folia medica

Folia Medica 65(6):929-932
DOI: 10.3897/folmed.65.e108196

Original Article

Clinical Profile of Levodopa-Carbidopa-Entacapone Intestinal Gel Infusion in Patients with Advanced Parkinson's Disease

Karina A. Atanasova-Ivanova[1,2], Sonya I. Hristova[1,2], Ivan G. Milanov[1,2]

[1] *Department of Neurology, Medical Faculty, Medical University of Sofia, Sofia, Bulgaria*
[2] *St Naum University Hospital for Active Treatment in Neurology and Psychiatry, Sofia, Bulgaria*

Corresponding author: Karina A. Atanasova-Ivanova, Department of Neurology, Medical Faculty, Medical University of Sofia, Sofia, Bulgaria; Email: karyatanasova92@gmail.com; Tel.: +359 888 350 836

Received: 18 June 2023 ♦ **Accepted:** 16 July 2023 ♦ **Published:** 31 Dec 2023

Citation: Atanasova-Ivanova K, Hristova SI, Milanov IG. Clinical profile of levodopa-carbidopa-entacapone intestinal gel infusion in patients with advanced Parkinson's disease. Folia Med (Plovdiv) 2023;65(6):929-932. doi: 10.3897/folmed.65.e108196.

Abstract

Introduction: Parkinson's disease in its advanced stage is a progressive condition that can be treated with levodopa. The long-term complications of this treatment are difficult to manage. A new device-aided therapy has recently been developed to minimize these effects.

Aim: The purpose of this study was to assess the efficacy and safety of the intestinal gel containing levodopa - carbidopa - entacapone, as well as to see if it had any impact on the disease's non-motor symptoms. Additionally, we sought to identify the criteria for selecting among the various treatments that were offered.

Materials and methods: This study includes the first five patients who started receiving the levodopa-carbidopa-entacapone gel for Parkinson's disease in the Department of Neurology and Psychiatry at St Naum University Hospital for Active Treatment in Sofia, Bulgaria. To evaluate the influence of motor and non-motor symptoms of the disease, we used neurological examination and the Movement Disorder Society - Unified Parkinson's Disease Rating Scale. The Parkinson's Disease Quality of Life Questionnaire was used to assess the quality of life of the patients.

Results: All patients showed improvement in their motor functions, quality of life, and sleep problems in comparison with those receiving oral levodopa. No patient experienced an increase in the dyskinesias. The postural stability continued to be impaired. For now, the medication has shown a protective effect against the levodopa-induced polyneuropathy. The main side effects were diarrhea and weight loss.

Conclusions: Levodopa-carbidopa-entacapone therapy is a promising new modality of treatment for advanced Parkinson's disease. The medication has been found to improve the patients' motor functions and exert a positive effect on some non-motor symptoms. The drug has shown a good safety profile and tolerance. There is still a lack of clear criteria for choosing between the levodopa-carbidopa-entacapone and levodopa-carbidopa intestinal gels.

Keywords

Parkinson's disease, therapies

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition that occurs with dopaminergic loss of neurons in substantia nigra. The disease is treated mainly with levodopa, but the long-term use of this drug causes some complications, such as motor fluctuations with on- and off-periods and dyskinesia. This stage of the disease is se-

verely disabling not only for the patients but also for their families; it has a significant impact on the patients' quality of life as well as on healthcare resources. Currently, the therapies for advanced Parkinson's disease include deep brain stimulation, continuous subcutaneous infusions of apomorphine hydrochloride, intestinal infusion of levodopa-carbidopa and, quite recently, intestinal infusion of levodopa-carbidopa-entacapone (LECIG, LECIGON). The latter method has been in use in Bulgaria since the end of 2021, but its clinical experience has yet to be fully investigated. The medication is administered percutaneously by an endoscopic gastric jejunostomy (PEG-J) system using a smaller cartridge-and-pump system than that used in the levodopa-carbidopa infusion. It contains entacapone, an inhibitor of the enzyme catechol-o-methyl-transferase (COMT), which increases levodopa bioavailability by inhibiting this enzyme, resulting in lowering the overall daily doses of levodopa.[1,2] The cartridges contain levodopa and entacapone in equal doses of 20 mg/ml and carbidopa in a dose of 5 mg/ml. The total daily dose is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose, and the extra bolus doses to control any repetitive "off" episodes. When deciding on doses, we should keep in mind that the continuous dose should be reduced by 35% based on the COMT genotype when compared to people treated with levodopa and carbidopa.[3] The medication is currently well tolerated and has an excellent safety profile. The major adverse events that are expected to occur are surgical and post-surgical complications, some device problems, and others that are medically determined, such as nausea, diarrhea, weight loss, dyskinesia, muscle pain, and hematuria. Additionally, the COMT inhibitor may be able to prevent the onset of levodopa-induced peripheral neuropathy.[2,4] It is crucial to have a standardized set of guidelines to determine which medication to choose given the diversity of therapies that are currently available and the emergence of new ones. According to the Bulgarian consensus on identification and management of advanced Parkinson's disease, utilizing the Delphi-panel approach, we used the 5-2-1 criterion: ≥5-times daily oral levodopa doses, ≥2 h "off" symptoms/day, and ≥1 h of troublesome dyskinesia/day.[5,6] Due to overlapping indications, choosing the best device-assisted therapies can be difficult. The selection criteria should be even clearer between the levodopa and carbidopa intestinal infusion and levodopa-carbidopa-entacapone infusion given their similar composition and mode of application. For patients transitioning from levodopa-carbidopa infusion to levodopa-carbidopa-entacapone infusion, who have an existing PEG-J system, a temporary connection adapter can be used initially to connect to the LECIG pump. The dose can easily be calculated. In this way, the effectiveness and tolerability of the new medication could be tested in patients already treated with intestinal infusion.

