one oral anti-parkinsonian medication, including levodopa in all cases. After LCIG initiation, the prescription of oral antiparkinsonian medications decreased slightly in both groups: all oral anti-parkinsonian drugs were discontinued in 17 of the 63 PD patients (27%) and 3 of the 7 MSA-P patients (43%). The oral medications most frequently prescribed in combination with LCIG were prolonged-release levodopa in the PD group and amantadine in the MSA-P group **(Table 2)**. Data about CGI scale are detailed in **Table 2**.

DISCUSSION

The objective of the present study was to analyze the safety profile of LCIG infusion in MSA-P patients with levodopa-induced motor complications. This single-center study was performed in a specialist center with the largest cohort of LCIG-treated PD patients in France. This type of continuous dopaminergic stimulation therapy gives satisfactory results in patients with advanced and fluctuating PD[8,10], and the use of LCIG to treat MSA-P is reported here for the first time.

The MSA-P group's demographic characteristics were in line with the literature data. Given the mean disease duration of 8 years, our MSA-P population had late-stage disease; the mean survival time in MSA-P is around 7 to 9 years[11].

In both the MSA-P and PD groups, the calculation of the daily dose of LCIG was based on the patient's previous daily intake of oral levodopa[9]. LCIG treatment led to the discontinuation of oral dopaminergic treatment in 43% of the MSA-P patients and 27% of the PD patients. Polymedication is often associated with higher symptoms burden and we also could suppose that LCIG treatment could improves quality of life for patient with MSA-P as seen in PD[5]. The treatment appeared to be used over 24 hours in 30% of MSA-P patients and in 20% of the PD patients. Concerning the therapeutic strategy, the effective dose and the duration of LCIG infusion therapy were similar in the PD and MSA-P groups. In contrast, the proportion of patients receiving enteral nutrition was higher in the MSA-P group. These results suggest that continuous levodopa administration is effective, and that PEG-J tube placement is doubly

useful: it optimizes the care of patients with autonomic disorders and swallowing difficulties. We should consider that the amelioration on the CGI scale could also be due in part to the amelioration in the nutritional status.

The incidence of adverse events was similar in the PD and MSA-P patients. Some of the AEs related to dopaminergic therapy might be related to disease progression. The higher death rate among MSA-P patients might well be due to a shorter life expectancy than among PD patients.

This retrospective study had some limitations. Firstly, we lacked data on the effectiveness for motor symptoms and changes in quality of life. However, the CGI scale data and the fact that only one patient discontinued LCIG therapy due to a lack of effectiveness suggest that LCIG treatment was at least as effective as oral levodopa treatment. Another limitation is the lack of pathological confirmation, but MSA-P diagnosis was supported by clinical and MRI data. Finally, some of the authors declared conflicts of interest with the LCIG producer. However, this study was a retrospective evaluation of the current practice in our center and was not funded by the LCIG producer.

The results of this case series show that LCIG infusion in levodopa-responsive MSA-P patients may be a last-line treatment for reducing motor impairments. The safety profile in MSA-P appears to be similar to that in PD. In patients with advanced PD, LCIG therapy reduces motor fluctuations causing by erratic gastric emptying[5], which can also be observed in MSA-P patients. Medico economic aspects should also be considered. Previous data in PD had shown that LCIG treatment could be considered cost-effective compared to standard care in late stage disease[12] and healthcare cost must be evaluated in the MSA-P population.

These results are preliminary and concern a small cohort of patients. A prospective study of the effect of LCIG therapy on motor impairments and quality of life in patients with MSA-P is now warranted.

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