Abdominal Pain: A Symptom of Levodopa End of Dose Wearing off in Parkinson's Disease

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ABSTRACT

Long-term levodopa use is associated with the "End of Dose Wearing Off" (EODWO) phenomenon wherein Parkinsonian symptoms return before a patient's next scheduled dose of levodopa. Wearing off symptoms may include a variety of autonomic, emotional, motor, psychological and sensory abnormalities. Abdominal pain may be an important wearing off symptom as an early indicator of the development of EODWO in Parkinson's disease (PD) patients. In this report, we present two patients on levodopa therapy for PD who developed acute abdominal pain as a symptom of EODWO.

Keywords: Abdominal, levodopa

Dolor Abdominal – un Síntoma de Deterioro de Fin de Dosis de Levodopa en la Enfermedad de Parkinson

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RESUMEN

El uso de levodopa a largo plazo está asociado con el fenómeno conocido como "deterioro de fin de dosis" (en inglés, EODWO), en el que los síntomas parkinsonianos regresan antes de la siguiente dosis de levodopa programada para un paciente. El deterioro de los síntomas puede incluir una variedad de anomalías autonómicas, emocionales, psicológicas, motoras y sensoriales. El dolor abdominal puede ser un importante síntoma de "wearing off" o deterioro de fin de dosis, que constituye un indicador temprano del desarrollo de EODWO en los pacientes de la enfermedad de Parkinson (EP). En este informe, presentamos dos pacientes bajo tratamiento con levodopa para la EP, que desarrollaron dolor abdominal agudo como un síntoma de EODWO.

Palabras claves: Abdominalgia, levodopa

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INTRODUCTION

Initiating levodopa treatment is usually followed by a significant improvement in Parkinsonian symptoms ("Honeymoon Period") (1); the response to an individual levodopa dose wears off slowly (2). However, with disease progression, most patients experience a gradual shortening in the duration of levodopa's beneficial effect End of Dose Wearing Off [EODWO] (3). Patients may suffer motor abnormalities, anxiety, dysthymia, double vision, numbness and excessive perspiration related to EODWO (2, 4, 5). Herein, we describe two patients on levodopa therapy for Parkinson's disease (PD) who developed EODWO-related abdominal pain.

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CASE REPORTS

Case 1

NV, a 61-year-old right-handed male, was diagnosed with PD at the age of 58 years. His initial symptoms included rigidity and bradykinesia on the right side of the body. The patient was initially started on levodopa/carbidopa 100/25 mg three times daily, which resulted in a significant improvement of bradykinesia and rigidity. After four years on levodopa, however, he began to experience EODWO 90 minutes prior to each scheduled dose of levodopa/carbidopa. He reported significant slowness in activities of daily living and stiffness

in his body. Moreover, he would complain of severe abdominal pain as each dose of levodopa/carbidopa wore off; this abdominal pain would improve on taking levodopa. The abdominal discomfort was a feeling of severe intra-abdominal cramping without any nausea or vomiting. Although he was examined in the emergency department several times, the cause of his abdominal pain could not be identified. Abdominal CT, MRI spine and chest X-ray were all normal. Analgesics and spasmolytics were ineffective in addressing his abdominal discomfort. Eventually, the patient consulted his neurologist with respect to the recurring episodes of intense abdominal pain at the end of each levodopa dose. The addition of controlled-release levodopa successfully ameliorated the abdominal pain, the rigidity and bradykinesia. Delaying the scheduled dose of levodopa would cause the return of EODWO symptoms, including abdominal pain.

Case 2

A 71-year-old right-handed male was diagnosed with Parkinson's disease at the age of 67 years. His initial symptoms included drooling, micrographia, bradykinesia and loss of facial expression. MRI brain and EMG/NCS were both unremarkable. He was started on levodopa/carbidopa 100/25 mg three times daily; subsequently, the patient noticed a marked improvement of bradykinesia and drooling. The levodopa dosage was gradually increased to 100/25 mg, two tablets four times daily. Entacapone was later added to alleviate EODWO. Roughly three years into levodopa/carbidopa therapy, the patient began to experience intense abdominal pain around 3 am – six hours after his last scheduled dose of levodopa/carbidopa – as the evening dose of levodopa/carbidopa wore off. The patient would achieve relief of this abdominal discomfort only upon taking his next scheduled dose of levodopa/carbidopa at 5 am. Upon being informed of these nightly bouts of abdominal pain, the patient's neurologist surmised that his symptoms were related to a wearing off effect of the evening dose of levodopa. Addition of a bed-time dose of controlled-release levodopa/carbidopa at 11:30 pm successfully ameliorated the patient's abdominal pain. The patient has continued on levodopa/carbidopa treatment without episodic abdominal pain.

DISCUSSION

Patients on prolonged Parkinson's disease levodopa therapy frequently suffer EODWO. In fact, according to Nutt *et al* (4), nearly 50% of all patients will experience one or more EODWO symptoms after an average of five to six years of levodopa use. Wearing-off symptoms are extremely diverse and may include a variety of psychological, emotional, autonomic and sensory abnormalities. Severe abdominal pain resulting from EODWO may lead to hospitalization and an erroneous diagnosis of acute abdomen as described by Kułakowska *et al* (2). Patients may undergo extensive investigations, such as abdominal ultrasound, CT scans or GI endoscopy to identify the cause of the pain. In rare cases, patients may be subjected to exploratory laparotomy. Recurrent abdominal pain may be a key indicator of the development of EODWO in patients on levodopa therapy. Careful history taking may allow physicians to relate the levodopa dosing schedule to the manifestation of abdominal pain. Increasing the frequency of levodopa treatment may resolve EODWO symptoms. For some patients, controlled-release levodopa preparations may relieve EODWO. With controlled-release therapy, the plasma concentration of levodopa may be maintained at sufficient concentrations so as to preclude the manifestation of wearing off symptoms (including abdominal pain) for over 8 hours (6). Lees reported that patients on controlled-release therapy may require considerably larger doses of levodopa (6). The work of Hauser in 2004 and Hauser *et al* in 1998 supports adding a cathechol O-methyltransferase inhibitor such as Entacapone or monoamine oxidase-B inhibitor such as Selegiline to alleviate EODWO (7, 8). Entacapone and Selegiline inhibit the enzymatic degradation of levodopa, thereby prolonging levodopa's half-life and preventing premature EODWO.

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