AIM

This study's main objective was to assess the efficiency and safety of this novel drug in our country. We also wanted to see if LECIG had any impact on patients' quality of life and some of the non-motor symptoms of Parkinson's disease. Additionally, we sought to identify the criteria for selecting levodopa-carbidopa-entacapone intestinal gel over the levodopa-carbidopa intestinal gel.

MATERIALS AND METHODS

This is an observational study which included the first patients in the Clinic of Movement Disorders who started receiving LECIG in the Department for Parkinson's Disease at St Naum Hospital in Sofia, Bulgaria. Eight patients (4 women and 4 men) were included. Three of them dropped out of treatment: one for personal reasons, another because of failure to switch from levodopa-carbidopa gel, and one for gastrointestinal problems, such as nausea and loss of appetite. Five patients (2 women and 3 men) out of 8 continued with the levodopa-carbidopa-entacapone intestinal gel. The treatment was initiated in all patients by using a temporary nasojejunal tube to titrate and optimize the dose before placing the PEG-J system. The median age was 74 years, and the median duration since PD diagnosis was 13 years. The median doses were 9.6 mL as a morning dose, 2.22 mL/h as infusion rate, and 1 mL as an extra dose. To evaluate the influence of motor and non-motor symptoms of the disease, we used neurological examination and the MDS-UPDRS. The Parkinson's Disease Quality of Life Questionnaire (PDQ-8) was used to assess the quality of life of patients.[7,8]

RESULTS

Since the beginning of the year, eight patients have started LECIG therapy in our clinic. Three of them were excluded - one for personal reasons, another for failure to switch from levodopa-carbidopa intestinal gel because of violent generalized severely disabling hyperkinesis and unsatisfactory effects on motor fluctuations, and another one for gastrointestinal problems (nausea and loss of appetite). Five patients continued to receive the therapy. These were all in the advanced stage of Parkinson's disease according to the 5-2-1 criterion. Three patients were switched from levodopa and benserazide tablets and two from levodopa-carbidopa-entacapone tablets (Stalevo). We have not yet had a patient to successfully transition from levodopa-carbidopa intestinal gel. All patients showed improvement in their motor functions and time spent with rigidity according to the Movement Disorder Society (MDS)-UPDRS in comparison with patients on oral levodopa. No patient experienced an increase in dyskinesias. The patients' postural stability continued to be impaired, leading to falls in three of five patients, with subsequent fractures and surgery af-

ter treatment began. However, all patients claimed to have improved their quality of life, particularly their ability to communicate fully with others and to feel no embarrassment as a result of having Parkinson's disease. The treatment improved some of the non-motor symptoms, most notably during sleep. Everyone reported that their sleep improved within the first few days of treatment. Four of the five patients continued to receive levodopa by mouth before going to bed. All five patients had no clinical or electromyographic evidence of polyneuropathy at the start of treatment and one year later. The main side effects were diarrhea and weight loss of 30 kg per year, as reported by one patient. This patient was found to have helicobacter pylori infection, which was successfully treated, and the treatment with LECIG was continued. Overall, the drug's safety profile and tolerance were good.

DISCUSSION

In a recent study, the initial experience with LECIG therapy in clinical settings was evaluated in 24 patients.[9] Their median age was 71.5 years, and the median duration since Parkinson's disease diagnosis was 15.5 years. The median doses used in this study were 6.0 mL as a morning dose, 2.5 mL/h as infusion rate, and 1.0 mL as an extra dose. Twelve patients were switched from levodopa-carbidopa intestinal infusion. Six patients discontinued the therapy, three due to diarrhea, one due to hallucinations, and two deceased (one due to COVID-19, one due to pulmonary embolism and cardiac arrest). In general, the patients were happy with the size and weight of the pump. Most of them reported improvement in the ability to perform daily activities and in their self-rated quality of life. Compared to our results, the patient's profile was similar. Also, the median morning dose was slightly elevated while the median infusion rate was lower. The patients spent longer hours without rigidity, but postural stability did not improve. The authors claimed that with the LECIG therapy, it may not be necessary to keep the oral bedtime sustained-release levodopa dose because the decline of levodopa concentration is slower than levodopa-carbidopa infusion which may be of benefit when choosing between the two methods. In our study, most of the patients continued with the oral administration of levodopa before going to bed. During the use of LECIG therapy, it is necessary to evaluate the effectiveness of the medication not only on the motor but also on the non-motor symptoms in advanced Parkinson's disease like in levodopa-carbidopa infusion.[10] One of the non-motor symptoms we assessed was sleep disturbance. There are studies we found in the literature reporting that the intake of oral levodopa-carbidopa-entacapone (Stalevo) may be a useful treatment for sleep disturbance, specifically the sleep onset, sleep maintenance, and rapid eye movement sleep behavior disorder in advanced PD patients with motor fluctuations.[11] In our study, the patients reported improvements of their sleep at the beginning of treatment. Currently, the medication shows a protective effect against the development of peripheral neuropathy. In addition, some of the people had been taking oral levodopa-carbidopa-entacapone before the intestinal gel with the same composition which might be in favor of selection. By contrasts, people with intolerance to entacapone, low weight, and tumultuous dyskinesias at baseline should be treated with other medication including levodopa-carbidopa intestinal gel. There are still no clear criteria for choosing between the two medications for advanced Parkinson's disease.

CONCLUSIONS

Levodopa-carbidopa-entacapone intestinal gel is a promising new modality to treat advanced Parkinson's disease. The medication improves the patients' motor functions compared with patients with oral levodopa administration and has a positive effect on some non-motor symptoms such as sleep disorders and on quality of life. At this stage, the LECIG therapy shows good safety with satisfactory patient compliance. There are still lack of clear criteria when choosing between levodopa-carbidopa-entacapone and levodopa-carbidopa intestinal gels. Long-term studies need to be done.

Acknowledgments

This study is supported by the Bulgarian Ministry of Education and Science under the Young Scientists and Postdoctoral Students-2 National Program (No. 250/31.10.2022)

Competing Interests

The authors have declared that no competing interests exist.

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Клинический профиль инфузии кишечного геля леводопы-карбидопы-энтакапона у пациентов с прогрессирующей болезнью Паркинсона

Карина А. Атанасова-Иванова[1,2], Соня И. Христова[1,2], Иван Г. Миланов[1,2]

[1] *Кафедра неврологии, Факультет медицины, Медицинский университет – София, София, Болгария*

[2] *Университетская больница активного лечения неврологии и психиатрии „Св. Наум", София, Болгария*

Адрес для корреспонденции: Карина А. Атанасова-Иванова, Кафедра неврологии, Факультет медицины, Медицинский университет – София, София, Болгария; Email: karyatanasova92@gmail.com; тел.: +359 888 350 836

Дата получения: 18 июня 2023 ♦ **Дата приемки:** 16 июля 2023 ♦ **Дата публикации:** 31 декабря 2023

Образец цитирования: Atanasova-Ivanova K, Hristova SI, Milanov IG. Clinical profile of levodopa-carbidopa-entacapone intestinal gel infusion in patients with advanced Parkinson's disease. Folia Med (Plovdiv) 2023;65(6):929-932. doi: 10.3897/folmed.65.e108196.

Резюме

Введение: Болезнь Паркинсона на поздней стадии представляет собой прогрессирующее заболевание, которое можно лечить с помощью леводопы. С долгосрочными осложнениями этого лечения трудно справиться. Недавно была разработана новая аппаратная терапия, позволяющая минимизировать эти эффекты.

Цель: Целью данного исследования было оценить эффективность и безопасность кишечного геля, содержащего леводопу, карбидопу и энтакапон, а также выяснить, оказывает ли он какое-либо влияние на немоторные симптомы заболевания. Кроме того, мы стремились определить критерии выбора среди различных предложенных методов лечения.

Материалы и методы: В данное исследование включены первые пять пациентов, которые начали получать гель леводопа-карбидопа-энтакапон при болезни Паркинсона в отделении неврологии и психиатрии университетской больницы активного лечения Святого Наума в Софии, Болгария. Для оценки влияния моторных и немоторных симптомов заболевания мы использовали неврологическое обследование и Единую оценочную шкалу болезни Паркинсона Общества двигательных расстройств. Для оценки качества жизни пациентов использовался опросник качества жизни при болезни Паркинсона.

Результаты: У всех пациентов наблюдалось улучшение двигательных функций, качества жизни и проблем со сном по сравнению с теми, кто получал перорально леводопу. Ни у одного пациента не наблюдалось усиления дискинезий. Постуральная стабильность продолжала нарушаться. На данный момент препарат продемонстрировал защитный эффект против полинейропатии, вызванной леводопой. Основными побочными эффектами были диарея и потеря веса.

Заключение: Терапия леводопа-карбидопа-энтакапон является многообещающим новым методом лечения прогрессирующей болезни Паркинсона. Установлено, что препарат улучшает двигательные функции пациентов и оказывает положительное влияние на некоторые немоторные симптомы. Препарат показал хороший профиль безопасности и переносимости. До сих пор отсутствуют чёткие критерии выбора между кишечными гелями леводопа-карбидопа-энтакапон и леводопа-карбидопа.

Ключевые слова

Болезнь Паркинсона, методы лечения